

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
MCPA (MCPA-Acid)

Chemical Code # 786 (2326 MCPA-acid), Tolerance # 50773 (51956 MCPA-acid)
SB 950 # 730
August 6, 1998
Revised: 3/17/00

I. DATA GAP STATUS

Chronic/Onco, Rat:	No data gap, no adverse effect
Chronic Toxicity, Dog:	No data gap, no adverse effect
Oncogenicity, Mouse:	No data gap, no 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 138207 (MCPA-dimethylamine salt--50773) and 169905 (MCPA-acid, 51956) were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T000317

Kishiyama & Silva, 8/6/98, M. Silva, 3/17/00

All record numbers through.

** indicates an acceptable study.

Several compounds related to MCPA were grouped in 1993 under SB950 #-s: 788 (MCPA-sodium salt), 786 (MCPA-dimethylamine salt), 2326 (MCPA-acid).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

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

COMBINED, RAT

** 50773-025 072695: AStudy on the Chronic Toxicity and Oncogenicity Potential of MCPA in Rats - Administration in the Diet for 24 Months,@(Fleig, H., BASF Aktiengesellschaft, FRG.; Project No. 71S0046/8345; 5/16/88). MCPA (purity = 94.8%) was fed in diet to Wistar rats (75/sex/dose) at 0, 20, 80, and 320 ppm for 24 months (equivalent to: MALE-- 0, 1.1, 4.4 & 17.6 (main group) or 0, 1.3, 5.1 and 20.4 mg/kg/day (satellite); FEMALE: 0, 1.4, 5.7 & 23.0 (main group) or 0, 1.6, 6.4 or 25.5 mg/kg/day (satellite) for 0, 20, 80 & 320 ppm, respectively). Chronic NOEL = 20 ppm (Body weights were intermittently significantly decreased in main group males at 320 ppm, however it was less than 10%. Triglycerides and GPT levels were affected in both sexes of Satellite II (terminated at 24 months) at \geq 80 ppm. Males in Satellite I (terminated at 12 months) showed increased severity in chronic progressive nephropathy and increased hematographic pigment in spleen at 320 ppm.) Oncogenic NOEL > 320 ppm (No increase in oncogenicity was observed at any dose.) ACCEPTABLE with no adverse effects. (Kishiyama & Silva, 5/11/98).

CHRONIC TOXICITY, DOG

** 50773-027 072702: AReport on the Study of the Toxicity of MCPA in Beagle Dogs after 12-Month Administration in the Diet,@(Hellwig, BASF Department of Toxicology, Ludwigshafen, West Germany. 10/13/86). MCPA (purity = 94.8%) was fed in diet to Beagle dogs (6/sex/dose) at 0, 6, 30, or 150 ppm for 12 months (equivalent to 0, 0.2, 1 & 5 mg/kg/day). NOEL = 6 ppm (Food consumption (females) and body weights (male) were decreased at \geq 30 ppm. Blood chemistry parameters were increased in both sexes at \geq 30 ppm, indicating possible kidney damage. Brain weights (relative & absolute--female) were decreased and thyroid weights (relative & absolute--male) were increased at 150 ppm. Male thyroids showed a whitish-yellow stipulation (at necropsy) and focal hyperplasia of the follicles (histopathology) at 150 ppm. Kidneys at 150 ppm (male) and at \geq 30 ppm (female) showed dark brown coloration, possibly lipofuscin.) ACCEPTABLE. No adverse effect. (Kishiyama & Silva, 5/28/98).

ONCOGENICITY, MOUSE

** 50773-026 072700 AStudy on the Oncogenicity Potential of MCPA in Mice - Administration in the Diet over 104 weeks,@(K?hborh, B., BASF Aktiengesellschaft, FRG; Project No. 80S0046/8358, 7/13/88). MCPA (purity = 94.8%) was fed in diet to B6 F1 Crl BR mice (50/sex/dose--main or 10/sex/dose--satellite) at 0, 20, 100 or 500 ppm for 104 weeks (main) or 52 weeks (satellite). **NOEL = 100 ppm** (Male body weights in the main group were consistently decreased at \geq 100 ppm throughout the study. Kidney weights (absolute and relative) were increased for both sexes at 500 ppm. Heart weights at 500 ppm (males) and \geq 100 ppm (females) were decreased. Kidney histopathology showed an increased incidence in slight intratubular calcification, tubular hyaline-proteinaceous casts (more apparent in females than males) and hyperplasia of renal tubular epithelium (males) at 500 ppm.) There was no evidence of oncogenicity in the study. Oncogenicity NOEL = 500 ppm. ACCEPTABLE. (Kishiyama & Silva, 5/26/98).

