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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: October 26, 2000

SUBJECT: PP#s 7F4896, 7E4865, & 8E3628. **CLOMAZONE IN/ON RICE, TANIER, CASSAVA, YAMS, ARRACACHA, AND CUCURBIT VEGETABLES. HED Risk Assessment.**
Barcodes D257269, D259809, & D259622. PC Code 125401. Cases 289005, 292322, & 289118. Submissions S528836, S569018.

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THROUGH: G. Jeffrey Herndon, Acting Branch Senior Scientist
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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered and proposed uses of clomazone in/on rice, tanier, cassava, yams, arracacha, and cucurbit vegetables.

A summary of the findings and an assessment of human risk resulting from the proposed uses of clomazone is provided in this document. The risk assessment was provided by Jessica Kidwell of Registration Action Branch 1 (RAB1), the hazard characterization by Guruva Reddy of RAB1, the residue chemistry data review by George Kramer, Ph.D. of RAB1, the dietary risk assessment by Jennifer Rowell of RAB1, the occupational/residential exposure and risk

assessment by Dana Vogel of RAB1, and the drinking water assessment by James Breithaupt of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration

Provided that Section F is revised, the residue chemistry and toxicological databases support the establishment of the following permanent tolerances for the residues of the herbicide clomazone (2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone) *per se*:

Vegetable, tuberous and corm, except potato, subgroup	0.05 ppm
Vegetable, cucurbit, group	0.05 ppm
Rice, grain	0.02 ppm
Rice, straw	0.02 ppm

Registration should be made conditional upon submission of the following data:

1) Chemistry

- Revised label for Command 3ME.

2) Toxicology

- 21-day dermal toxicity study in rats using the technical grade active ingredient (TGAI) (OPPTS 870.3200) (data gap).

- 28-day inhalation toxicity study. This study was requested by HIARC for further characterization of inhalation risk assessments. Due to the potential for inhalation exposure, there is concern for toxicity by the inhalation route. The 28-day inhalation toxicity study would give a dose and endpoint examined via the route of exposure of concern (i.e., route specific study) and thus would avoid using an oral study and route-to-route extrapolation. The protocol for the existing 90-day inhalation toxicity study (OPPTS 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.

Note to RD: Although the carcinogenicity study in the mouse, which is graded Unacceptable/guideline, is **not** considered a data gap for the current use pattern, a new carcinogenicity study in the mouse is required if additional requests for new uses will increase dietary and/or worker exposure.

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1.0. EXECUTIVE SUMMARY

Clomazone is a broad spectrum herbicide used to control annual grasses and broadleaf weeds. FMC Corporation, Agricultural Products Group, has submitted a petition proposing tolerances for residues of clomazone [(2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone)] in/on rice commodities following pre-emergent application. The proposed tolerances are:

Rice, grain	0.02 ppm
Rice, straw	0.02 ppm
Polished Rice	0.05 ppm

Dr. D. L. Kunkel, Project Coordinator, on behalf of the Interregional Research Project No. 4 (IR-4) and the Agricultural Experiment Station of Puerto Rico requests the establishment of tolerances for the herbicide clomazone (2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone) in/on tanier, cassava, yams, and arracacha at 0.05 ppm.

Dr. D. L. Kunkel, Project Coordinator, on behalf of IR-4 and the Agricultural Experiment Stations of AR, CA, DE, FL, KY, LA, MI, NJ, NC, OR, TN, VA, WA and WI requests the establishment of tolerances for the herbicide clomazone (2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone) in/on cucurbit vegetables at 0.1 ppm.

Permanent tolerances for residues of clomazone have been established in 40 CFR §180.425(a) in/on soybeans, peas (succulent), sweet potatoes, snap beans and peppers at 0.05 ppm and on pumpkins, squash, cucumber and cabbage at 0.1 ppm. A time-limited tolerance established under 40 CFR §180.425(b) for residues in/on watermelons at 0.1 ppm is set to expire on 5/30/01. Currently, a time-limited tolerance of 0.05 ppm and section 18 registration are being proposed for use of clomazone on sugarcane in Louisiana.

There are no proposed or registered residential uses for clomazone.

