March 12, 2003

MEMORANDUM

SUBJECT: 4-Chlorophenoxyacetic Acid: HED Human Health Risk Assessment for the Tolerance Reassessment Eligibility Document (TRED). [PC Code 019401, DP Barcode D288835, Reregistration Case Number #2115.]

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Purpose

The purpose of this document is to provide a summary of the hazard, exposure and risk characteristics of the re-registration chemical 4-chlorophenoxyacetic acid (4-CPA). This document has been revised to reflect comments received from the registrant, Conagra Grocery Products Company, on March 5, 2003. Comments incorporated into this revised risk assessment include: a recommendation to revise the tolerance level to 0.2 ppm and a reference to the ongoing discussion concerning the most appropriate animal model to use when assessing the potential toxicological effects in humans upon exposure to phenoxy herbicides. The Office of Pesticide Programs (OPP) is evaluating this chemical as part of its tolerance reassessment process. Due to the chemical's low toxicity and low exposure potential, 4-CPA was evaluated using the Lower Toxicity Pesticide Chemical Focus Group's (LTPCFG) methodology. However, if use patterns change significantly or if uses are added to the label for this chemical, the Health Effects Division (HED) will perform a comprehensive exposure assessment for 4-CPA, which may require that additional data be submitted. At this time, a summary of the use pattern, regulatory history, toxicological database, endpoint selection, and dietary exposure and risk information for 4-CPA is presented. There are no uses currently registered for the residential environment and the occupational exposure and risk scenarios were evaluated at the time of the Reregistration Eligibility Decision (RED) document and will not be re-evaluated now. The toxicological profile of the chemical and a summary of structurally similar chemical analogs are presented in Appendices A and B, respectively. These materials were prepared by David Anderson, the toxicologist for this chemical review, to augment the hazard characterization for this action. Mark Corbin (Environmental Fate and Effects Division (EFED)) prepared the Drinking Water exposure and risk summary included in Appendix C.

Regulatory History

A pesticide product formulated with 4-CPA as an active ingredient was first registered in the United States in 1969. It was registered for use as a plant growth regulator for mung beans and later registered as a fruiting bloom set for tomatoes. The technical registrant is La Choy Company.

Data call-in's were issued in December 1984 and in June 1987 for both chronic toxicological data and formation of impurities in the manufacturing process. Additional data call-in's were issued in June 1991 and June 1994 to both characterize the chemistry, human health effects, and environmental fate of the chemical as well as to allow other end-use product manufacturers to support use on tomatoes. The tomato use has since been voluntarily cancelled.

In 1994, OPP approved a Low Volume/Minor Use status for this chemical. Data requirements given the minor use status were as follows: acute toxicity studies, developmental toxicity study in one species, two subchronic toxicity studies, and a battery of mutagenicity studies. Due to 4-CPA's lack of overt toxicity in these studies, the lack of acute dietary exposure concern, and the low volume/minor use status, EPA waived the requirements for chronic toxicity, carcinogenicity, and reproductive effects, which are normally required for food-use chemicals.

The RED, issued in March 1995, included product chemistry data requirements. In addition, the RED recommended approval of a registrant petition to lower the tolerance from 2.0 ppm to 0.2 ppm, the elimination of the metabolite 4-chlorophenol from the tolerance expression, and the revocation of the tolerance for use on tomato due to voluntary cancellation of this use. The current food tolerances are listed at 40 CFR 180.202.

Use Profile

The chemical 4-CPA is used in the food industry as a plant growth regulator to restrict root growth during seed germination of mung beans. This chemical is applied to a water bath to soak the beans. After the beans have soaked for several hours, they are washed to remove the surface residues, and are then germinated indoors for several days. After sprouting, the hulls and roots are discarded, and the remaining portion is packaged and sold for human consumption.

The active ingredient 4-CPA is formulated in a soluble concentrate end-use product. It is applied by direct pour or by closed delivery systems. Use practice limitations prohibit the feeding bean parts or hulls previously treated with 4-CPA to livestock. Contamination of water, food, or feed by the storage or disposal of 4-CPA also is prohibited. According to the registrant, the average annual use is 20 pounds active ingredient per year and only three laboratory employees are in contact with 4-CPA during mixing, measuring and use. The use pattern has not changed for many years. The registrant is currently supporting the use of 4-CPA on mung bean only. If, in the future, the use profile changes considerably additional data may be required.

Toxicological Assessment

There have been no new toxicological data submitted since the time of the RED (1995). The Agency based its RED judgement upon required data on acute toxicity data, subchronic feeding studies, and developmental toxicology and mutagenicity studies. The acute toxicity studies show 4-CPA to be a severe eye irritant and the chemical is classified as Toxicity Category I for eye irritation in mammalian species. It is slightly toxic through the oral and dermal routes (Toxicity Category III). It is only mildly toxic through the inhalation route and is classified as non-irritating for primary dermal irritation (Toxicity Category IV). The chemical is not a skin sensitizer. See Appendix A for the Toxicological Profile of 4-CPA.

Table 1: Summary of Acute Toxicity Data on 4-CPA (Technical Grade 4-CPA)

Test	Results	Category
Oral LD50–rat	2,703 mg/kg	III
Dermal LD50–rabbit	>2000 mg/kg	III
Inhalation LC50–rat	>5.25 mg/L	IV
Eye Irritation–rabbit	severe irritation	I

Dermal irritation–rabbit	non-irritating	IV
Dermal sensitization–guinea pig	non-sensitizing	Not Applicable

The results of the subchronic studies in rats and dogs showed a clear NOAEL and LOAEL and the NOAEL for the dog was at the highest dose tested. The chemical causes a decrease in fetal body weights and induces skeletal variations in rats. In a subchronic toxicity study with rats, the NOAEL was 2000 ppm (132 mg/kg/day). The LOAEL was 8000 ppm (517 mg/kg/day), based on decreased body weight gain in both sexes, decreased food consumption in females, increased urine volume in females, and increased incidence of slight hepatic lymphohistiocytic infiltrates and slight individual hepatocellular necrosis. In a subchronic toxicity study with dogs, the NOAEL was 500 ppm (18 mg/kg/day), the highest dose tested. Malnutrition was noted at 1600 and 3200 ppm in a range-finding study. In the main study, effects included decreased body weight gain and food consumption during the first four weeks at the highest dose, which may have been related to palatability, and slightly higher incidence of vomiting. Also, it is known that the chemicals 2,4-D and 4-CPA have substantially similar metabolism patterns. Specifically, the dog is not able to excrete the phenoxy acids as rapidly as the rat. This possibly accounts for the large differences in the No Observable Adverse Effect Levels between the subchronic studies for 4-CPA. Other structural analogs of 4-CPA were reviewed to better characterize the subchronic toxicity of 4-CPA. In that review, 4-CPA was among the least toxic of the analogues. (See Appendix B.)

In a developmental toxicity study in rats, the maternal and developmental NOAEL (150 mg/kg/day) and LOAEL (300 mg/kg/day) were the same doses. The maternal LOAEL was based on body weight decrement and developmental LOAEL was based on unossified sternebrae and reduced fetal body weight gain. At higher doses, tremors, uncoordinated movements, recumbent posture, languidness, and cold body were noted in mothers and other skeletal variations and fetal weight decrement were noted in fetuses. The results of this study do not show increased quantitative/qualitative susceptibility of fetuses and offspring to 4-CPA.

The chronic toxicity and carcinogenicity studies have been waived for 4-CPA. However, 4-CPA tested in an in vitro mammalian mutation assay did not induce forward mutations in mouse lymphoma cells. In the Ames Salmonella/mammalian-microsome reverse mutation assay, 4-CPA was not mutagenic, with or without activation. This chemical was not clastogenic in an in vivo mouse micronucleus assay. Due to the lack of chronic toxicity and carcinogenicity studies, a number of structurally similar chemical compounds were evaluated to better characterize the hazard potential of 4-CPA. Only 1 out of 16 mutagenicity studies available for the structural analogs was positive for mutation. (See Appendix B for the comparison of structurally similar compounds to 4-CPA and their associated toxicities.)