REPRODUCTION, RAT

** 50773-028 072705 ATwo-Generation Reproduction Study with MCPA in Rats,@(MacKenzie, K.M., Hazleton Laboratories America, Study No. 6148-100; 11/3/86). MCPA (purity = 94.8%) was fed in diet to Sprague-Dawley rats (25/sex/dose) at 0, 50, 150, or 450 ppm for two generations with 2 litters/generation. **Parental NOEL = 150 ppm** (F1 body weight was decreased for both sexes, primarily

at 450 ppm. F0 and F1 females at 450 ppm showed decreased body weight gain (not statistically significant) overall, days 0 -21 of lactation (F1a & b; F2a & b litters). Food consumption was increased for F1 parents during pre-mating and rest periods at ≥ 150 ppm. F0 and F1 adult females had increased ovary weights (absolute) at 450 ppm. F0 males showed increased kidney weights and F0 and F1 females showed increased relative ovary weights at 450 ppm.) **Pup NOEL = 50 ppm** (F1a & b and F2 a & b female pup body weight gain was decreased at 450 ppm (days 14-21). F2a male pup body weight gain was decreased at 450 ppm (days 14-21). F2a male pup weights (day 14) and weight gain (day 4 postculling to day 14) were decreased significantly at 450 ppm. Day 21 F2a & b pup weights (both sexes) at 450 ppm were decreased. Day 21 F2a pups had significantly decreased body weight gain at ≥ 150 ppm.) **Reproductive NOEL = 450 ppm** (There were no significant reproductive effects at any dose.) No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 5/21/98).

TERATOLOGY, RAT

50773-029 072714 AMCPA Oral Teratogenicity Study in the Rat, (Irvine, L.F.H., Hazleton Laboratories, Europe LTD, Report No.: 1996-277/7b, June 1980). MCPA (purity not stated) was administered via oral gavage to mated Sprague-Dawley rats (16-38/dose) at 0 (1% methyl cellulose), 0 (aspirin), 20, 50 or 125 mg/kg/day days 6-15 after mating. Maternal NOEL > 125 mg/kg (There was no effect on body weight or clinical signs.) Developmental NOEL = Insufficient information. There was no evidence of teratogenicity with MCPA in this report. UNACCEPTABLE (Test article purity and stability; analysis of dosing material, GLP and QA were not included in the report, inadequate justification of dose selection, mating over a 6-week span with no explanation, misdosing of 8 dams in the high dose over 2-3 days.) (Kishiyama & Silva, 6/11/98)

Supplemental:

029 072716 ATeratogenic Effects of 4-Chloro-2-methylphenoxyacetic Acid Ethylester (MCPEE) in Rats, (Yasuda, M., and Maeda, H., Toxicology and Applied Pharmacology 23, 326-333; 1972).

PROTOCOL: MCPEE (94.12%) was fed in diet to mated Wistar rats (16-22/sex/dose) at 0, 40, 500, 1000, 2000 ppm (0, 2.7, 30, 60 and 100 mg//kg/day) during gestation days 8-15. Body weights were measured from day 8-21 of gestation. Food and water consumption were recorded daily after day 8 of gestation. All dams at 500 and 1000 ppm and 3/4ths of the dams at 0, 40 or 2000 ppm were sacrificed day 21 of gestation. The number of living and resorbed fetuses were recorded. Live fetuses were removed, sexed, examined (externally visible malformations and cleft palate), weighed, then examined internally (abnormalities, ventricular septal defects and skeletal effects). The remaining pregnant rats were allowed to litter naturally and the postnatal development of the young was observed. Newborns were examined and the state of each (live, dead, malformed) was recorded. Live young were sexed, weighed and allowed to nurse and were weighed weekly. At 4 weeks, the dam was killed and the number of implantation sites in the uterus was noted. Weanlings were raised for 6 weeks, were sacrificed, then were examined internally and externally for anomalies.