Hazard Assessment

Clomazone has low acute toxicity (Category III and IV) via oral, dermal and inhalation routes. It is non-irritating to the eye and mildly irritating to the skin. It is not a skin sensitizer. The primary target organ for clomazone in the rat and dog studies is the liver. It is not a carcinogen in either the rat or mouse. No systemic toxicity was observed at the highest dose tested in the 2-year rat, mouse oncogenicity or chronic dog studies. The doses ranged from 84.8 mg/kg/day for the 2-year rat study to 1038 mg/kg/day for the chronic dog study. There was no evidence of neurotoxicity in either the chronic or subchronic studies. The available genetic toxicology studies indicate that clomazone is not mutagenic in bacteria (*Salmonella typhimurium*) and does not induce chromosomal aberrations in rat bone marrow. Similarly, clomazone did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes. Based on the results of acceptable studies, there is no concern for mutagenicity at this time.

There is no quantitative or qualitative evidence of susceptibility of rats or rabbit fetuses to *in utero* exposure in the available developmental studies. In the 2-generation reproduction study, no qualitative or quantitative evidence of increased susceptibility was observed. In a metabolism study in rat, clomazone is absorbed from the digestive tract and extensively metabolized by the liver and excreted in the urine and feces within 24 hours. Sixteen metabolites including the parent compound were identified. The predominant metabolites were FMC 87010[1], FMC 83918[2], and FMC 60217[3]. The predominant route of excretion was in urine (64-83% total recovery of radioactivity). A total of 75-85% of the administered dose was recovered for all routes and doses, except the single high dose females which accounted for 48% (fecal excretion was suppressed in these females). The total recovery after 48 hours was generally comparable between all groups and sexes and ranged from 91-100%. The quantities of metabolites varied with the dose regimen, sex, and route of administration but were the same qualitatively both in the urine and the feces in all groups.

Dose Response Assessment

On August 10, 2000, the HED Hazard Identification Assessment Review Committee (HIARC) selected endpoints for risk assessment and addressed the potential enhanced sensitivity of infants and children from exposure to clomazone as required by the Food Quality Protection Act (FQPA). The additional 10X safety factor to account for increased sensitivity of infants and children was reduced to 1X by the FQPA Safety Factor Committee (SFC) in a meeting on August 28, 2000. The Committee concluded that the safety factor could be removed for clomazone because: 1) There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; 2) A developmental neurotoxicity study is **not** required; and 3) The dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children (there are currently no registered residential uses).

An acute reference dose (aRfD) of 1.0 mg/kg/day was established for females 13-50 years old based on a developmental no-observed-adverse-effect level (NOAEL) of 100 mg/kg/day from a developmental toxicity study in the rat. An uncertainty factor of 100 (10-fold for interspecies extrapolation and 10-fold for intraspecies variability) was applied to the NOAEL to derive the RfD. The developmental lowest-observed-adverse-effect level (LOAEL) of 300 mg/kg/day was based on indications of delayed ossification in the form of either partial ossification or the absence of the manubrium, sternebrae 3-4, xiphoid, caudal vertebrae, and meta-carpals. The FQPA safety factor of 1X is applicable for acute dietary risk assessment. Thus, the acute

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[1]FMC 87010 = 4',5'-dihydrodiol-5-hydroxy-2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone

[2]FMC 83918 = 4',5'-dihydroxy- 2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone

[3]FMC 60217 = 5'-hydroxy-2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone

population adjusted dose (aPAD) is equivalent to the aRfD of 1.0 mg/kg/day. An aRfD was not established for the U.S. general population, including infants and children, because a dose and endpoint attributable to a single exposure were not identified from the available oral toxicity studies, including maternal toxicity in the developmental toxicity studies.