The Office of Pollution and Prevention and Toxics (OPPT) Structural Activity Relationship (SAT) workgroup evaluated 4-CPA and its associated analogues for carcinogenic potential. The workgroup concluded that there is a low, marginal concern for the carcinogenicity of this

compound. In addition, there is a limited analogy that could be made to the drug clofibrate ((2-(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester). This compound is a well known peroxisome proliferator, however, and the peroxisome proliferation is likely due to the branching of the acid portion and not the acetic acid moiety. Information about clofibrate's use over decades is available. This information did not indicate a strong potential for carcinogenesis. The International Agency for Research on Cancer (IARC) evaluated the potential carcinogenicity of clofibrate in 1996. There conclusions were: "There is inadequate evidence in humans for the carcinogenicity of clofibrate. There is limited evidence in experimental animals for the carcinogenicity of clofibrate."

Endpoint Selection or Dose/Response

In the 1995 RED, no effect was identified for the acute dietary exposure scenario. The NOAEL from the subchronic dog study was selected for assessment of chronic dietary exposure because this was the lowest effect level identified in the database. There is an ongoing discussion as to whether the rat or the dog is the most appropriate animal model to assess potential toxicological effects in humans who are exposed to phenoxy herbicides. However, it is clear in the case of 4-CPA that the use of the dog study to establish a chronic dietary endpoint is the most conservative and appropriate approach. The NOAEL was 500 ppm (18.6 mg/kg-b.w./day and 17.4 mg/kg b.w./day, males and females, respectively), at the highest dose tested. There are no residential uses listed for this chemical, therefore no endpoints were identified for these exposure scenarios. Additionally, for this tolerance reassessment eligibility document (TRED), occupational exposure and risk will not be assessed. This pathway was fully assessed at the time of the RED, and there has been no change in the use pattern.

FQPA Safety Factor Determination

A 10x database uncertainty factor was applied to the NOAEL of 18.6 mg/kg/day from the subchronic dog study to determine the chronic RfD. It has been shown in the scientific literature that dogs are more sensitive than rodents to chlorophenoxy acetic acids. Acceptable rabbit developmental toxicity and two-generation reproduction toxicity studies are lacking for 4-CPA. However, because of 4-CPA's status as a low volume/minor use chemical, these studies were waived. The Agency believes that because the endpoint was selected from the most sensitive species, the dog, it is health protective for all populations. The Agency believes that these doses and endpoints provide a reasonable certainty of no-harm for all populations. In addition, there are no uncertainties in the exposure database. There are no uses of 4-CPA in the residential environment and the chronic dietary exposure and risk assessment will not underestimate exposure to the chemical. Consequently, no additional database uncertainty factor or special hazard based FQPA safety factors are considered necessary particularly when the exposure and use-pattern for this chemical are taken into consideration.

Risk Assessments

Dietary Exposure and Risk Assessment

The dietary exposure and risk assessment will reflect the tolerance levels and tolerance expression currently included in 40 CFR 180.202. The dietary exposure assessment will utilize tolerance level residue values of 2.0 ppm for mung bean to assess the exposure to 4-CPA and its metabolite 4-chlorophenol. The residue estimates for use of 4-CPA on tomato will not be included in the dietary exposure and risk assessment because this use has already been removed from the label, therefore no exposure is expected.

The metabolism of 4-CPA (and its metabolite) is adequately understood in plants and in animal commodities based upon previously submitted and reviewed plant and animal metabolism studies. In addition, residue analytical methods, storage stability, magnitude of the residue in plants, processed food/feed, and in meat, milk, poultry and eggs, and confined field rotation studies are either acceptable or not required, based upon the use pattern. See the March 1995 RED for more detail. (EPA document number 738-R-97-001 found at http://www.epa.gov/REDs/2115red.pdf.)

The dietary exposure assessment includes the chronic exposure scenario only. HED used the NOAEL of 18.6 mg/kg b.w./day based upon decreased body weight gain and food consumption from the subchronic toxicity study in the dog to assess chronic dietary risk. Standard uncertainty factors of 10x were applied for inter- and intra-species variability. In addition, a database uncertainty factor of 10x was applied due to lack of toxicological studies as an added measure of protection, even though many of these studies were previously waived due to 4-CPA's status as a low toxicity/minor use chemical. Therefore, the chronic population adjustment dose (cPAD) is 0.018 mg/kg/day. Comparing to current tolerance level residue values for mung bean (2.0 ppm), the chronic dietary risk is 0.2% of the cPAD for the general population and 0.1% of the cPAD for children 1-6 years of age. The registrant has proposed revising this tolerance from 2.0 ppm to 0.2 ppm, and the respective cPAD values would be lowered substantially if this revised tolerance level were used in the chronic dietary exposure and risk assessment.

Drinking Water Exposure and Risk Assessment

The chemical 4-CPA is expected to be mobile in soil and aquatic environments because it will exist as an anion (dissociated carboxylic acid) in most environments. The soil partitioning coefficient for 4-CPA cannot be estimated from structural analysis. Disposal of 4-CPA treated water, after treatment of mung beans, should be performed in compliance with all appropriate discharge permits and requirements, i.e., the National Pollutant Discharge Elimination System (NPDES). By analogy, the phenoxy herbicides as a class are generally degraded under aerobic conditions by microbially mediated processes and aqueous photolysis, and are generally stable to hydrolysis, soil photolysis, and under anaerobic conditions.

Hydrolysis data were the only data required to support the indoor use (e.g. root suppression of mung bean sprouts) of 4-CPA. From an acceptable study, parent 4-CPA was stable with a reported half life of greater than 30 days to abiotic hydrolysis in three buffer solutions (MRID 42819601). No additional environmental fate data are required to support the use of 4-CPA on mung beans.

No estimated exposure concentrations for drinking water are presented in this assessment due to the limited indoor use of 4-CPA. However, should additional uses for 4-CPA be considered, EFED should be consulted to evaluate whether these uses may impact drinking water sources and what additional data may be needed for registration. Disposal of any waste will be to landfills or publicly-owned sewage treatment facilities, thereby precluding exposure to drinking water from non-point sources. (See Appendix C for the Drinking Water memorandum.)

Aggregate Exposure and Risk Assessment

Aggregate exposure and risk assessment was not performed for 4-CPA. The only exposure anticipated is via the food pathway of exposure. There is no exposure expected through consumption of drinking water given the enclosed nature of the chemical's use, and there are no uses registered in the residential environment. Therefore, aggregating exposures from the food, drinking water and residential pathways of exposure is not necessary.

Cumulative Risk Assessment

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide chemical's residues and "other substances that have a common mechanism of toxicity." Although HED compared toxicities of other chlorophenoxy acetic acids to 4-CPA to improve the hazard characterization, EPA does not have, at this time, available data to determine whether 4-CPA has a common mechanism of toxicity with other substances.

HED Recommendation

HED recommends that the tolerance level be revised to 0.2 ppm from 2.0 ppm, based upon previously reviewed and accepted residue chemistry studies.