RESULTS: Maternal NOEL = 40 ppm (Food consumption was reduced at 2000 ppm and body weight gains were lower at ≥ 500 .) Developmental NOEL = 40 ppm (Fetal mortality was increased at ≥ 500 ppm. Fetal weights were decreased and the number of fetuses and litters with malformations (cleft palate, ventricular septal defect and kidney anomalies) were increased at ≥ 1000 ppm. The number and percent of resorptions was increased at ≥ 500 . The number of live fetuses was decreased at ≥ 500 ppm. A case of hydronephrosis and an increase in the number of dead pups was observed at 2000 ppm. Possible adverse effect, since effects to fetuses were more severe than maternal effects at the same dose levels. Unacceptable. (Kishiyama & Silva, 6/16/98).

**51956-012 169903, AStudy of the Prenatal Toxicity of MCPA-Acid in Rats After Oral Administration (Gavage) (J. Hellwig, BASF Aktiengesellschaft, Department of Toxicology, D-W6700 Ludwigshafen, Germany, Project # 30R0374/91096, 22 February 1993). 25 mated female Wistar (Chbb:THOM (SPF)) rats per group received MPCA - Acid (94.22% purity) by gavage at 0 (0.5% aqueous carboxymethyl

cellulose solution), 15, 60, and 120 mg/kg/day on gestation days 6 through 15. Maternal NOEL = 60 mg/kg (There was decreased bodyweight & food consumption at 120 mg/kg). Developmental NOEL = 60 mg/kg/day (There were decreased fetal weights (12% less than controls), increased incidence in skeletal retardations (incompletely ossified skull and incompletely/not ossified sternebrae) and fetal external malformations at 120 mg/kg. **Developmental toxicity was not indicated. Acceptable.** (H. Green & M. Silva, 2/18/00).

TERATOLOGY, RABBIT

50773-029 072715 AMCPA Oral Teratogenicity Study in the Dutch Belted Rabbit,@(Irvine, L.F.H., Hazleton Laboratories, England, Report No.: 1737R-277/5, March 1980). MCPA (purity not stated) was administered by gavage to artificially inseminated Dutch Belted rabbits (11-30) at 0 (1% methyl cellulose), 0 (thalidomide), 5, 12, 30 and 75 mg/kg from day 6 to day 18 post-insemination. Maternal NOEL > 75 mg/kg (Body weights were decreased at 75 mg/kg/day but not significantly. Dam mortality, abortions and total litter resorptions were increased slightly at 75 mg/kg/day.) Developmental NOEL > 75 mg/kg (There no significant effects observed). This study is unacceptable and not upgradeable (A NOEL was not achieved, no MCPA characterization, analysis of dosing suspensions or GLP or QA sign-offs, no justification of dose selection, or clarification of fetal exams). No adverse effect indicated. (Kishiyama & Silva, 6/16/98).

51956-013 169905, AStudy of the Prenatal Toxicity of MCPA - Acid in Rabbits After Oral Administration (Gavage)@ (J. Hellwig, BASF Aktiengesellschaft, Department of Toxicology, D-W6700 Ludwigshafen, Germany, Project # 40R0374/91095, 22 February 1993). Inseminated Himalayan (Chbb:HM (outbred strain) 15/dose) rabbits received MCPA - Acid by gavage at 0 (0.5% aqueous carboxymethyl cellulose solution), 15, 30 and 60 mg/kg/day on gestation days 7 through 19. Food consumption was reduced (10% to 19%) at 60 mg/kg/day during the treatment period and on the first days of treatment (10%) at 30 mg/kg/day. Also, the incidence of animals with no defecation, with abortions and with blood in the bedding was increased at ≥ 30 mg/kg/day compared to controls. Deaths were increased at 60 mg/kg (2/15 - 1 died & 1 sacrificed after abortion). Maternal NOEL = 15 mg/kg/day. **Developmental toxicity was not treatment-related. Developmental NOEL = 60 mg/kg/day. (No treatment-related effects at any dose.) **Acceptable.** (H. Green & M. Silva, 2/18/00).