The chronic reference dose (cRfD) of 0.84 mg/kg/day was determined on the basis of a 2-year combined toxicity/oncogenicity study in rats, a 90-day oral toxicity study in rats, and a 2-generation reproduction toxicity study in rats. The NOAEL of 84.4 mg/kg/day (highest dose tested) from the 2-year chronic/onco rat study was selected. An uncertainty factor (UF) of 100 (10-fold for interspecies extrapolation and 10-fold for intraspecies variability) was applied to the NOAEL of 84.4 mg/kg/day to derive the RfD. In the combined toxicity/oncogenicity study, there were no compound related effects observed. Despite the absence of systemic toxicity at this dose, the HIARC concluded that this dose was adequate to assess the chronic toxicity and carcinogenicity in rats. This conclusion was supported by the results (decreased body weight/body weight gain) observed in the 90-day oral toxicity and the 2-generation reproduction study in rats, two co-critical studies. In the 90-day study, the NOAEL was 160 mg/kg/day and the LOAEL was 319 mg/kg/day based on statistically significant decrease in body weight and body weight gain in female rats. In the 2-generation reproduction study, the NOAEL was 50 mg/kg/day and the LOAEL was 100 mg/kg/day. Even though the NOAEL (50 mg/kg/day) is lower in the 2-generation reproduction study, the HIARC selected the NOAEL (84.4 mg/kg/day) from the 2-year rat study, since the difference is due to differences in the calculated food intake (mg/kg/day) between these two studies. The 2-year rat study used actual consumption data (measured weekly), whereas the two generation study used the standard food conversion values to estimate consumption. Therefore, the chronic study provides more reliable chemical consumption measurements. In addition, in the reproduction study the dose spacing was wider, so the true NOAEL could be higher. The FQPA safety factor of 1X is applicable for chronic dietary risk assessment. Thus, the chronic population adjusted dose (cPAD) is equivalent to the cRfD of 0.84 mg/kg/day.

The HIARC classified clomazone as a "not likely human carcinogen" based on the lack of a carcinogenic response in rats and mice and the lack of mutagenic concern. Therefore, a cancer risk assessment is not required for this action.

Short-term dermal and inhalation endpoints were chosen from a developmental toxicity study in the rat. The maternal NOAEL of 100 mg/kg/day was based on chromorhinorrhea and abdominogenital staining seen at the maternal LOAEL of 300 mg/kg/day. The intermediate- and long-term dermal and inhalation endpoints were chosen from a combined chronic/carcinogenicity study in the rat, a 90-day oral toxicity study in the rat, and a 2-generation reproduction toxicity study in the rat. The NOAEL was 84.4 mg/kg/day (highest dose tested); there were no compound related effects observed. Despite the absence of systemic toxicity at this dose, the HIARC concluded that this dose was adequate to assess the chronic toxicity and carcinogenicity in rats. (See chronic RfD for detailed explanation.) Since an oral route was used, 100% dermal and inhalation absorption factors were used for route-to-route extrapolation. However, since the

uses under consideration in the current risk assessment do not include long-term dermal and inhalation exposure, long-term dermal and inhalation risk assessments were not performed.

Margin of Exposure (MOE): An MOE of 100 is adequate for dermal and inhalation occupational exposure risk assessment.

Occupational Handler Exposures

Based on use patterns, short-term exposures are expected for the private applicators (farmers treating their own crops). Both short- and intermediate-term dermal exposures are expected for the commercial applicators. In the absence of chemical specific data, handler exposures addressing mixer/loaders and applicators have been assessed using data available in the Pesticide Handlers Exposure Database (PHED Ver 1.1, 1998) Surrogate Exposure Guide. As established on the label, the unit exposure corresponding to the 'single layer, gloves' scenarios was used. PHED does not contain exposure scenarios for the ME formulation. The best available surrogate exposure data for the ME formulation is the liquid mixer/loader and applicator scenarios from PHED. These data were used to represent both the EC and ME formulations. The MOEs are 840 and greater for all handling activities for the proposed uses of clomazone. Since HED's level of concern for clomazone is for MOEs below 100, exposure to handlers does not exceed the level of concern.

Occupational Post-application Exposures

Due to the method and timing of applications and typical cultural practices for these crops, low potential for exposure is expected for the proposed uses of clomazone. Therefore, no post-application exposure assessment was done. In lieu of estimating a specific REI, HED recommends a 12-hour REI that follows the Worker Protection Standard (WPS) criteria on setting REIs based on the acute toxicity of the active ingredient. An updated review of clomazone poisoning incident reports shows that relatively few incidents of illness have been reported due to clomazone (Memo. J. Blondell and M. Spann, September 27, 2000, D268806). The emulsifiable concentrate formulation does have a potential for health effects to the skin or eyes if not protected. None of the four exposures reported for the microencapsulated formulation had symptoms that were likely to be related to their exposures.

