

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

MCPP

Chemical Code # 000374, 5333, Tolerance # 50779, 52223

September 15, 1999

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect.
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, possible adverse effect.
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, possible adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 163973 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study in review.

File name: T990915

MCPP = the racemic mixture.

MCPP-p = the optically active (right-hand) isomer.

MCPP- D form = the optically active (right-hand) isomer.

MCPP-pDMAS = dimethylamine salt (CC:5333, Tolerance # 52223)

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 50779 008 114820, "Study on the Chronic Toxicity and Oncogenic Potential of MCPP in Rats, Administration in the Diet Over 24 Months", (Dr. B. Kuhborth, BASF Aktiengesellschaft, FRG, Report # 71S0047/8352, 22 August 1988). Test article is identified as MCPP mix (2-(4-chloro-2-methyl-phenoxy)propionic acid) with 92.7% purity. 75 Wistar (Chbb = THOM (SPF)) rats/sex/group received 0 (Kliba rats/mice/hamsters maintenance diet, "A" 343 meal), 20, 100, and 400 ppm in the diet for 24 months. 10 per sex per group were sacrificed after 12 months. Increased relative kidney weights were noted for mid and high dose groups in males at interim sacrifice and at the high dose group at term. Histopathology did not reveal a marked pattern of adverse effects in the kidneys. **Adverse oncogenic effects are not indicated.** Chronic NOEL = 20 ppm (1.1 mg/kg males; 1.4 mg/kg females) based on increased relative kidney weights. **Acceptable.** (H. Green, and P. Iyer, 4/23/99).

CHRONIC TOXICITY, DOG

50779-022 157710, "Mecoprop-p - Chronic Oral Toxicity Study in Beagle Dogs, Administration in the diet for 12 months", (Dr. S. Bachmann, et al., BASF Aktiengesellschaft, FRG, Project # 33D0002/91166, 12 September 1997). 5 Beagle dogs per sex per group received Mecoprop-p (89.9% purity) in the diet at concentrations of 0, 60 (2 mg/kg/day), 180 (5 mg/kg/day), and 600 (19 mg/kg/day) ppm for 12 months. Group mean bodyweights were reduced 3.0% to 5.5% (relative to controls) at the high dose and group mean bodyweight gain was decreased for males (75%) and females (25%) for days 0 through 49 and for males (15%) for days 0 through 364. Decreases in hemoglobin and hematocrit in males and inorganic phosphate and calcium in females were noted at the high dose level. NOEL = 180 (5 mg/kg/day) based on reduced body weight and body weight gain. **Adverse effects were not indicated. Acceptable. (H. Green, and P. Iyer, 8/5/99).

Sub-chronic Dog:

50779-017, 009 130900, 114821 "Subchronic (13-Week) Oral Toxicity Study with Mecoprop (MCPP) in Beagle Dogs", (Dr. P.G.J. Reuzel and Dr. C.F.M. Hendriksen, Centraal Instituut Voor Voedingsonderzoek TNO (Central Institute for Nutrition and Food Research), Utrechtseweg 48, Zeist, Netherlands; Report # R 6105; May 1979). 4 Beagle dogs per sex per group received Mecoprop technical (MCPP, 93.3% purity) in the diet at concentrations of 0, 4, 16, or 64 mg/kg bodyweight/day for 13 weeks. Reduced bodyweight; decreased hemoglobin content, packed cell volume, and erythrocytes; and increased urine pH was reported at 16 mg/kg body weight /day. At 64 mg/kg/day, reduced bodyweight; decreased hemoglobin content, packed cell volume, and erythrocytes; increased serum urea; increased urine pH; increased relative heart, liver, and kidney weights; and discolored fat tissue in the pericardium and/or mesenterium were reported. NOEL = 4 mg/kg. No worksheet. (P. Iyer, 8/4/99).

ONCOGENICITY, MOUSE

50799 **021 152442 Mecoprop-P: Carcinogenicity Study in B6C3F1/CrIBR Mice Administration in the Diet for 18 Months. (Mellert, W., et al., BASF Aktiengesellschaft, FRG, Project No.: 76S0002/91102. June 21, 1996). Mecoprop-P, purity 92.7%, was admixed with the feed at concentrations of 0, 25, 250 or 2500 ppm to 50 mice/sex/group (equivalent to 4, 43, 662 mg/kg) for 18 months. The high dose 2500 group was discarded, due to severe body weight impairment

(27 - 37%), after 11-12 months. Increased kidney weight (14-21%) and incidence of chronic nephropathy for 250 ppm females; Chronic NOAEL = 25 ppm (4 mg/kg) for females; 250 ppm (43 mg/kg) for males. Ovary weight values appear to decrease with Mecoprop-P treatment. **The data suggest an oncogenic response (carcinomas in the lung in males).** Acceptable. (Kishiyama, J. and P. Iyer., 8/18/99).