Appendix A: Executive Summaries and Toxicological Profile of 4-CPA

The requirements (CFR 158.340) for a food use for 4 chlorophenoxyacetic acid are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1: Toxicology data requirements for a food use pesticide and whether or not they have been satisfied.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	Yes	Yes
870.1200	Acute Dermal Toxicity	Yes	Yes
870.1300	Acute Inhalation Toxicity	Yes	Yes
870.2400	Primary Eye Irritation	Yes	Yes
870.2500	Primary Dermal Irritation	Yes	Yes
870.2600	Dermal Sensitization	Yes	Yes
870.3100	Oral Subchronic (rodent)	Yes	Yes
870.3150	Oral Subchronic (nonrodent)	Yes	Yes
870.3200	21-Day Dermal	Yes	No [1]
870.3250	90-Day Dermal	No	No [2]
870.3465	90-Day Inhalation	No	No [2]
870.3700a	Developmental Toxicity (rodent)	Yes	Yes
870.3700b	Developmental Toxicity (nonrodent)	Yes	No [1]
870.3800	Reproduction	Yes	No [1]
870.4100a	Chronic Toxicity (rodent)	Yes	No [1]
870.4100b	Chronic Toxicity (nonrodent)	Yes	No [1]
870.4200a	Oncogenicity (rat)	Yes	No [1]
870.4200b	Oncogenicity (mouse)	Yes	No [1]
870.4300	Chronic/Oncogenicity	No[3]	-
870.5100	Mutagenicity—Gene Mutation - bacterial	Yes	Yes
870.5300	Mutagenicity—Gene Mutation - mammalian	Yes	Yes
870.5395	Mutagenicity—Structural Chromosomal Aberrations	Yes	Yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	No	-
870.6100a	Acute Delayed Neurotox. (hen)	No [4]	-
870.6100b	90-Day Neurotoxicity (hen)	No [4]	-
870.6200a	Acute Neurotox. Screening Battery (rat)	No	-
870.6200b	90 Day Neuro. Screening Battery (rat)	No	-
870.6300	Develop. Neuro	No	-
870.7485	General Metabolism/rats	Yes	No[1]
870.7600	Dermal Penetration	No	-

[1] A data waiver was granted for this guideline study. [2] Not required for this use category. [3] Either 870.4200a or 870.4300 can fulfil this requirement. [4] Required only for organophosphate pesticides.

Table 2: Acute Toxicity Data on 4CPA (Technical Grade 4-CPA)

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
870.1100	Acute Oral	41837001	LD_{50} = 2703 mg/kg	III
870.1200	Acute Dermal	42522601	LD_{50} = >2000 mg/kg	III
870.1300	Acute Inhalation	42968201	LC_{50} = >5.25 mg/L	IV
870.2400	Primary Eye Irritation	42339101	Severe irritation	I
870.2500	Primary Skin Irritation	42306801	Non-irritating	IV
870.2600	Dermal Sensitization	42339102	Not a sensitizer	NA

Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

870.3100 90-Day Oral Toxicity - Rat

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 42902501) 4-chlorophenoxyacetic acid (99.8% a.i., batch/lot # HWI TM No. 0020A4) was administered to 12 Crl:CDBR VAF/PLUS rats/sex/group in diet at dose levels of 0, 100, 2000 or 8000 ppm (equivalent to 0, 6.6, 132.4 or 516.9 mg/kg bw/day for males and 0, 7.99, 153 or 625.9 mg/kg bw/day for females). Animals were subjected to the following: (1) observed twice daily, (2) body weights measured weekly, (3) food consumption measured weekly, (4) ophthalmic examination, (5) hematology, clinical chemistry, urinalysis at week 5 and 14, and (6) at 13 weeks, fasted and sacrificed for organ weights and gross examination and microscopic examination of selected tissue and organs.

Male body weights were consistently nominally lower (-0.05% by week 7 to -1.8% by week 14) than control weights at 8000 ppm. Significantly lower body weights ($p<0.05$) were seen in females (-9% by week 3 to -14% by week 14) at 8000 ppm. Body weight gain was significantly decreased in males and females dosed at 8000 ppm for the first week and for week 10 for males and week 5 for females. Since food efficiency was less than controls in males (-8%) and females (-8%) at 8000 ppm, the decrease in weight may have been due to toxicity rather than decreased food consumption. Alkaline phosphatase was slightly, but statistically elevated at 5 weeks (29%) and 14 weeks (57%) in females only. At 8000 ppm, glucose was statistically significantly lower by 16% in females. Urine volumes were increased in males (17% at week 5 and 2% at week 14) and significantly increased in females (233% at week 5 and 198% at week 14) at 8000 ppm. The specific gravity of urine from females was decreased significantly at week 5 (-2%) and week 14 (-2%) in the 8000 ppm group. At histological examination, an increased

number of males showed liver lymphohistiocytic infiltration (1 in control and 5 at 8000 ppm) and individual hepatocyte necrosis (0 in control and 6 at 8000 ppm).

The LOAEL is 8000 ppm (517 mg/kg/day for males and 626 mg/kg/day for females), based on body weight decrement in males and females and lymphohistiocytic infiltration and individual hepatocyte necrosis in males and increased urine volume in females. The NOAEL is 2000 ppm (132 mg/kg/day for males and 153 mg/kg/day for females).

This 90-day oral toxicity study in the rodent is acceptable guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rodent species. The acceptability of the study is unchanged from TXR# 0010794 and the NOAEL/LOAEL are unchanged.

870.3150 90-Day Oral Toxicity - Dog

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 42968301) 4-chlorophenoxyacetic acid (99.8%% a.i., batch/lot HWI 0020A4) was administered to 4 Beagle dogs/sex/group in the diet at dose levels of 0, 20, 100 or 500 ppm (equivalent to 0, 0.80, 3.3 or 18.6 mg/kg/day for males and 0, 0.78, 4.0 or 17.4 mg/kg/day for females; average for males and females; 0, 0.792, 3.67 and 18.0 mg/kg bw/day). Doses were based on a 4-week range-finding study in 2 dogs/sex/group dosed at 0, 40, 200, 400, 800, 1600 or 3200 ppm (MRID 43045301). In this range-finding study, the dogs were offered test material for 3 hour for 1 day followed by basal diet for 2 days; the regimen was followed subsequently at the next higher dose until the 3200 ppm dose was reached. These treated dogs were then offered 1600 ppm for the remaining ten days from day 19 to 28. In this range-finding study, decreased palatability at 1600 and 3200 ppm resulted in decreased body weight and changed clinical chemistries, while absolute and relative organ weight changes were associated with decreased nutritional status of the dogs. No specific toxicity was seen grossly or microscopically.

In the 90-day study, body weights and food consumption were measured weekly in the 0, 20, 100 and 500 ppm groups (MRID 42968301). No dose related statistical differences were seen. Male body weight were nominally lower throughout the study. Males showed a nominal body weight gain decrement of 250 g week 1-13 (-8%), but females showed a nominal 25 g body weight gain week 1-13 (+1%) at 500 ppm. Male food consumption was statistically significantly depressed week 9 and 12 at the 100 ppm dose level. There was no dose related differences in food consumption or food efficiency for females on study. Male dogs showed a nominal -19% decreased food efficiency for the first 4 weeks of the study, but a nominal 9% increase during the last 9 weeks of the study for no change for the entire 13 week study.

Clinical observations, hematology, and clinical chemistry data showed no differences by study termination. The author stated that red feces and vomiting were seen in all dose groups, but that it appeared to be more frequent in the two top dose levels. No dose related differences were seen in organ weights or relative organ weights or pathology at microscopic examination. Statistically significant ovarian weight increase seen in the left ovary at 20 and 500 ppm, were not seen in the combined ovarian weights. The ovarian weight changes were considered incidental and not dose related. The study showed only suggestive body weight gain decrement at 500 ppm, but no definitive toxicity in any parameter .

Possibly based on the nominal male body weight gain decrement, the study author concluded that the LOAEL was 500 ppm (HDT). It is concluded that the suggestive toxicity in

male body weight gain decrement at 500 ppm (18.6 mg/kg/day) may have approached a LOAEL. However, the demonstrated NOAEL is 500 ppm (18.6 mg/kg/day for males and 17.4 mg/kg/day for females or an average of 18.0 mg/kg/day for males and females).