Dietary Risk Estimates

Tier 1 acute and chronic conservative analyses were performed using existing and proposed tolerance level residues, 100% crop treated (CT) information for all commodities, and DEEM™ default processing factors. For the acute dietary risk, HED's level of concern is >100% aPAD. The acute dietary exposure estimate (food only) for females 13-50 years old (the only population subgroup of concern) was <1% of the aPAD at the 95th percentile. The results of the acute analysis indicate that the estimated acute dietary risk associated with the existing and proposed uses of clomazone is below HED's level of concern for females 13-50 years old. For chronic

dietary risk. HED's level of concern is >100% cPAD. The chronic dietary exposure estimates (food only) for the general U.S. population and all population subgroups were <1% of the cPAD. The results of the chronic analysis indicate that the estimated chronic dietary risk associated with the existing and proposed uses of clomazone is below HED's level of concern for the U.S. population and all population subgroups.

Drinking Water

EFED provided environmental fate and drinking water assessments for both parent clomazone and FMC 65317 [N-[(2-chlorophenol)methyl]-3-hydroxy-2,2-dimethyl propanamide], the major environmental degradate of clomazone. The predicted maximum ground water estimated environmental concentration (EEC) for both parent clomazone and FMC 65317, using the Tier 1 screening model SCI-GROW2 [Screening Concentration in Ground Water], was 2.4 ppb which was considered as both an acute and chronic value for risk assessment purposes. The acute and chronic surface water EECs for both parent clomazone and FMC 65317 were estimated by the Tier 1 screening model GENEEC (Generic Estimated Environmental Concentration) and GENEECX. For surface water, the maximum acute EEC was 95 ppb and the maximum chronic (56-day) EEC was 68 ppb. HED interim policy allows the 56-day GENEEC value to be divided by an adjustment factor of 3 to obtain a value for chronic risk assessment calculations. Therefore, a surface water value of 23 ppb was used for chronic risk assessment.

Aggregate Exposure and Risk Assessment

Acute aggregate risk estimates are below HED's level of concern. A Tier 1 acute dietary exposure analysis for clomazone was performed using existing and proposed tolerance level residues, 100% crop treated for all commodities, and DEEM™ default processing factors. The acute analysis applied to females 13-50 years old only. The acute dietary exposure estimate (food only) for this population subgroup was <1% of the aPAD at the 95th percentile. Thus, the acute dietary risk associated with the existing and proposed uses of clomazone does not exceed HED's level of concern (>100% aPAD). The surface and ground water EECs were used to compare against the back-calculated drinking water level of comparison (DWLOC) for aggregate risk assessment. For ground and surface water, the EECs for clomazone are less than HED's DWLOC for clomazone in drinking water as a contribution to acute aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of clomazone in drinking water do not contribute significantly to the acute aggregate human health risk at the present time.

Chronic aggregate risk estimates are below HED's level of concern. A Tier 1 chronic dietary exposure analysis for clomazone was performed using existing and proposed tolerance level residues, 100% crop treated for all commodities, and DEEM™ default processing factors. The chronic analysis applied to the U.S. population and all population subgroups. The chronic dietary exposure estimates (food only) for the general U.S. population and all population subgroups were <1% of the cPAD. Thus, the chronic dietary risk associated with the existing and proposed uses of clomazone does not exceed HED's level of concern (>100% cPAD). The

surface and ground water EECs were used to compare against back-calculated DWLOCs for aggregate risk assessments. For ground and surface water, the EECs for clomazone are less than HED's DWLOCs for clomazone in drinking water as a contribution to chronic aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of clomazone in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time.

Short- and intermediate-term and cancer aggregate risk assessments were not performed because there are no registered or proposed residential non-food uses and clomazone is not carcinogenic, respectively.

Recommendation for Tolerances and Registration

Provided that Section F is revised, the residue chemistry and toxicological databases support the establishment of the following permanent tolerances for the residues of the herbicide clomazone (2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone) *per se*:

Vegetable, tuberous and corm, except potato, subgroup	0.05 ppm
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Registration should be made conditional upon submission of the following data:

1) Chemistry

- Revised label for Command 3ME.

2) Toxicology

- 21-day dermal toxicity study in rats using the TGAI (OPPTS 870.3200) (data gap).