REPRODUCTION, RAT

50779 010, 015 114823, 124207, "Reproduction Study with MCPD in Rats, Continuous Dietary Administration Over 2 Generations", (Dr. J. Hellwig, BASF Aktiengesellschaft, Department of Toxicology, Federal Republic of Germany, Report # 92/10869, Project # 70R0047/83078, 31 July 1992). Test article is identified as MCPD mix with 92.7% purity. 25 Wistar (Chbb = THOM (SPF)) rats per sex per group received 0 (ground Kliba maintenance diet rat/mouse/hamster GLP 343 meal), 20, 100, and 500 ppm in the diet (equivalent to 2, 10 and 50 mg/kg) through 2 generations with two litters in the first generation and 1 litter in the second. Treatment began 70 days prior to the first mating of the first parental generation. Increased absolute and relative kidney weights are noted for F0 and F1 mid and high dose parents. **Adverse effects are not indicated. Parental NOEL = 100 ppm (increased kidney weight without histopathology). Offspring NOEL = 100 ppm (reduced fourteen and twenty-one day bodyweights at 500 ppm in F2a). No effect on reproduction parameters at 500 ppm. **Acceptable.** (H. Green and P. Iyer, 7/2/99).

52223-023, 024, 025, 026 163937, 163938, 163939, and 163940, Duplicate of record numbers 114823 and 124207.

TERATOLOGY, RAT

** 50779 010, 013 114824, 124203, "Teratogenicity - Rat, Study of the Prenatal Toxicity of Mecoprop-P (MCPD-P) in Rats After Oral Administration (Gavage)", (Dr. J. Hellwig, BASF, FRG, Report #93/10160, Project # 30R30002/91013, 16 February 1993). The test article is identified as Mecoprop-P (D form) with 92.2% purity. 25 mated Wistar (Chbb:THOM (SPF)) female rats per group received concentrations of 0 (0.5% Carboxymethyl cellulose), 20, 50, and 100 mg/kg/day by gavage on gestation days 6 through 15. Maternal food consumption was reduced by 21% on gestation days 6 to 8 at 100 mg/kg/day. **Adverse effects are not indicated.** Maternal NOEL = 50 mg/kg/day (reduced food consumption (10% to 22%) on gestation days 6 to 10 at the high dose level). Developmental NOEL = 50 mg/kg/day (delayed ossification and increased rudimentary cervical ribs at the 100 mg/kg/day). **Acceptable.** (H. Green and P. Iyer, 8/3/99).

52223-021 163935, Duplicate of record #124203

TERATOLOGY, RABBIT

50779 010, 014 114825, 124206, "Chronic Testing: Teratogenicity - Rabbit Study of the Prenatal Toxicity of Mecoprop-P (MCPD-P) in Rabbits After Oral Administration (Gavage)", (Dr. J. Hellwig, BASF Aktiengesellschaft, Department of Toxicology, D-67056 Ludwigshafen/Rhein, FRG, Report # 93/10161, Project # 40R0002/91014, 16 February 1993). 15 artificially inseminated Himalayan (Chbb:HM (outbred strain)) female rabbits received Mecoprop-p (optically active D-form, 92.2% purity) at 0 (0.5% aqueous carboxymethyl cellulose), 5, 20, and 50 mg/kg/day by gavage on gestation days 7 through 19. **Adverse effects are not indicated. Maternal NOEL = 50 mg/kg/day. Developmental NOEL = 50 mg/kg/day. **Acceptable** (H. Green, and P. Iyer, 7/9/99).