TERATOLOGY, MOUSE

50773-028 072704 AEffect of MCPA on Pregnancy of the Mouse,@(Palmer, A.K. and M.R. Lovell, Huntingdon Research Centre, 4463/71/618. MCPA (Hormotex 750, with 75% ai) was administered by gavage to pregnant CD-1 mice (20/dose) at doses of 0 (Na Cl), 5, 25, 100 mg/kg during gestation days 5 through 16. Maternal NOEL = 25 mg/kg (Dam bodyweights were decreased at 100 mg/kg.) Developmental NOEL = 25 mg/kg (Decreased fetal bodyweight and retarded ossification were observed at 100 mg/kg.). No adverse effect. UNACCEPTABLE (Test article not of technical grade. Analysis to confirm test article homogeneity, stability and content was not provided. Age of animals was not reported. Rationale for dose selection was not discussed. Food consumption was not reported. No GLP or QA sign-off were provided. Study dates were not reported. Environmental conditions were not reported. Corpora lutea were not discussed.) Not upgradeable. (Kishiyama & Silva, 6/3/98).

GENE MUTATION

** 50773-052 128114 AAmes *Salmonella Typhimurium* Bacterial Reverse Mutation Assay on MCPA DMAS,@(Jones, E., J. Kitching, A. Anderson, and I.S. Dawe; Huntingdon Research Centre Ltd., England, HRC Study No. JEL 24/921053; November 18, 1992). MCPA-DMAS (purity = 77.3%, w/w as the

dimethylamine salt (DMA)) at 0, 50, 150, 500, 1500 and 5000 µg/plate was evaluated for mutagenicity after 3 days exposure using *Salmonella typhimurium* strains TA 1535, TA1537, TA100 and TA 98. There were no increases in revertant colonies which would indicate gene mutation due to MCPA-DMAS treatment. ACCEPTABLE. (Kishiyama & Silva, 7/3/98).

** 50773-052 128116 AChinese Hamster Ovary/HGPRT Locus Assay MCPA DMAS,@ (Adams, K., S. Ransome, A. Anderson & I.S. Dawe., Huntingdon Research Centre Ltd., England, HRC Study No. JEL 27/921113, March 19, 1993). MCPA DMAS (purity = 77.3%, w/w as DMA) was used on Chinese hamster ovary cells at 250 to 3000 µg/ml (+/-S9) in **Test 1** and from 250 to 2750 µg/ml (+/-S9) in **Test 2** to evaluate for potential mutagenicity (exposure time = 4 hours). Mutant frequency did not significantly increase with selected MCPA DMAS doses in the presence and/or absence of S-9 Mix. Cell survival ranged from 0% to 143%. ACCEPTABLE. (Kishiyama & Silva, 7/7/98).

** 51956-053 128118: AAmes *Salmonella Typhimurium* Bacterial Reverse Mutation Assay on MCPA Acid,@ (Jones, E., J. Kitching, A. Anderson, and I.S. Dawe., Huntingdon Research Centre Ltd., England, HRC Study No. JEL 26/290957, February 12, 1993). MCPA acid (purity = 94.22%, w/w a.i.) at concentrations of 0, 50, 150, 500, 1500 and 5000 µg/plate (triplicate plates) was evaluated for mutagenicity after 3 days exposure using *Salmonella typhimurium* strains TA 1535, TA1537, TA100 and TA 98. The test was repeated. No significant treatment-related increases in the number of revertants were observed in this study. ACCEPTABLE. (Kishiyama & Silva, 7/29/98).