- 28-day inhalation toxicity study. This study was requested by HIARC for further characterization of inhalation risk assessments. Due to the potential for inhalation exposure, there is concern for toxicity by the inhalation route. The 28-day inhalation toxicity study would give a dose and endpoint examined via the route of exposure of concern (i.e., route specific study) and thus would avoid using an oral study and route-to-route extrapolation. The protocol for the existing 90-day inhalation toxicity study (OPPTS 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.

Note to RD: Although the carcinogenicity study in the mouse (which is graded Unacceptable/guideline) is **not** considered a data gap for the current use pattern, a new

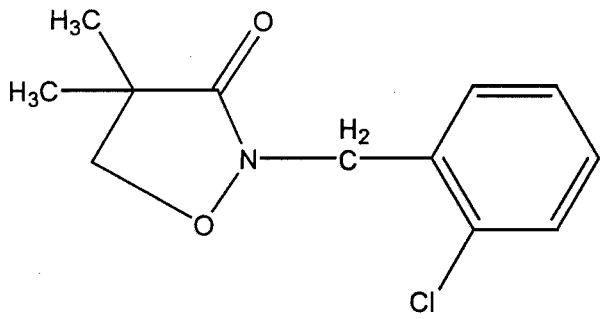
carcinogenicity study in the mouse is required if additional requests for new uses will increase dietary and/or worker exposure.

2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1. Identification of Active Ingredient

Chemical Name:	[(2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone)
Common Name:	Clomazone
Trade Name:	Command
Chemical Type:	Herbicide
PC Code Number:	125401
CAS Registry No.:	81777-89-1
Empirical Formula:	$C_{12}H_{14}ClNO_2$
Molecular Weight:	239.7

2.2. Structural Formula



2.3. Physical and Chemical Properties

Vapor Pressure:	1.4×10^{-4} mm Hg (volatile)
Water Solubility:	1100 ppm
Octanol/Water Partition Coefficient:	350

3.0. HAZARD CHARACTERIZATION

The existing toxicity database for clomazone is adequate for this Food/Feed Use registration, except for the following studies: 1) 21-day dermal toxicity study in rats using the TGAI (OPPTS 870.3200) (a data gap) [guideline requirement (40 CFR 158) for Food/Feed Use]; and 2) 28-day inhalation toxicity study (See Section 6 "Data Gaps" for further explanation).

3.1. Hazard Profile

Clomazone has low acute toxicity (Category III and IV) via oral, dermal and inhalation routes. It

is non-irritating to the eye and mildly irritating to the skin. It is not a skin sensitizer. The primary target organ for clomazone in the rat and dog studies is the liver. It is not a carcinogen in either the rat or mouse. No systemic toxicity was observed at the highest dose tested in the 2-year rat, mouse oncogenicity or chronic dog studies. The doses ranged from 84.8 mg/kg/day for the 2-year rat study to 1038 mg/kg/day for the chronic dog study. There was no evidence of neurotoxicity in either the chronic or subchronic studies. The available genetic toxicology studies indicate that clomazone is not mutagenic in bacteria (*Salmonella typhimurium*) and does not induce chromosomal aberrations in rat bone marrow. Similarly, clomazone did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocyte. Based on the results of acceptable studies, there is no concern for mutagenicity at this time.

There is no quantitative or qualitative evidence of susceptibility of rats or rabbit fetuses to *in utero* exposure in available developmental studies. In the 2-generation reproduction study, no qualitative or quantitative evidence of increased susceptibility was observed.

In a metabolism study in rat, clomazone is absorbed from the digestive tract and extensively metabolized by the liver and excreted in the urine and feces within 24 hours. Sixteen metabolites including the parent compound were identified. The predominant metabolites were FMC 87010[4], FMC 83918[5], and FMC 60217[6]. The predominant route of excretion was in urine (64-83% total recovery of radioactivity). A total of 75-85% of the administered dose was recovered for all routes and doses, except the single high dose females which accounted for 48% (fecal excretion was suppressed in these females). The total recovery after 48 hours was generally comparable between all groups and sexes and ranged from 91-100%. The quantities of metabolites varied with the dose regimen, sex, and route of administration but were the same qualitatively both in the urine and the feces in all groups.