5223-022 163936, duplicate of record # 124206

GENE MUTATION

50779 011 114826, "Report on the Study of 2-(4-Chloro-2-Methylphenoxy)Propionic Acid (MCPD) in the Ames Test", (Dr. G. Engelhardt, BASF Aktiengesellschaft, 27 April 1981 (Original German Report 18 March 1981)). Test article is described as MCPD = Mecoprop (2-(4-chloro-2-methylphenoxy) propionic acid) with approximately 96% purity. The reversion assay was performed in quadruplicate with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 at 0 (DMSO), 20, 100, 500, 2500, and 5000 µg/plate in the presence and absence of rat liver activation with 48 hour exposure. **An increased reversion rate was not indicated. Acceptable. (H. Green, and P. Iyer, 4/14/99).

50779-016 130755, "Ames Salmonella Typhimurium Bacterial Reverse Mutation Assay on MCPD-p Acid", (Eryl Jones, *et al.*, Huntingdon Research Centre Ltd., England; Report # JEL 53/921060, 19 May 1993). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed in the presence and absence of activation to MCPD-p acid (92.6% purity) concentrations of 0, 50, 150, 500, 1500, and 5000 µg/plate with incubation for 3 days with a repeat assay. **An increase in the reversion frequency was not indicated. Acceptable. (H. Green, and P. Iyer, 4/21/99).

52223-056 163971, "MCPD-p DMAS, Micronucleus Test", (Raymond J. Proudlock, *et al.*, Huntingdon Research Centre Ltd., England, Report # JEL 54/921201, 21 May 1993). 15 or 20 (high dose) SPF CD-1 mice per sex per group received a single oral dose of MCPD-p DMAS (65.62% w/w) by gavage at 0 (water), 144, 288, and 576 mg/kg followed by bone marrow sampling 24, 48, and 72 later. Mitomycin C was functional as the positive control. **An increase in the incidence of micronucleated polychromatic erythrocytes was not indicated. Acceptable. (H. Green, and P. Iyer, 8/24/99).

52223-057 163972, "Chinese Hamster Ovary/HGPRT Locus Assay MCPD-pDMAS", (Kevin Adams *et al.*, Huntingdon Research Centre Ltd., England, Report # JEL 60/921617, 19 July 1993). Chinese hamster ovary cells (CHO-K1-BH₄) were exposed (4 hours) in duplicate (vehicle control in quadruplicate) to MCPD-p DMAS (65.62%w/w) concentrations of 0, 500, 1000, 1500, 2000, 2250, 2500, 2750, and 3000 µg/ml without activation and 0, 250, 500, 1000, 1250, 1500, 1750, 2000, 2250, and 2500 µg/ml with activation (two trials). The positive controls, ethyl methanesulfonate and 20-methylcholanthrene, were functional. **An increase in forward mutation frequency was not indicated. Acceptable. (H. Green, and P. Iyer, 8/24/99).

** 522233 -028 163942, "Chinese Hamster Ovary/HGPRT Locus Assay, MCPD-p acid", (K. Adams *et al.*, Huntingdon Research Centre LTD., England. Report # JEL 87/931132, 9 December 1993). Chinese hamster ovary cells (CHO-K1-BH₄) were exposed (4 hours) in duplicate (vehicle control in quadruplicate) to MCPD-p acid (92.6%) concentrations of 0, 23.2, 46.3, 50.0, 92.6, 100.0, 185.2, 200.0, 370.4, 400.0, 463.0, 500, 578.8, 625.0, 694.5, 750.0, 800.0 and 850.0 Fg/ml without activation and 0, 25, 46.3, 50.0, 92.6, 100.0, 185.2, 200.0, 370.4, 400.0, 694.5, 750.0, 810.3, 875.0, 925.0, 926.0, 1000.0 and 1041.8 Fg/ml with activation in two trials with rat liver S9. 6 Thioguanine was used to select mutants following a 7 day expression period. Positive controls were functional. **An increase in forward mutation was not indicated. Acceptable.** (H.Green and P. Iyer, 8/27/99).

**50223-055 163970, "Ames *Salmonella Typhimurium* Bacterial Reverse Mutation Assay on MCPD-p DMAS", (Eryl Jones, *et al.*, Huntingdon Research Centre Ltd., England, Report # JEL

51/921058, 19 May 1993). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were exposed to MCPD-p DMAS (65.625 W/W) concentrations of solvent (purified water), 0, 50, 150, 500, 1500, and 5000 µg/plate for 72 hours in triplicate with two trials. Positive controls were functional. **An increase in the reversion rate was not indicated. Acceptable.** (H. Green, and P. Iyer., 8/20/99).