A LOAEL was not demonstrated. The NOAEL is 500 ppm (18.0 mg/kg/day)(HDT).

This 90-day oral toxicity study in the dog is acceptable/guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3150; OECD 409) in non-rodent species. Although the study shows no definitive toxicity, repeating the study is not likely to produce meaningful information on this unpalatable test material. Dogs suffered from malnutrition at higher dose levels in a range-finding study (MRID# 43045301). This malnutrition was caused by the unpalatable test material in the diet resulting in decreased food consumption. The acceptability of the study (MRID 42968301) is not changed from TXR# 10794, however, the NOAEL has been changed from100 ppm in TXR# 10794 to 500 ppm in the current Executive Summary, with no LOAEL.

870.3700a Prenatal Developmental Toxicity Study - Rat

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 42322602) 4-chlorophenoxyacetic acid (99-100% a.i., batch/lot # HWI 0020A1 and 0020A2) was administered to 25 Crl:CDBR VAF/PLUS rats/group by gavage at dose levels of 0, 150, 300, 600 or 1000 mg/kg bw/day from days 6 through 15 of gestation.

Mean body weight gains of dams were significantly decreased and were dose related during gestational days 6 through 9 (-44%) and 6 through 16 (-14%) at 300 mg/kg/day and greater. Dams at 1000 mg/kg/day showed yellow staining of the ano-genital area, tremors, uncoordinated movements, recumbent posture, languidness, and cold to touch. Also at 1000 mg/kg/day, 1 dam died and 3 were killed in a moribund condition.

There were no differences among control and treated groups in pre- or post implantation loss, resorptions or corpora lutea. Fetal weights were significantly lower than control in the 600 (-8%) and 1000 mg/kg/day groups (-19%). There were no dose related soft tissue or skeletal malformations. Statistically significant dose related increases occurred in unossified sternebrae 5 for fetuses at all dose levels, but not for litters. Litters in the 150 mg/kg/day group showed the same incidence as concurrent control litters and historical control litters. The litter incidence did not reach statistical significance below the 600 mg/kg/day dose level. At the 1000 mg/kg/day dose, other variations increased, increases were seen in misaligned sternebrae and 7th cervical ribs in fetuses and litters.

The LOAEL for developmental effects in fetuses and litters was the 300 mg/kg/day dose level. The study author stated that the LOAEL for developmental effects was 600 mg/kg/day because the litter incidence was significantly increased at 600 mg/kg/day. Although the incidence in litters was not significantly affected until the 600 mg/kg/day dose level was reached, the increased fetal incidence was statistically significant at 300 mg/kg/day (27% versus 13% in control) and showed a good dose related response and the litter incidence was nominally increased at 300 mg/kg/day (52% versus 73% in control) and showed a dose related response. The response in fetuses and litters at 300 mg/kg/day and above suggests that the increased litter incidence was also treatment related.

The maternal LOAEL is 300 mg/kg bw/day, based on decreased body weight between gestational days 6 and 9 and 6 to 16. The maternal NOAEL is 150 mg/kg bw/day.

The developmental LOAEL is 300 mg/kg bw/day, based on unossified sternebrae 5 (incidence was statistically significant in fetuses and nominally increased in litters). The developmental NOAEL is 150 mg/kg bw/day.

The developmental toxicity study in the rat is classified acceptable/guideline; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat. The acceptability of the study and NOAEL/LOAEL are not change from TXR# 009556. The developmental effect of concern is presented in the Table below.

Doses	0	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day	1000 mg/kg/day
Percentage with unossified sternebrae 5 in each group, *p=>0.05, **p=>0.01					
Fetuses	13	20*	27*	35*	81**
Litters	52	50	73	80*	100*
The range in historical control litter incidence of unossified sternebrae 5 is 0-50%.					

870.3700b Prenatal Developmental Toxicity Study - Rabbit

Summary of the rabbit range-finding study: No definitive study was conducted. A 1965 range-finding study was conducted in pregnant rabbits on 5 animals/group at 0, 5, 10 or 25 mg/kg/day (MRID# 00144733; TXR# 005712). However, since maternal weight for controls was not reported, it is impossible to determine maternal weight decrement. Total litter weight was reported but no individual fetal weights. The viability index was nominally decreased (11% compared with control) at the HDT, but no statistics were reported. The study was considered unacceptable/not upgradable for these and other reasons. The study report authors however, stated that no effects were observed in fetuses or dams. A data waiver was granted for the study requirement.

Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: Due to a data waiver, no additional study is required at this time.

870.3800 Reproduction and Fertility Effects - Rat

EXECUTIVE SUMMARY: 4-CPA (technical) was administered in the diet to 20 female and 10 male Sprague Dawley rat per group at 0, 25, 125 or 250 ppm for 60 days to the parental generation, mated 2:1 to produce Fa and Fb litters for three generations (MRID# 00083274). After weaning the F3a and F3b litters, the study was terminated. Animals were kept on diet continuously except females were rested for 10 days after weaning the first litter; the second litter was used for F1 and F2 parents. Thus females producing the litter from which parents were to be selected for the next generation were not dosed for 10 days prior to mating.

No dose related effects occurred in offspring or parents. However, since the highest dose administered was only 12.5% of the NOAEL in the 90-day study in rats, the dose levels

administered were too low to show any effects. The NOAEL in the 90-day study in rats 2000 ppm.

A number of mothers died and/or cannibalized their offspring. For example, from the F2a group from control to the high dose 14 to 3 mothers died with loss of their litters and 30 to 64 pups were cannibalized in control and each dose group. The pup viability index was too variable to show dose related effects, if there were any to see; it was lower in control (38%) than in the high dose group (49%) at day 21 of lactation. There appeared to be no dose relationship with variable numbers per generation and among groups. The authors speculated that a respiratory disease in the colony may have been responsible. Parts of the report that were readable suggested that no effects in parents or offspring were seen in the study at the HDT of 12.5 mg/kg/day. However, the parts of the submission that could verify these results were unreadable.

This study is unacceptable/not upgradable for a multi generation study of reproduction in the rat. The study was conducted at a dose that was insufficient to cause any effects. [Note: The NOAEL/LOAEL = 2000/8000 ppm (ca. 132/517 mg/kg/day) in the 90-day subchronic study in rats.] In addition, dietary concentrations were no measured, equal numbers of males and females were not used, dosing was not continuous and the data too variable for assessment.

Mutagenicity

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered adequate based on pre-1991 mutagenicity guidelines. All three studies conducted at toxic doses were negative.