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[4]FMC 87010 = 4',5'-dihydrodiol-5-hydroxy-2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone

[5]FMC 83918 = 4',5'-dihydroxy- 2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone

[6]FMC 60217 = 5'-hydroxy-2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone

Table 1. Acute Toxicity Data on Clomazone Technical

Guideline No./Study Type		MRID #s	Results	Toxicity Category
870.1100	Acute Oral - rat	00117121	LD_{50} = 2077.0 mg/kg ♂ 1369.0 mg/kg ♀	III
870.1200	Acute Dermal - rabbit	00117122	LD_{50} > 2000.0 mg/kg	III
870.1300	Acute Inhalation - rat	00117123	LC_{50} = 6.52 mg/L ♂ 4.23 mg/L ♀	IV
870.2400	Primary Eye Irritation - rabbit	00117124	Almost non-irritating at 1 hour in washed and unwashed eyes	III
870.2500	Primary Skin Irritation - rabbit	00117125	Minimally irritating at 24 and 72 hours	III
870.2600	Dermal Sensitization - guinea pig	00117126	non-sensitizer	N/A

N/A = not applicable

Table 2. Toxicity Profile of Clomazone

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rat	00132586 (1982) Acceptable/guideline Males: 0, 1.4, 6.9, 34.5, 68.2, 135.2, 273, 552.2 mg/kg/day Females: 0, 1.6, 8.2, 41.9, 83.4, 160.9, 319.3, 629.4 mg/kg/day	NOAEL = 135.2/160.9 mg/kg/day, males/females LOAEL = 273/319.3 mg/kg/day, males/females, based on based on decreased body weight, body weight gains, food consumption and increased absolute and relative liver weights in females and increased absolute liver weights in males
870.3100 90-Day oral toxicity mouse	00132585 (1983) Acceptable/guideline 0, 3, 15, 75, 150, 300, 600, 1200 mg/kg/day	NOAEL ≥1200 mg/kg/day (limit dose) LOAEL >1200 mg/kg/day

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a Prenatal developmental rat	00150291 (1984) Acceptable/guideline 0, 100, 300, 600 mg/kg/day (gavage)	**Maternal** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on chromorhinorrhea and/or abdominal staining **Developmental** NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on indications of delayed ossification in the form of either partial ossification or the absence of manubrium, sternebrae 3-4, xiphoid, caudal, and met-carpals
870.3700b Prenatal developmental rabbit	00133220 (1982) Acceptable/guideline 0, 30, 240, 1000/700 mg/kg/day	**Maternal** NOAEL = 240 mg/kg/day LOAEL = 700 mg/kg/day based on effects seen at 1000 mg/kg/day, which included mortality, abortions, decreased body wt. gain, and decreased defecation or no feces **Developmental** NOAEL ≥ 700 mg/kg/day (HDT) LOAEL > 700 mg/kg/day
870.3800 Two-Generation Reproduction and Fertility Effects	00151108 (1984) Acceptable/guideline 0, 5, 50, 100, 200 mg/kg/day	**Parental** NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on statistically significantly decreased body wt. & body wt. gain during pre-mating, and decreased body wt. during gestation & lactation M & F. In addition decreased food consumption in females and hydro-nephritic kidneys in males. **Offspring** NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight in F2a and F2b litters
870.4100b Chronic toxicity dogs	00150290 (1984) Acceptable/guideline Males: 0, 19, 94, 487, 1038 mg/kg/day Females: 0, 21, 106, 502, 1012 mg/kg/day	NOAEL ≥1038/1012 mg/kg/day, males/females (HDT) LOAEL >1038/1012 mg/kg/day