50779-012 115690 Protocol for 130755. Not reviewed.

CHROMOSOME EFFECTS

**** 50779 011 114827**, "Cytogenetic Investigations in Chinese Hamsters After a Single Oral Administration of MCPD - Bone Marrow Chromosome Analysis", (Dr. G. Engelhardt, BASF Aktiengesellschaft, Project # 10M0047/8306, 1 April 1985). The test article is identified as Mecoprop (MCPD) (2-(4-chloro-2-methylphenoxy) propanoic acid) with 92.7% purity. 10 to 15 Chinese hamsters per sex per group received a single oral dose at concentrations of 0 (0.5% carboxymethyl cellulose), 60, 470, or 3800 mg/kg. Bone marrow was sampled 6, 24, and 48 hours post-dosing. Clinical signs were seen at 3800 and 470 mg/kg after dosing with one death at 3800 mg/kg. **Possible increased frequency of chromosomal aberrations was indicated. Acceptable.** (H. Green, and P. Iyer, 4/16/99).

**** 50779 011 114829**, "Cytogenetic Investigations in Chinese Hamsters After a Single Oral Administration of MCPD - D Form, Bone Marrow Chromosome Analysis", (Dr. G. Engelhardt, BASF Aktiengesellschaft, Project # 10M0020/8346, 17 July 1985). The test article was identified as MCPD - D Form (R)-(2-(4-chloro-2-methylphenoxy)-propanoic acid) with 99% purity. 5 to 15 Chinese hamsters per sex per group were treated once by gavage at 0 (0.5% carboxymethyl cellulose), 650, 1300, or 2600 mg/kg. Bone marrow was sampled 6, 24, or 48 hours after treatment at the high dose and at 24 hours for all other groups. Clinical signs were seen at all doses. Cyclophosphamide was the positive control. **The frequency of chromosomal aberrations was not increased. Acceptable.** (H. Green, and P. Iyer, 4/19/99).

****50779-016 130752**, "Chromosome Aberration Assay in Human Lymphocytes *In Vitro* with Mecoprop-P Acid", (Dr. Albrecht Heidemann, Cytotest Cell Research GmbH & Co. F.R.G., Project # CCR Project 429401, 8 February 1994). Two trials with duplicate cultures. Human lymphocytes were exposed to mecoprop-p acid (92.2% purity) concentrations of 0 (ethanol), 100, 300, 600, 1000, and 2000 µg/ml for 20 or 44 hours in the absence of activation and 4 hours with activation. **Increased frequency of chromosomal aberrations in the absence of activation is indicated in one trial but not confirmed in a repeat trial. Acceptable.** (H. Green, and P. Iyer, 5/26/99).

****52223-058 163973**, MCPD-p DMAS "Metaphase Chromosome Analysis of Human Lymphocytes Cultured *In Vitro*", (Leslie C. Akhurst, *et al.*, Huntingdon Research Centre Ltd., England, Report # JEL 62/921576, 28 June 1993). Male human blood lymphocytes were exposed in duplicate (solvent control in quadruplicate) without activation to MCPD-p DMAS concentrations of 0, 100, 250 (13 hour harvest time); 0, 500, 750, and 1000 µg/ml (21 hour harvest) and with activation at 0, 500, 1000, 2500, 3000, 4000, and 5000 µg/ml (For 3 hours treatment, 16 hour harvest time). **Chromosomal aberrations were increased in the presence of activation at a cytotoxic dosing level of 2500 µg/ml (highest concentration scored with activation). Acceptable.** (H. Green, and P. Iyer, 8/27/99).

****50779 011 114828**, "Cytogenetic Investigations in Chinese Hamsters After a Single Oral

Administration of MCPD - Sister Chromatid Exchange", (Dr. G. Engelhardt, BASF Aktiengesellschaft, Project # 16M0047/8307, 2 April 1985). Test article is identified as Mecoprop (2-(4-chloro-2-methyl-phenoxy) propanoic acid) with 92.7% purity. 5 Chinese Hamsters per sex per group received a single oral treatment at 0 (0.5% carboxymethyl cellulose), 60, 470, or 3800 mg/kg. Bone marrow sampling was performed 24 hours post-dosing. Clinical signs were seen at 470 and 3800 mg/kg after dosing and included apathy, twitching, piloerection and squatting posture. Cyclophosphamide was the positive control. **A slight increase in sister chromatid exchanges was noted at 470 and 3800 mg/kg. Acceptable.** (H. Green, and P. Iyer, 4/16/99).