Gene Mutation

Guideline # 870.5100, Reverse mutation in S. typhimurium MRID 41837002 Acceptable	A dose range of 0-5000 µg/plate of 4CPA was used for strains TA98, TA100, TA 1535, TA 1537, and TA 1538 of S. typhimurium. The test was negative up to cytotoxic doses of 5000 µg/plate with no activation (-S9), and up to doses of 5000 µg/plate with activation (+S9) where no cytotoxicity was seen.
Guideline# 870.5300, Gene mutation MRID 41837004 Acceptable	4-CPA (99%) was evaluated for potential to induced forward mutations at the TK+/- locus in L5178Y TK+/- cells in two independently performed trials. Without S9 activation, 4-CPA was not mutagenic at doses of 100, 500, 1000, 1600, 2000, 2500, 3000, 3500, or 4000 µg/mL: higher levels (5000 µg/mL) were severely cytotoxic. In the presence of S9 activation at 10, 50, 100, 250, 300, 750, 1000, 1300, 1600 or 2000 µg/mL (cytotoxic at doses 1300 µg/mL), non-dose related increases in mutation frequency (MF) were obtained in both trials. Although there was a tendency for elevated MFs at doses ranging from 300 to 1600 µg/mL +S9, doubling of the MF over concurrent controls was only seen at 600 µg/mL (Trial 1) and 1000 µg/mL (Trial 2). The evidence suggesting a mutagenic response, was however, insufficient to conclude the 4-CPA was positive. **The test material was not mutagenic in this in vitro mammalian cell assay.**

Cytogenetics

Guideline # 870.5395, In vivo mammalian erythrocyte micronucleus test MRID 41837003 Acceptable	In an ICR mouse bone marrow micronucleus assay, 5/sex/group were treated gavage with 4-chlorophenoxyacetic acid (99%) at doses of 0, 450, 900 or 1800 mg/kg-bw. Bone marrow cells were harvested at 24, 48 and 72 hours post-treatment. There were signs of toxicity, languidness and prostration, and most animals died within 24 hours at 1800 mg/kg during the study. Hematopoiesis was adversely affected at 1800 mg/kg. There were 5000 polychromatic erythrocytes and < 5 micronucleated polychromatic erythrocytes (MPE) per group with no dose response. 4-CPA was tested at an adequate dose based on mortality. The positive control induced the appropriate response. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.**

Other Genotoxicity

Guideline #, study type MRID 00141673 classification	Dose range and brief conclusions of study (see gene mutation summary instructions)

REFERENCES:

00083274 Booz-Allen Applied Research (1964) The Effect of 4-Chlorophenoxyacetic Acid on Reproduction in the Rat: Project No. 4031. (Unpublished study, including letter dated Nov 3, 1965 from R.A.Turner to Nathan G. Fox, received Nov 16, 1965 under PP0360; submitted by Chun King Corp., Duluth, Minn.; CDL:090390-A)

00144733 Turner, R. (1965) A Study of the Effect of P-chlorophenoxyacetic Acid on Teratogenicity in the Rabbit: BSL4054. Unpublished study prepared by Biological Science Laboratory, Foster D. Snell, Inc. 14 p.

41837001 Glaza, S. (1991) Acute Oral Toxicity Study of 4-Chlorophenoxyacetic Acid in Rats: Final Report: Lab Project Number: HLA/00801531. Unpublished study prepared by Hazleton Laboratories America, Inc. 53 p.

42306801 Glaza, S. (1992) Primary Dermal Irritation Study of 4-Chlorophenoxyacetic Acid in Rabbits: Lab Project Number: HWI 20200490. Unpublished study prepared by Hazleton Wisconsin, Inc. 21 p.

42322602 Henwood, SM (1992) Teratology Study with 4-Chlorophenoxyacetic acid. Laboratory name Hazelton Wisconsin, Inc. Laboratory report number, HWI 6341-101 (May 14, 1992) Unpublished

42339101 Glaza, S. (1992) Primary Eye Irritation Study of 4-Chlorophenoxyacetic Acid in

Rabbits: Lab Project Number: HWI 20200491. Unpublished study prepared by Hazleton Wisconsin, Inc. 36 p.

42339102 Glaza, S. (1992) Dermal Sensitization Study of 4-Chlorophenoxyacetic Acid in Guinea Pigs--Closed Patch technique: Final Report: Lab Project Number: HWI 20200492. Unpublished study prepared by Hazleton Wisconsin, Inc. 33 p.

42522601 Glaza, S. (1992) Acute Dermal Toxicity Study of 4-Chlorophenoxyacetic Acid in Rabbits: Final Report: Lab Project Number: HWI 20700133. Unpublished study prepared by Hazleton Wisconsin, Inc. 28 p.

42902501 Henwood, SM (1993) 13-Week Dietary Toxicity Study with 4-Chlorophoxyacetic acid in Rats. Laboratory name Hazleton Wisconsin, Inc. Laboratory report HWI 6341-102. Unpublished

42968201 Nachreiner, D. (1993) 4-Chlorophenoxyacetic Acid: Acute Dust Inhalation Toxicity Study in Rats: Revised Report: Lab Project number: 92N1192 REVISED: 92N1192. Unpublished study prepared by Union Carbide and Plastics Co., Bushy Run Research Center. 58 p.

42968301 Henwood, SM (1993) 13-Week Dietary Study with 4-Chlorophenoxyacetic Acid in Dogs. Laboratory name Hazleton Wisconsin, Inc. Laboratory report number, HWI 6341-108. September 30,1993. Unpublished

43045301 Hewood, SM (1992) Dietary Escalating Dose Tolerance Study with 4-Chlorophenoxyacetic acid in Dogs. Laboratory name Hazleton Wisconsin, Inc. Laboratory report number, HWI 6341-106. September 11, 1992. Unpublished

Other References:

Clock, Mary (1994); Memorandum to Jay Ellenburger; Dated 12/22/94. The HED Chapter of the Regististration Eligibility Decision Document (RED) for 4-chlorophenoxyacetic acid (4CPA), 019401 (TXR# 011819)

USEPA (1997) Regregistration Eligibility Decision (RED) 4-Chlorophenoxyacetic Acid (4CPA). EPA 738-R-97-001 March 1997

Toxicity Profile Summary Tables

Subchronic, Chronic and Other Toxicity Tables

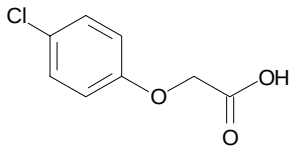
Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	42902501 Acceptable/guideline 0, 100, 2000 or 8000 ppm M: 0, 6.6, 132.4, 516.9 mg/kg/day F: 0, 7.99, 153, 625.9 mg/kg/day	NOAEL = M/F; 132/153 mg/kg/day LOAEL = M/F; 517/626 mg/kg/day based on based on body weight decrement in males and females and lymphohistiocytic infiltration and individual hepatocyte necrosis in males and increased urine volume in females.
870.3150 90-Day oral toxicity in dogs	42968301 Acceptable/guideline 0, 20, 100 or 500 ppm M; 0, 0.80, 3.3 and 18.6 mg/kg/day F; 0, 0.78, 4.0 or 17.4 mg/kg/day Average for males and females; 0, 0.792, 3.67 and 18.0 mg/kg/day.	NOAEL = M/F 18.0 mg/kg/day (HDT) LOAEL = None mg/kg/day based on no effects at the top dose. There was a nominal body weight decrement at the top dose, which was insufficient to be considered a toxic effect.
870.3200 21/28-Day dermal toxicity	-	No study available
870.3250 90-Day dermal toxicity	-	No study available
870.3465 90-Day inhalation toxicity	-	No study available
870.3700a Prenatal developmental in rats	42322602 Acceptable 0, 150, 300, 600 or 1000 mg/kg/day	**Maternal** NOAEL = 150 mg/kg/day LOAEL = 300 mg/kg/day based on body weight. **Developmental** NOAEL = 150 mg/kg/day LOAEL = 300 mg/kg/day based on unossified sternebrae 5 (incidence was statistically significant in fetuses and nominal in litters).
870.3700b Prenatal developmental in rabbits	00144733 Unacceptable 0, 5, 10, 25 mg/kg/day (range-finding study, 5 rabbits/group)	**Materna**l NOAEL = 25 mg/kg/day LOAEL = Not determined. **Developmenta**l NOAEL = 25 mg/kg/day LOAEL = Not determined.
870.3800 Reproduction and fertility effects	00083274 Unacceptable 0, 25, 50, 250 ppm 0, 1.25, 2.5, 12.5 mg/kg/day	**Parental/Systemic** NOAEL = 12.5 mg/kg/day LOAEL = Not determined. **Reproductive** NOAEL = 12.5 mg/kg/day LOAEL = Not determined. **Offspring** NOAEL = 12.5 mg/kg/day LOAEL = Not determined.
870.4100a Chronic toxicity rodents	Unavailable	No study available