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Chronic Toxicity/ Carcinogenicity rats	00132586 Acceptable/guideline Males: 0, 0.9, 4.3, 21.5, 42.9, 84.8 mg/kg/day Females: 0, 1.1, 5.5, 27.8, 56.5, 112.9 mg/kg/day	NOAEL = 84.4/112.9 mg/kg/day, males/females (highest dose tested) LOAEL >84.4/112.9 mg/kg/day, males/females Classified as a "not likely human carcinogen"
870.4300 Carcinogenicity mice	00132585, 00132587, 00144244 Unacceptable/ guideline 0, 3, 15, 75, 150, 300 mg/kg/day	NOAEL = 300 mg/kg/day (highest dose tested) LOAEL = >300 mg/kg/day Classified as a "not likely human carcinogen"
870.5100 Gene Mutation *(Salmonella typhimurium* and *Escherichia coli* reverse gene mutation assay)	00150292 Acceptable FMC 57020 (clomazone, 93.4% a.i.)	The test article was assayed up to cytotoxic concentrations (5000 μg/plate), but in no instance were appreciably increased number of revertants to histidine prototrophy (*his*$^+$) found in any of the tester strains, either in the presence or absence of metabolic activation.
870.5395 Cytogenetics *In vivo* rat	00133222 Acceptable FMC 57020 (clomazone, 88.8%)	Negative. The incidence of aberrations and the aberrations/cell were not significantly increased.
870.5550 Other Effects *In vitro* UDS assay in primary rat hepatocytes	00133223 Acceptable FMC 57020 (clomazone, 88.8%)	Clomazone was tested up to cytotoxicity (relative toxicity at 0.10 μL/mL was 88.6%), but in no cultures treated with test article was a significant increase in mean net nuclear counts indicative of UDS recorded.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.7485 Metabolism and pharmacokinetics	00142234, 00142233 Acceptable	Clomazone is extensively metabolized by the liver and excreted in the urine and feces within 24 hours. Sixteen metabolites, including the parent, were identified; and the predominant route of excretion was in urine.

3.2. FQPA Considerations

On August 10, 2000, the HIARC reviewed the recommendations of the toxicology reviewer for clomazone with regard to the acute and chronic RfDs and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments (Attachment 1). The potential for increased susceptibility of infants and children from exposure to clomazone was also evaluated as required by the FQPA of 1996. The HIARC concluded the following:

▸The pre- and post-natal toxicology data base for clomazone is complete with respect to FQPA considerations. There is no quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to *in utero* exposure in developmental studies. Although there was a suggestion of susceptibility in the rat developmental study based on the presence of delayed ossification in the fetuses, the HIARC concluded that the fetal effects were no more severe than the maternal effects because:

- there is no dose response relationship for delayed ossification (i.e., absence of increased incidence with increase in dose);
- low fetal/litter incidences;
- delayed ossifications were not considered to be severe; and
- no visceral or skeletal malformations were seen.

▸A developmental neurotoxicity (DNT) study is not required at this time. Neurotoxicity data is not available nor is it required as the chemical is not a cholinesterase inhibitor and has shown no indications of central or peripheral nervous system effects in any other studies and does not appear to be structurally related to any other chemical that causes adverse nervous system effects.

The additional 10X safety factor to account for increased sensitivity of infants and children was reduced to 1X by the FQPA SFC in a meeting on 8/28/00 (Memo, B. Tarplee, September 19, 2000; HED Doc. No. 014327) (Attachment 2). The Committee concluded that the safety factor could be removed for clomazone because:

- There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;
- A developmental neurotoxicity study is **not** required; and
- The dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children (there are currently no registered residential uses).

3.2.1. Cumulative Risk

EPA does not have, at this time, available data to determine whether clomazone has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that clomazone has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether clomazone shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for clomazone need to be modified or revoked.

3.2.2. Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, clomazone may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

3.3. Dose Response Assessment

Acute Dietary Endpoint: An aRfD of 1.0 mg/kg/day was established for females 13-50 years old based on a developmental NOAEL of 100 mg/kg/day from a developmental toxicity study in the rat. An uncertainty factor of 100 (10-fold for interspecies extrapolation and 10-fold for intraspecies variability) was applied to the NOAEL to derive the RfD. The developmental LOAEL of 300 mg/kg/day was based on indications of delayed ossification in the form of either partial ossification or the absence of the manubrium, sternebrae 3-4, xiphoid, caudal vertebrae, and meta-carpals. The skeletal anomalies are presumed to occur after a single dose (acute exposure) and are appropriate for females 13-50 years old since they occur *in utero*. **The FQPA safety factor of 1X is applicable for acute dietary risk assessment. Thus, the aPAD is equivalent to the aRfD of 1.0 mg/kg/day.**

An aRfD was not established for the U.S. general population, including infants and children, because a dose and endpoint attributable to a single exposure were not identified from the available oral toxicity studies, including maternal toxicity in the developmental toxicity studies.