DNA DAMAGE

50779-018 134632, "In vivo/in vitro Unscheduled DNA Synthesis in Rat Hepatocytes with Mecoprop-p Acid", (Dr. Rolf Fautz, Cytotest Cell Research GmbH & Co. KG, D-64380 Rossdorf, Germany, Project # 429402, 21 December 1994). 4 Wistar Hanlbm: WIST (SPF) male rats received mecoprop-p acid (92.2% purity) by gavage at 0, 50, 200, and 500 mg/kg followed by sampling at 2 or 16 hours and cell labelling with ³HTdR. Positive controls were functional. **An increase in unscheduled DNA synthesis was not indicated. Acceptable. (H. Green, and P. Iyer, 4/21/99).

52223-027 163941, duplicate of record# 130755

52223-029 163943, duplicate of record # 130752

50779-012 115689 Protocol for 163971 Not reviewed.

NEUROTOXICITY

52223-016; 163930; "Mecoprop-P-Acute Oral Neurotoxicity Study in Wistar Rats" (Mellert, W. et al, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Laboratory Project Identification 20S0002/91155, 4/13/95). 818. Mecoprop-P (Batch No. N 31, purity=89.9%), prepared in 0.5% aqueous carboxymethyl cellulose, was administered by gavage in a single dose at concentrations of 0 (vehicle), 175, 350 or 700 mg/kg to 10 Wistar (Chbb: THOM (SPF)) rats per sex per dose level. No animals died. In males during FOB, treatment-related effects including eyelids permanently half-closed (home cage), abdominal position (open field), hypoactivity (open field), slight ataxia (open field), and increased mean landing footsplay were observed at 350 and 700 mg/kg on day 0 (between 2 and 8 hours after treatment (time of peak effect)). In females during FOB, treatment-related effects including abdominal position (home cage), hypoactivity (open field), and decreased mean number of rearings (open field) were observed at 350 and 700 mg/kg at day 0. In addition, treatment-related effects including eyelids permanently half-closed (home cage), abdominal position (open field), slight ataxia (open field), and hypothermia (open field) were observed during FOB in females at 700 mg/kg on day 0. All effects observed during FOB on day 0 cleared by day 7. During motor activity assessment, a statistically significant decrease in the mean total number of beam interrupts were observed on day 0 at 350 and 700 mg/kg in males and at 700 mg/kg in females clearing in all by day 7. Pathological examination revealed no abnormalities in the central or peripheral nervous system. **No adverse effects.** NOEL (M/F)=175 mg/kg (based on multiple FOB endpoints). **Acceptable.** (Corlett and Leung, 5/11/99)

SUBCHRONIC STUDIES

52223-017; 163931; "Mecoprop-P-Subchronic Oral Dietary Toxicity and Neurotoxicity Study in

Wistar Rats" (Mellert, W. et al, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/ Rhein, Germany, Laboratory Project Identification 50C0002/91157, 7/14/95). Combined 821 and 827. Mecoprop-P (Batch No. N 31, purity=89.9%) was admixed to the feed at concentrations of 0, 75, 500, 2500 (males only) or 3000 (females only) ppm (0, 5, 35, or 189 mg/kg/day, respectively, for males and 0, 6, 41, or 240 mg/kg/day, respectively, for females) and fed to 15 Wistar (Chbb: THOM (SPF)) rats per sex per dose continuously for a period of 3 months. No animals died. No clinical signs were observed. Treatment-related decreased mean body weight, decreased mean food consumption, and increased mean water consumption were observed in males at 2500 ppm and in females at 3000 ppm. Treatment-related increased mean red blood cell, hemoglobin, and hematocrit levels in males at 500 and 2500 ppm and in females at 3000 ppm were observed. Treatment-related increases in mean alkaline phosphatase in both sexes, in mean alanine aminotransferase in females, in mean urea in both sexes, and in mean creatinine in males were observed at HDT. A treatment-related increase in transitional epithelial cells in the urine was observed in males at 2500 ppm. Treatment-related increases in mean relative liver weights in both sexes at HDT and in mean relative kidney weights in both sexes at 500 ppm and HDT were observed. Macroscopic examination revealed treatment-related discoloration of the adrenal glands in both sexes at HDT. Microscopic examination revealed a dose-related decrease in fat storage in the liver in males at 500 and 2500 ppm and in females at 3000 ppm, and treatment-related bile duct proliferation, severe cytoplasmic eosinophilia of hepatocytes, hepatocytes with granular cytoplasm (moderate to severe), and lipid storage in the adrenal cortex were observed in both sexes at HDT. No treatment-related effects were observed during FOB and motor activity assessments. No neurotoxic effects were observed at gross necropsy or microscopic examination. **No adverse effects.** Subchronic feeding NOEL (M)=5 mg/kg/day (75 ppm) (based on increased mean red blood cell, hemoglobin, and hematocrit levels and increased mean relative kidney weight) and (F)=6 mg/kg/day (75 ppm) (based on increased mean relative kidney weight). Subchronic neurotoxicity NOEL (M)=189 mg/kg/day (2500 ppm) and (F)=240 mg/kg/day (3000 ppm) (based on no effects at HDT). **Acceptable.** (Corlett and Leung, 5/11/99)