** 51956-053 128120: AChinese Hamster Ovary/HGPRT Locus Assay MCPA Acid@ (Adams, K., D. Kirkpatrick, A. Godfrey, A. Anderson, and I.S. Dawe; Huntingdon Research Centre Ltd., England, HRC Study No. JEL 27/921115; March 19, 1993). MCPA acid (purity = 94.22%, w/w a.i.) was used on Chinese hamster ovary cells at concentrations ranging from 50 to 1000 µg/ml (+/- S-9 Mix) in test 1 and from 200 to 900 (- S-9 Mix) or 400 to 1200 µg/ml (+ S-9 Mix) in test 2. Cells were evaluated for potential mutagenicity of MCPA acid (4 hour exposure). Mutant frequency was increased with 800 and 1000 µg/ml MCPA acid treatments in test 2, but was reported not an indication of a positive response (page 8) since they were not dose related, within the upper limit of the historical control range and were not reproducible. Cell survival ranged from 0% to 134%. ACCEPTABLE. (Kishiyama & Silva, 7/31/98).

CHROMOSOME EFFECTS

** **50773-029 072710:** ACytogenetic Investigations in Chinese Hamsters after a Single Oral Administration of MCPA,@ (Englehardt, G., BASF Aktiengesellschaft, Ludwigshafen, Project No. 16M0046/8305; 4/1/85). MCPA (purity = 94.8%) administered once, by gavage to Chinese hamsters (5/sex/dose) at 0 (0.5% CMC), 33, 200, and 1200 mg/kg to test for genotoxicity. Animals were sacrificed 24 hours after dosing. Thirty metaphases were evaluated per animal. Cyclophosphamide was the positive control. NOEL = 33 mg/kg--nominal (There was an increased incidence in sister chromatid exchange rate and clinical signs at ≥ 200 mg/kg.) Chemical analysis indicated MCPA low, mid and high doses were 30 mg/kg, 170 mg/kg and 865 mg/kg. Possible adverse effect. **Slight dose related increase of SCE-s in mid and high dose groups.** ACCEPTABLE (Kishiyama & Silva, 6/18/98)

50773-029 072711 ACytogenetic Investigations in Chinese Hamsters after a Single Oral Administration of MCPA,@ (Englehardt, G., BASF Aktiengesellschaft, Ludwigshafen, Project No. 16M0046/8356; April 4, 1985). MCPA (purity = 94.8%) was administered once to Chinese hamsters (5/sex/dose), via gavage at 0 (0.5% CMC) and 1200 mg/kg (actual dose = 1020 mg/kg) to test for genetic activity and confirm the

results of a previous study (Project No. 16M0046/8305; W072710). Thirty metaphases were scored/animal. Results indicate a slight increase in SCEs with MCPA at 1200 mg/kg and confirms similar results in the earlier trial. Possible adverse effect indicated. These data are supplementary. (Kishiyama & Silva, 6/30/98).

50773-029 072712 ACytogenetic Investigations in Chinese Hamsters after a Single Oral Administration of MCPA,@(Englehardt, G.; BASF Aktiengesellschaft, Ludwigshafen, Project No. 10M0046/8304; April 1, 1985). MCPA (purity = 94.8%) was administered once, via gavage to Chinese hamsters (5/sex/dose/time point) at 0 (0.5% CMC), 33, 200, and 1200 mg/kg to test for induction of chromosomal aberrations. Animals were sacrificed at 6, 12 and 24 hours. The negative control group had 10/sex, with only a 24 hour sacrifice time. Aberrant cells for the solvent control, including gaps, was reported to be unusually high (2.63%) compared to the historical control (0.67- 1.33%). The value excluding gaps was also high. Therefore, the effects of MCPA on Chinese hamster bone marrow cells was inconclusive. These data are supplemental. Not acceptable and not upgradeable. (Kishiyama & Silva, 7/1/98).

** 50773-029 072713 ACytogenetic Investigations in Chinese Hamsters after a Single Oral Administration of MCPA,@(Englehardt, G., BASF Aktiengesellschaft, Ludwigshafen, Project No. 10M0046/8367, February 10, 1985). MCPA (purity = 94.8%) was administered once, via gavage to Chinese hamsters (5/sex/dose/time point) at nominal doses of 0 (0.5% CMC), 33, 200, and 1200 mg/kg to test for chromosomal aberrations. Animals were sacrificed at 6, 24 & 48 hours post-dosing and bone marrow was assessed. NOEL = 200 mg/kg (At 1200 mg/kg there was an equivocal increase in chromosome aberrations.) No adverse effect. ACCEPTABLE. (Kishiyama & Silva, 7/2/98).