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4100b Chronic toxicity dogs	Unavailable	No study available
870.4200 Carcinogenicity rats	Unavailable	No study available
870.4300 Carcinogenicity mice	Unavailable	No study available
870.5100, Gene Mutation, reverse mutation in S. typhimurium	41837002 Acceptable 0, 100, 333, 667, 1000, 3300 or 5000 µg/plate	Negative without activation at cytotoxic doses and negative with activation at 5000 µg/plate.
870.5300, Gene Mutation, Mouse L5178Y lymphoma cells	41837004 Acceptable 0-4000 µg/mL -S9 0-2000 µg/mL +S9	Negative -S9 and +S9 at cytotoxic doses.
870.5395, Cytogenetics, In vivo mouse erythrocyte micronucleus test	41837003 Acceptable 0, 450, 900 or 1800 mg/kg	Negative at toxic doses.
870.6200a Acute neurotoxicity screening battery	-	NA
870.6200b Subchronic neurotoxicity screening battery	-	NA
870.6300 Developmental neurotoxicity	-	NA
870.7485 Metabolism and pharmacokinetics	-	NA
870.7600 Dermal penetration	-	NA
Special studies	-	NA

NA = Not available

Appendix B:
Toxicity Studies with 4-chlorophenoxyacetic acid (4-CPA) and Structures Related to 4-CPA.

Structure of 4-chlorophenoxyacetic acid (4-CPA) (PC 019401)

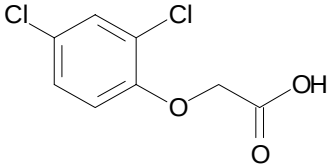


The following are brief summaries of the cancer findings for each of the structural analogs for which there are studies. In some cases the Cancer Assessment Review Committee (CARC) has not evaluated the pesticide. Comparison of the results from toxicity studies are made for 4-CPA and the four analogs, 2,4-

dichlorophenoxyacetic acid, 2-methyl-4-chlorophenoxyacetic acid, 3-chlorophenoxy-2-propionic acid, and 2-methyl-4-chlorophenoxybutyric acid (Table 1). More structurally remote chlorophenoxy acid pesticides are: (1) 2,4-dichlorophenoxybutyric (not carcinogenic in rats or mice), (2) 2,4-dichlorophenoxy-2-propionic acid (not carcinogenic in rats or mice), (3) 2,4,5-trichlorophenoxyacetic acid (evidence of carcinogenicity in total tumors in female mice, but not rats), and (4) 2,4,5-trichlorophenoxy-2-propionic acid (no studies available). These latter pesticides are not shown and not summarized further. [Information from Carcinogenicity Peer Review (4th) of 2,4-D, 1/29/97.]

Although there are no carcinogenicity studies on 4-CPA, the weight of the evidence does
not suggest that 4-CPA would be carcinogenic in life-time studies at reasonable doses not causing excessive toxicity.

Structure of 2,4-dichlorophenoxyacetic acid (2,4-D)(PC 030001)



The following is a summary of the findings from the fourth and last cancer assessment of 2,4-D. This pesticide has the largest toxicity data base of all the analogs. The Cancer Peer Review Committee (CPRC) concluded that 2,4-D should remain classified 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.

2,4-D was initially classified as a possible human carcinogen, based on a significant 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 both studies 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.

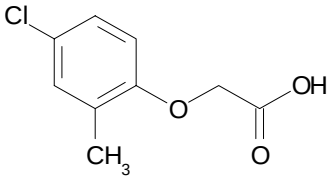
Mutagenicity studies showed consistently negative results without activation and positive and negative result with activation. The CPRC concluded that although cytogenic activity was seen, there was no concern for mutagenicity.

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 uncharacterized compounds and 4 to 10% was excreted as the parent in feces. Total excretion (98 to 99.5%) occurred within 48 hours.

The CPRC and SAP agreed on a "Group D" classification.

[Information from Carcinogenicity Peer Review (4th) of 2,4-D, 1/29/97.]

Structure and results on 2-methyl-4-chlorophenoxyacetic acid (MCPA) (PC 030501)

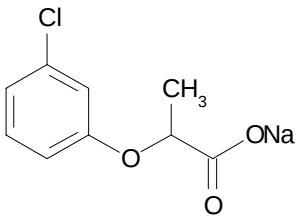


MCPA has not been reviewed by the CARC, but a toxicology reviewer indicated that no dose related tumors were

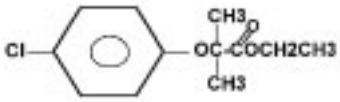
seen in rats or mice at adequate doses to test for carcinogenicity. A battery of mutagenicity studies shows a positive study for chromosomal aberrations in human lymphocyte cells and weakly mutagenic response in an in vivo sister chromatid exchange study. The remaining 6 in vivo and in vitro mutagenicity studies conducted were negative. The metabolism studies in the rat shows that 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%).

[Information from the 1-liners and Paul Chin reviewer].

Structure and results on sodium 3-chlorophenoxy-2-propionate (cloprop, sodium salt) (PC 021201)



Life-time carcinogenicity studies have been conducted with cloprop, but there are no definitive conclusions. There was a statistically significantly increasing trend and pair-wise comparison with control for mortality in male and female rats at the top dose. The registrant refused to submit historical control data on morality among the rats used in the carcinogenicity study. Consequently the Peer Review of cloprop was canceled and the pesticide withdrawn.



Clofibrate

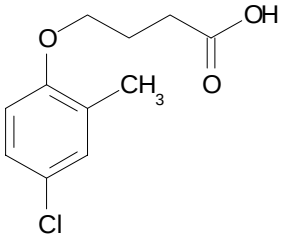
In the mouse study, there was statistically significantly pair-wise comparison of male liver adenomas/carcinomas and male liver carcinomas at the highest dose tested and in females for liver adenomas and carcinomas at the two lowest doses tested, but not at the highest dose tested. One reviewer believed that there was no evidence for carcinogenicity in mice, however another reviewer believed there was evidence of liver cancer in mice. The issue has never been resolved because the pesticide was withdrawn.

Cloprop is negative in a battery of mutagenicity studies.

There are no metabolism studies in rats, but in goats, cloprop is excreted as the parent.

[Information from 1-liners and a memorandum from John Redden.]

Structure and results on 2-methyl-4-chlorophenoxybutryic acid (MCPB) (PC 019201)



No life-time carcinogenicity studies have been conducted with MCPB.

A battery of mutagenicity studies are negative. One study for chromosomal abnormalities with S9 produced chromosomal abnormalities at high doses.

There are no adequate metabolism studies, but a reference from the literature suggest that bacteria split off acetic acid from the butyric acid residue in plants and cows.

[Information from 1-liners and DERs.]

Structure and results on 2(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester; the Drug Clofibrate (lowers plasma triglycerides and cholesterol)

An International Agency for Research on Cancer (IARC) Monograph on clofibrate states that there is inadequate evidence in humans for carcinogenicity and limited evidence in animals for carcinogenicity.

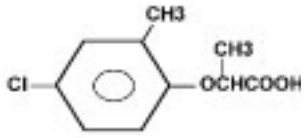
Clofibrate is peroxisome proliferator and is excreted rapidly in human urine as the parent. (http://193.51.164.11/htdocs/monographs/vol66/clofibrate.html).