52223-018; 163932; "Report on the Oral Toxicity of Mecoprop-P Acid in B6C3F1 Mice Administered in the Diet for 3 Months" (Mellert, W., Department of Toxicology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Study Identification 35C0002/91002, 9/8/93). Mecoprop-P acid (Batch No./Lab. J. No.: 91-1, purity=96.5%) was admixed to the feed at concentrations of 0, 100, 1000, or 2500 ppm (0, 20, 220, or 740 mg/kg/day, respectively, for males and 0, 30, 330, or 930 mg/kg/day, respectively, for females) and fed to 10 B6C3F1 mice per sex per dose continuously for a period of 3 months. No animals died. No clinical signs were observed. A dose-related decrease in mean body weight in both males and females at 1000 and 2500 ppm at day 91 was observed. Blood chemistry analysis revealed dose-related increases in mean urea in males beginning at 1000 ppm and in females beginning at 100 ppm, and in mean creatinine in males beginning at 1000 ppm. Treatment-related increases in alkaline phosphatase (in both sexes), in alanine aminotransferase (in females), and in cholesterol (in both sexes) at 2500 ppm were observed. A statistically significant ($p \neq 0.001$) increase in cyanide-insensitive palmitoyl CoA-oxidation in liver homogenate in both sexes at 2500 ppm was observed. A treatment-related increase in mean relative liver weights in both sexes at 2500 ppm was observed. Macroscopic examination revealed treatment-related discolored livers at 2500 ppm in both sexes. Microscopic examination revealed cytoplasmic eosinophilia of hepatocytes and of tubular epithelial cells of kidneys in both sexes at 2500 ppm and a decrease of lipid storage in the liver in both sexes at 1000 and 2500 ppm. **No adverse effects.** NOEL (M)=20 mg/kg/day (100 ppm) (based on dose-related increases in mean urea and mean creatinine levels, decreased lipid storage in the liver, and reduced body weight) and (F)< 30 mg/kg/day (100 ppm) (based on a dose-related increase in mean urea levels and reduced body weight). **Supplemental study** (no ophthalmological examinations conducted). (Corlett, 5/14/99)

52223-019; 163933; "Twenty-one Day Dermal Toxicity Study in the Rabbit with MCPD-p Acid" (Allan, S.A. et al, Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, England, HRC Study Report No. JEL 50/921436, 6/22/93). 822. Mecoprop-p acid (Batch No. 91-1, purity=92.6%), moistened with distilled water, was applied to the clipped skin of 5 New Zealand White rabbits per sex per dose levels at concentrations of 0, 10, 100, or 1000 mg/kg/day for 6 hours per day for 21 (males) or 22 (females) consecutive days using an impervious wrap. No animals died. No treatment-related clinical signs were observed. Treatment-related minimal (grade 1) erythema and edema at 10 mg/kg/day, minimal to well-defined (grade 2) erythema and edema at 100 mg/kg/day, and minimal to well-defined erythema and minimal to moderate (grade 3) edema at 1000 mg/kg/day were observed at the test site during the study. Clinical chemistry revealed no treatment-related effects. Macroscopic and microscopic examinations of the internal organs revealed no treatment-related abnormalities. Microscopic examination of the treated skin revealed treatment-related diffuse acanthosis (minimal) at 1000 mg/kg/day in males and at 100 and 1000 mg/kg/day in females. **No adverse effects.** NOEL (systemic, M/F)=1000 mg/kg/day (based on no treatment-related effects at HDT), NOEL (dermal, M/F)< 10 mg/kg/day (based on a treatment-related erythema and edema). **Acceptable.** (Corlett , 5/20/99)