** **50773-052 128115** AMCPA DMAS Metaphase Chromosome Analysis of Human Lymphocytes Cultured *In Vitro*,@(Akhurst, L.C., J.D. King, A. Anderson and I.S. Dawe. Huntingdon Research Centre Ltd. England, HRC Study No. JEL 30/921176. April 23, 1993). MCPA DMAS (purity = 77.3% w/w as DMA) was used on human lymphocytes (3 hour exposure + S-9, duplicate cultures) at 50, 100 and 250 µg/ml (no S-9) and at 100, 250, 500 and 1000 µg/ml (+ S-9). Cultures were harvested after a 13 hour incubation. Another group of human lymphocytes (duplicate cultures) received 250, 500, 750, 1000 µg/ml (no S-9) and 250, 500, 1000, 1500, 2000 and 2500 µg/ml (+S-9) and these cultures were harvested at 21 hours. All cultures were examined for chromosomal aberrations (100 cells/slide were evaluated). **MCPA DMAS at 2000 µg/ml in the presence of S-9 Mix significantly increased (13.5%) the number of aberrant cells (21 hours harvest) compared to solvent controls (0.5%).** A statistically significantly increase (2.5%) at 1000 µg/ml without S-9 Mix was within the historical control range. ACCEPTABLE. (Kishiyama & Silva, 7/6/98).

** **51956-053 128119:** AMCPA Acid Metaphase Chromosome Analysis of Human Lymphocytes Cultured *In Vitro*,@(Akhurst, L.C., J.D. King, A. Anderson and I.S. Dawe., Huntingdon Research Centre Ltd. England, HRC Study No. JEL 32/921190. April 26, 1993). MCPA Acid (purity = 94.22 %, w/w a.i.) was used on human lymphocytes *in vitro* (3 hour exposure) at 50 to 250 µg/ml (- S-9 Mix) and at 500 to 2000 µg/ml (+ S-9 Mix) for cells harvested at 13 hours. A second harvest time (21 hours) was used with concentrations of 250 to 2000 µg/ml (- S-9 Mix) and 1250 to 2000 µg/ml (+ S-9 Mix). Cells were examined for chromosomal aberrations. **The lymphocytes treated with MCPA acid (1250- 2000 µg/ml, + S-9 Mix) showed a significant increase in the number of aberrant cells.** ACCEPTABLE. (Kishiyama & Silva, 7/30/98).

DNA DAMAGE

** 50773-052 128117 AMCPA DMAS Micronucleus Test,@(Proudlock, R.J., K. Taylor, A. Anderson and I.S. Dawe; Huntingdon Research Centre Ltd., England, HRC Study No. JEL 33/921197, April 22, 1993).

MCPA DMAS (purity = 77.3%, w/w as DMA) at doses of 144, 288 or 576 mg/kg was evaluated for potential mutagenicity. Sampling times were 24, 48 and 72 hours. There were 5 CD-1 mice/sex/dose/time point. No reported significant increase in polychromatic erythrocytes with MCPA DMAS. Mitomycin C (positive control, 24 hours) caused a significant increase in the frequency of micronucleated polychromatic erythrocytes. ACCEPTABLE. (Kishiyama & Silva, 7/28/98)

** 51956-053 128121 AMCPA Acid Micronucleus Test,@ (Proudlock, R.J., E.A. Elmore, A. Anderson and I.S. Dawe, Huntingdon Research Centre Ltd., England, HRC Study No. JEL 35/921198. April 23, 1993).

MCPA acid (purity = 94.22%, w/w a.i.) was administered to CD-1 mice (5/sex/dose/sacrifice time: 24, 48, 72 hours) in a single oral gavage administration at 0 (1% methyl cellulose), 96, 192 or 384 mg/kg to evaluate for potential mutagenicity. MCPA acid caused no significant increase in the number of micronucleated polychromatic erythrocytes. ACCEPTABLE. (Kishiyama & Silva, 8/3/98).

NEUROTOXICITY

Not required at this time