Structure and results on mecoprop [2-(2-methyl-4-chlorophenoxy)propionic acid] (PC 031501)

The acute toxicity of mecoprop is similar to that of 4-CPA. The NOAEL/LOAEL in the rat 90-day feeding study was lower than the NOAEL/LOAEL in rat 90-day neurotoxicity study, which showed no neurotoxic effects, in addition to being lower than 4-CPA in a rat 90-day feeding study. A rabbit developmental toxicity study showed a maternal NOAEL/LOAEL of 30/75 mg/kg/day, but no developmental toxicity at the highest dose tested. The rat developmental toxicity study showed developmental toxicity in the form of decreased crown-rump lengths, decreased ossification of sternebrae and increased intrauterine death at the highest dose tested, which was a maternally toxic dose. The rat developmental effects occurred at a lower dose than the effects from 4-CPA in a rat developmental toxicity study. No 90-day feeding study in dogs is available.

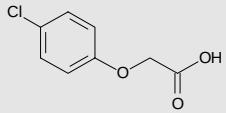
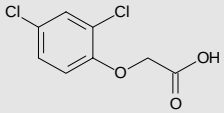
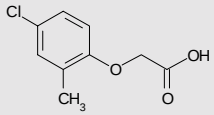
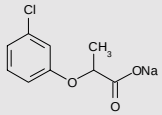
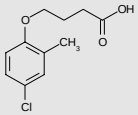
Potential carcinogenic effects have not been fully evaluated as yet, but there is suggestive evidence for increased liver tumors in mice. The rat carcinogenicity study was negative.

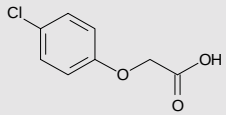
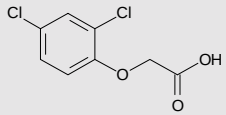
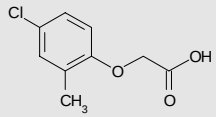
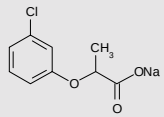
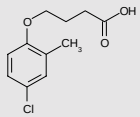
A reverse gene mutation study was acceptable and negative and chromosomal aberrations study was acceptable and negative for clastogenicity (MRID# 41013909, TXR# 009589). The remaining mutagenicity studies were unacceptable.

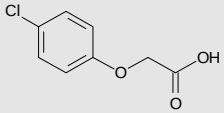
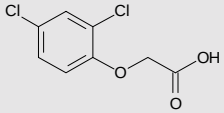
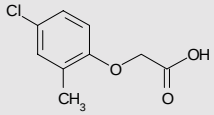
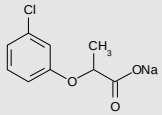
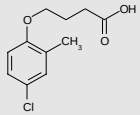


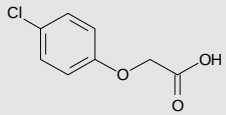
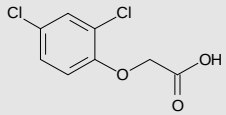
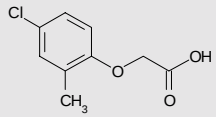
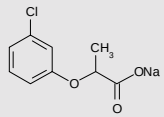
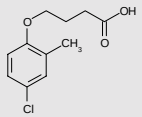
Mecoprop

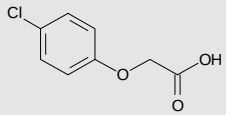
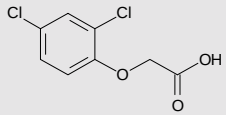
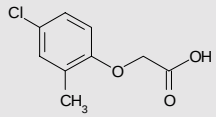
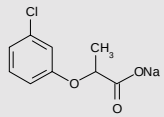
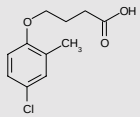
Table 1: Comparison of toxicity studies/results for 4-chlorophenoxyacetic acid (4-CPA) and four analogs of 4-CPA

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
	Results on (a.i.)	Results on (a.i.)	Results on (a.i.)	Results on (a.i.)	Results on (a.i.)
870.1100 Acute Oral ToxicityLD50	2703 mg/kg	3730mg/kg	3500 mg/kg	1567 mg/kg	1570 mg/kg
870.1200 Acute Dermal Toxicity/LD50	>2000 mg/kg	>2000 mg/kg	>2000mg/kg	-	1000 mg/kg
870.1300 Acute Inhalation Toxicity/LC50	>5.25 mg/L	>1.8 mg/L 4hr	> 6.3 mg/L	-	1.1 mg/L (acetone vehicle)
870.2400 Primary Eye Irritation	Severe	Mod/Severe	Mod/Severe	-	Mod/Severe
870.2500 Primary Dermal Irritation	Not irritating	None Irritating	Slight	-	-
870.2600 Dermal Sensitization	Not sensitizing	Not sensitizing	Not sensitizing	-	-
870.3100 Oral Subchronic (rat)	N/L=152/517mkd, Bwt dec & urine volume inc, liver individual cell necrosis	N/L=15/100mkd testes, liver, thyroid weight inc & spleen histop	N/L=50/150ppm N/L=2.5/7.5 mkd inc kidney weight with incr creatinine HDT, no histop	-	N/L=158/-m/k/d HDT palatability noted; kidney weight incr, histop neg
870.3150 Oral Subchronic (dog) . . .	N/L=18.6/-mkd HDT (Peer Rev); N/L=3.3/19mkd bwt & food decr; no histop changes seen (DER)	N/L=1.0/3.0 mkd, liver, kidney & testes histo	N/L=0.6/2.4 mkd liver inflammation & clinical chemistry (MCPA-Dimethylamine)	N/L=12.5/50 mkd, bwt decr, liver, kidney & spleen weight incr	N/L=12/40mkd Inc BSP retention, dec spermatogenic activity, prostate & testes tubular atrophy
870.3200 21-Day Dermal (rabbit) . .	-	N/L= 1000/-mkd	SystN/L=100/1000mkd Mineralization kidney tubules IrritationN/L= 10/100mkd	-	-
870.3250 90-Day Dermal	-	-	-	-	-
870.3465 90-Day Inhalation	-	-	-	-	-

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
870.3700a Developmental Toxicity (rat)	M N/L=150/300mkd Bwt dec & at 1000mkd mortality, tremors & uncoordinated movements D N/L=150/300mkd sternebrae unoss	M N/L=25/75mkd decr Bwt D N/L=25/75mkd, extra rib, dec oss, variations	M N/L=60/120 mkd Bwt D N/L=60/120 mkd Dec Bwt & dec oss	M N/L=400/-mkd HDT D N/L=400/-mkd UA, OPP added; acceptable with rabbit study	M N/L=25/100 mkd,bwt; D N/L=25/100mkd, dec oss
870.3700b Developmental Toxicity (rabbit)	M N/L= 25/–mkd, D N/L=10/25mkd fetal wt dec ascribed to maternal Bwt dec., but unsure of maternal Bwt dec Range-finding (5 rabbits/group) with no control weight. Invalid study, UA	M N/L=30/90mkd ataxia, motor control, dec Bwt D N/L=90/-mkd*	M N/L=30/60 mkd Dec Bwt, food consumption D N/L=60/- mkd	M N/L=100/200 mkd Bwt dec D N/L=100/200mkd Misshapen, compressed & small cerebral hemisphere & compressed cranial nerve & displaced eye	M N/L=5/20mkd, clinical signs, death D N/L=>20/-mkd HDT, NC
870.3800 Reproduction	[1] (Partly unreadable 1964-5 study) P N/L=12.5/–mkd Studied at too low of dose. No effects in parents or offspring. Since parts unreadable N/L unverifiable UA	P N/L=5/20mkd kidney Off N/L=7.5/20mkd, Bwt dec (same ppm dose as parents)*	P N/L=225/-mkd Off N/L=7.5/225mkd possible pup Bwt dec	P N/L=100/400mkd Off N/L= 100/400mkdec pup Bwt dec	-
870.4100a Chronic Toxicity (rodent)	-	-	-	-	-
870.4100b Chronic Toxicity (dog) . . .	-	N/L=1/5mkd, liver enzyme inc, histop liver & kidney	N/L=6/30mkd, liver histop & enzyme inc, histop kidneys	-	-
870.4200a Oncogenicity (rat)	-	-	-	-	-