52223-054; 163969; "Study of the Dermal Toxicity of MCPD-P-DMA Salt in Wistar Rats Application to the Intact Skin (21 Applications)" (Kirsch, P. et al, Department of Toxicology of BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany, Laboratory Project Identification 37H0210/91126, 1/10/95). 822. MCPD-P-DMA Salt (Batch No. 91-1/9158/7, calculated purity=63.5% as DMA salt and 52.7% as acid) was applied to the clipped skin of 5 Wistar rats per sex per dose level at concentrations of 0 (distilled water), 12 (diluted in distilled water), 120 (diluted in distilled water), or 1000 mg/kg/day for 6 hours per day 5 days per week for 4 weeks (21 applications) using a semi-occlusive wrap. No animals died. No treatment-related clinical signs were observed. Treatment-related very slight (grade 1) erythema to moderate or severe (grade 3) erythema at 1000 mg/kg/day was observed during the study. Clinical chemistry revealed no treatment-related effects. Macroscopic and microscopic examinations revealed no treatment-related abnormalities. **No adverse effects.** NOEL (systemic, M/F)=1000 mg/kg/day (based on no treatment-related effects at HDT), NOEL (dermal, M/F)=120 mg/kg/day (based on a treatment-related skin irritation). **Acceptable.** (Corlett , 5/26/99)

METABOLISM STUDIES

52223-060; 163975; "(¹⁴C)-Mecoprop-P-EHE and (¹⁴C)-Mecoprop-P-DMA: Absorption, Distribution, Metabolism, and Excretion in the Rat"; (G. Lappin; Covance Laboratories Ltd, North Yorkshire, HG3 1PY, England, The University of York, Department of Chemistry, York, Y01 5DD, England; Study No. 1149/14; 5/6/97); Groups of 5 male Wistar rats were dosed orally with 5 mg/kg of either (¹⁴C)-Mecoprop-P-EHE (radiochemical purity: 99.6%, spec. act.: 145.37 µCi/mg) (Groups A and C) or (¹⁴C)-Mecoprop-P-DMA (radiochemical purity (based on the acid): 99.8%, spec. act.: 114.79 µCi/mg) (Groups B and D). In Groups A and B (plasma pharmacokinetic study), blood samples were collected for 7 days. In Groups C and D, urine and feces were collected for 7 days. Expired air was collected for 48 hours. In the plasma pharmacokinetic analysis, T_{max} values were 3.6 and 2 hours for Groups A and B, respectively. T_{1/2} for elimination was 8.36 and 6.61 hours for Groups A and B, respectively. Absorption of the administered dose was at least 83.26 and 97.11% for Groups C and D, respectively (the total residual radiolabel in the tissues was not determined). Excretion was predominantly via the urine with the percentage of the total dose recovered in the urine 83.26 and 97.11%. In Groups C and D, respectively, 79.73 and 93.52% of the administered dose (calculated by the reviewer) was collected in the urine and the cage wash within the first 24 hours. The total radiolabel recovered in the feces was 3.29 and 4.68% of the administered dose for Groups C and D, respectively. No radiolabeled material was recovered in the expired air due to the positioning of the label on the phenyl ring. Radiolabel in the tissues and organs 7 days after dosing was largely limited to the

skin and fat. The only metabolite identified in the study was hydroxymethyl-Mecoprop-P. Overall, unaltered test material and the hydroxylated metabolite constituted 96% of the recovered radiolabel (calculated by the reviewer) in the first 48 hours after dosing. The parent material constituted 72.91 and 70.68 and the metabolite was 23.13 and 25.26% of the administered dose for Groups C and D, respectively. **Supplemental Study.** (Moore, 8/5/99)

52223-061; 163976; “(¹⁴C)-Mecoprop-p-DMA: [(¹⁴C)-Mecoprop-p-dimethylammonium]: Metabolism/degradation in Plasma, Gastro-intestinal Tract, Gastro-Intestinal Contents and Post-Mitochondrial Liver Fraction (S9)”; (S.A. John; Corning Hazleton (Europe), North Yorkshire, HG3 1PY, England; Study No. 1149/11; 6/9/95); The dissociation of Mecoprop-p-DMA salt into Mecoprop-P acid and dimethyl amine was examined in various *in vitro* biological test systems. (¹⁴C)-Mecoprop-p-DMA was formed by mixing (¹⁴C)-Mecoprop-p acid (radiochemical purity: 99.5%, chemical purity: 98.6%, specific activity: 138.92 µCi/mg) with a dimethylamine solution. The test material was incubated with plasma (I), stomach contents (II), the gastrointestinal tract (III) and liver S9 fraction (IV) derived from male Wistar rats. The concentrations of the test material in the incubations were 0.1 (I), 5 (II), 0.35 (III) and 0.1 (IV) mg/ml. The samples were incubated for 30 minutes at 37° C. Study results indicated that the test material had largely dissociated into Mecoprop-P acid and DMA. It was not apparent from these results whether the dissociation may have been wholly or partially mediated enzymatically. **Supplemental Study.** (Moore, 8/6/99)

52223-031; 163945; “(¹⁴C)-Mecoprop-P: Absorption, Distribution, Metabolism, and Excretion in the Rat”; (G. Lappin, Covance Laboratories Ltd, North Yorkshire, HG3 1PY, England, The University of York, Department of Chemistry, York, YO1 5DD, England; Study No. 1149/3; 5/6/97); Male and female Wistar rats with dosed orally with (¹⁴C)-Mecoprop-P (radiochemical purity: 99.5%, purity: 98.6%; spec. act.: 138.8 µCi/mg). Five rats/sex were dosed with 5 (Groups A, B, D) or 100 mg/kg (Groups C and E). The rats in Group B received 14 doses of unlabeled Mecoprop-P (purity: 99.8%) at 5 mg/kg/day prior to being dosed with the radiolabeled material. In addition, 12 rats/sex were dosed with 5 mg/kg (Group F). In Groups A, B and C, urine and feces were collected for 7 days. Expired air was collected from two males in Group C. In Groups D and E, blood samples were collected for 7 days. In Group F, four animals/sex/time point were euthanized at 0.5, 3 and 6 hours after dosing. Absorption of the administered dose ranged from 82.92 to 100.47% with the absorption minimally reduced in the repeated dosing regimen and at the higher dosing level (males: A. 100.47%, B. 94.58%, C. 92.34%; females: A. 94.62%, B. 92.07%, C. 82.92%). Excretion was predominantly via the urine with the percentage of the total dose recovered in the urine and cage wash ranging from 79.74 to 100.06%. In Group A, 95.29 and 92.29% of the administered dose was collected in the urine and the cage wash within the first 24 hours for males and females, respectively. Repeated dosing reduced the amount collected in the urine and the cage wash during the first 24 hours to 88.97 and 86.46% for males and females, respectively. Likewise, at the 100 mg/kg dosing level, the percentage collected in the urine and the cage wash during the first 24 hours was reduced to 61.18 and 56.78% for males and females, respectively. The total radiolabel recovered in the feces ranged from 3.56 to 12.52% of the administered dose. No radiolabeled material was recovered in the expired air due to the positioning of the label on the phenyl ring. Radiolabel in the tissues and organs 7 days after dosing was predominantly in the fat followed by the skin, adrenals, kidneys and liver. Maximal levels of radioactivity were recovered from the various tissues and organs assayed within 3 hours of dosing (Group F). In the plasma pharmacokinetic analysis, T_{max} values were 1.8 and 2.7 hours for males and females, respectively in Group D and 4.2 hours in Group E. T_{1/2} for elimination was 6.35 and 4.23 hours in Group D and 7.89 and 7.79 hours in Group E for males and females, respectively. The only metabolite identified in the study was hydroxymethyl-Mecoprop-P. A greater percentage of this metabolite was recovered in the urine of the males. Overall, unaltered test material and the hydroxylated metabolite constituted 92.29 to 95.34% (calculated by the reviewer) of the recovered radiolabel in the urine in the first 48 hours after dosing. For the males, the parent material was 52.17 to 67.08% and the metabolite was 28.26 to 41.39% of the administered dose. For the

females these values ranged from 84.31 to 90.03% for the parent compound and 5.16 to 10.25% for the metabolite. **Study acceptable.** (Moore, 8/4/99)