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
870.4200b Oncogenicity (mouse) . . .	-	N/L= 5/62.5 mkd, kidney & adrenal weight inc Inadequate doses No carcinogenicity.	N/L=15.7/79.5mkd histo kidney & wt & calcification No carcinogenicity	N/L=75/300 mkd liver pigmentation Equivocal oncogenicity, UA	-
870.4300 Chronic/Oncogenicity (rat)	-	N/L=5/75mkd, Bwt kidney, liver, liver enz & thyroid changes Not carcinogenicity to equivocal	N/L=1/4.4mkd liver enzyme inc., kidney histop No carcinogenicity	N/L=25/100mkd, liver, kid. need historical control to confirm carcinogenicity, refused submission Not carcinogenic.	-
870.5100 Mutagenicity—Gene Mutation - bacterial 870.5100 Mutagenicity—Gene Mutation - bacterial	Neg	Neg Neg	Neg Neg	Neg	Neg
870.5300 Mutagenicity—Gene Mutation - mammalian . . .	Neg	Pos	Neg		Neg
870.5375 Mutagenicity—Structural Chromosomal Aberrations	-	-	-	-	-
Nonguideline Chromosomal aberrations (human lymphocytes).....	-	One pos +/ one neg -	Pos.	-	-
Nonguideline Recom/Convers Assay (Saccharomyces)	-	-	-	Neg	-
Nonguideline Recomb/Convers Assay (Mouse).....	-	-	-	Neg	-

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
870. 5395 Mutagenicity—Structural Chromosomal Aberrations.	Neg	Neg	Neg	Neg	-
870.5450 Rodent Dominant Lethal	-	-	-	NOAEL>400 mg/kg Neg	-
870.5915 Sister Chromatid Exchange.....	-	Neg +S9/Pos -S9	Weakly Pos.	-	-
870.5550 Mutagenicity—Other Genotoxic Effects	-	Neg	-	-	-
870.6100a Acute Delayed Neurotox. (hen) . . . . . . 870.6100b 90-Day Neurotoxicity (hen)	- -	- -	- -	- -	- -
870.6200a Acute Neurotox. Screening Battery (rat) . . .	-	N/L=67/227mkd altered FOB, dec coordination SystN/L=227/-mkd	N/L=200/400mkd impaired gait males	-	-
870.6200b 90 Day Neuro. Screening Battery (rat)	-	-	N/L=34/177mkd dec motor activity, grip strength, liver histo.	-	-
870.6200 One-year Neuro. Toxicity study (rat)	-	N/L=75/150mkd incr relative forelimb grip strength	-	-	-
870.6300 Develop. Neuro	-	-	-	-	-

Study/Test	4-chloro-phenoxyacetic acid (4-CPA) 019401 Data from DERs & Peer Rev	(2,4-dichlorophenoxy)-2-acetic acid (2,4-D) 030001 Data from 1-Liner & Peer Rev	(2-methyl-4-chloro-phenoxy)-2-acetic acid (MCPA) 030501 Data from 1-Liner & Paul Chin	sodium (3-chlorophenoxy) -2-propionate (cloprop, sodium salt) 021201 Data from 1-Liner No info in Archives	(2-methyl-4-chlorophenoxy)-4-butyric acid (MCPB) 019201 Data from 1-Liner
					
870.7485 General Metabolism (Lab# 152/517)	-	Excreted as parent in urine (86-94%), 4-11% in the feces Small amounts of metabolites (0.6%-1.3%). 98-99.5% recovered within 48 hr. Excreted mostly un-metabolized	Mostly excreted as MCPA, 7-13% hydroxylated methyl MCPA. 98% excreted within 192 hr. Excreted mostly un-metabolized	Excreted as parent, mostly unmetabolized in the goat UC	Lit.; Bact-Splits off acetic acid from the butyric acid residue in plants and cows UA
870.7600 Dermal Penetration	-	-	-	-	-
Carcogenicity Classification.....	No studies	"D" not classifiable as a human carcinogen	Not likely to be a human carcinogen, but no HIARC or CARC review yet	Rats (historical control required) Chem withdrawn Mice increased pair-wise hepatocellular carcinomas at HDT Unclassified by CARC	No carcinogenicity studies

[1] This 3-generation reproduction study with 4-CPA is reasonably well conducted but the doses were too low (the highest dose tested was 12.5% of the NOAEL from the 90-day subchronic study in rats.). The highest dose tested was 250 ppm and the NOAEL in a 90-day rat study was 2000 ppm. In addition, the colony showed respiratory problems with weight loss with recovery and related marked cannibalism, and pup death due to maternal death. The material tested appeared to be reasonably pure from acid equivalent measurements, but since no units were reported, this cannot be verified. The study was conducted prior to GLPs and the test material in the diet was not measured. Therefore the study is unacceptable/not upgradable.

N/L = NOAEL/LOAEL followed by effects at LOAEL unless otherwise specified; mkd = mg/kg/day. - = No study conducted or available; UA = Unacceptable study; UC = Unclassified study; a.i. = active ingredient. inc=increase; dec=decrease; histop=histopathology; DER= data evaluation record; neg=negative; pos=positive; Syst=systemic; HDT=highest dose tested; mod=moderate; Bwt=body weight; unoss=unossified; oss=ossification; M=maternal; D=developmental; UA=unacceptable; P=parental; Off=offspring; FOB=Functional Observation Battery; CARC=Cancer Assessment Review Committee.

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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: **4-Chlorophenoxyacetic Acid (4-CPA) TRED**: Estimated Drinking Water Concentrations for 4-CPA for Use in the Human Health Drinking Water Risk Assessment. (Chemical Code 019401 ; DP Barcode D284988)

To: Christina Scheltema, Chemical Review Manager
Reregistration Branch III
Special Review and Reregistration Division (7505C)

From: Mark Corbin, Environmental Scientist
Environmental Risk Branch I
Environmental Fate and Effects Division (7507C)

Thru: Sid Abel, Branch Chief
Environmental Risk Branch I
Environmental Fate and Effects Division (7507C)

This memorandum transmits the FQPA drinking water assessment for the tolerance reassessment of 4-CPA. The use of 4-CPA is limited to indoor use as a root suppression agent for mung bean sprouts and therefore the agency only required the submission of hydrolysis data in support of the registration of 4-CPA. No drinking water assessment has been completed at this time for 4-CPA since an indoor use is expected to minimally impact drinking water sources.

Environmental Fate Assessment

Hydrolysis data were the only data required to support the indoor use (e.g. root suppression of mung bean sprouts) of 4-CPA. From an acceptable study, parent 4-CPA was stable with a reported half life of greater than 30 days to abiotic hydrolysis in three buffer solutions (MRID 42819601). No additional environmental fate data are required to support the use of 4-CPA on mung beans.

4-CPA is expected to be mobile in soil and aquatic environments because it will exist as an anion (dissociated carboxylic acid) in most environments. The soil partitioning coefficient (Kd) for 4-CPA cannot be estimated from structural analysis. Disposal of 4-CPA treated water, after

treatment of mung beans, should be performed in compliance with all appropriate discharge permits and requirements. By analogy, the phenoxy herbicides as a class are generally degraded under aerobic conditions by microbially mediated processes and aqueous photolysis, and are generally stable to hydrolysis, soil photolysis, and under anaerobic conditions.

Conclusions

No estimated exposure concentrations for drinking water are presented in this assessment due to the limited indoor use of 4-CPA and due to the limited environmental fate data. However, should additional uses for 4-CPA be considered EFED should be consulted to evaluate whether these uses may impact drinking water sources and what additional data may be needed for registration.