Chronic Dietary Endpoint: The chronic reference dose (cRfD) of 0.84 mg/kg/day was determined on the basis of a 2-year combined toxicity/oncogenicity study in rats, a 90-day oral toxicity study in rats, and a 2-generation reproduction toxicity study in rats. The NOAEL of 84.4 mg/kg/day (highest dose tested) from the 2-year chronic/oncogenicity rat study was selected. An uncertainty factor (UF) of 100 (10-fold for interspecies extrapolation and 10-fold for intraspecies variability) was applied to the NOAEL of 84.4 mg/kg/day to derive the RfD. In the combined toxicity/oncogenicity study, there were no compound related effects observed. Despite the absence of systemic toxicity at this dose, the HIARC concluded that this dose was adequate to assess the chronic toxicity and carcinogenicity in rats. This conclusion was supported by the results (decreased body weight/body weight gain) observed in the 90-day oral toxicity and the 2-generation reproduction study in rats, two co-critical studies. In the 90-day study, the NOAEL was 160 mg/kg/day and the LOAEL was 319 mg/kg/day based on statistically significant decrease in body weight and body weight gain in female rats. In the two generation reproduction study, the NOAEL was 50 mg/kg/day and the LOAEL was 100 mg/kg/day. Even though the NOAEL (50 mg/kg/day) is lower in the 2-generation reproduction study, the HIARC selected the NOAEL (84.4 mg/kg/day) from the 2-year rat study, since the difference is due to differences in the calculated food intake (mg/kg/day) between these two studies. The 2-year rat study used actual consumption data (measured weekly), whereas the 2-generation study used the standard food conversion values to estimate consumption. Therefore, the chronic study provides more reliable chemical consumption measurements. In addition, in the reproduction study the dose spacing was wider, so the true NOAEL could be higher. **The FQPA safety factor of 1X is applicable for chronic dietary risk assessment. Thus, the chronic population adjusted dose (cPAD) is**

equivalent to the cRfD of 0.84 mg/kg/day.

Carcinogenicity: The HIARC classified clomazone as a "not likely human carcinogen" based on the lack of carcinogenic response in rats and mice and the lack of mutagenic concern. [Although the HIARC classified the carcinogenicity study in the mouse as unacceptable/guideline due to no systemic toxicity observed at the highest dose tested, the committee considered that the data were adequate to assess the carcinogenicity in mice. **A new mouse study is not required for the current use pattern; however, if any petitions for new uses will increase dietary and/or worker exposure, a new study will be required.**] Further, there is no data in the literature or structure activity relationship (SAR) information to indicate carcinogenic potential (Yintak Woo personal communication, August 14, 2000). Therefore, a cancer risk assessment is not required.

Dermal Penetration: 100% (a very conservative default value). No dermal absorption studies are available and no dermal absorption values can be estimated from the available data base as there are no two studies in the same species with the same or similar endpoints nor is there any dermal study on the technical material alone. Only a 21-day dermal toxicity study (MRID 40279601) in rabbits with a formulation is available in the data base. This study was not utilized for dermal risk assessment because the test material was a mixture of clomazone and treflon plus (34.55% + 26.24%).

Short-Term Dermal and Inhalation Endpoints: The short-term dermal and inhalation endpoints were chosen from a developmental toxicity study in the rat. The maternal NOAEL of 100 mg/kg/day was based on chromorhinorrhea and abdominogenital staining seen at the maternal LOAEL of 300 mg/kg/day. The maternal NOAEL would be protective of developmental concerns. The 21-day dermal toxicity study done with the mixture is not appropriate for the dermal endpoint. Since an oral NOAEL was selected for both dermal and inhalation endpoints, 100% dermal and inhalation absorption factors were used for route-to-route extrapolation.

Intermediate- and Long-term Dermal and Inhalation Endpoints: The intermediate- and long-term dermal and inhalation endpoints were chosen from a combined chronic/carcinogenicity study in the rat, a 90-day oral toxicity study in the rat, and a 2-generation reproduction toxicity study in the rat. The NOAEL was 84.4 mg/kg/day (highest dose tested); there were no compound related effects observed. In spite of the absence of systemic toxicity at this dose, the HIARC concluded that this dose was adequate to assess the chronic toxicity and carcinogenicity in rats. (See chronic RfD for detailed explanation.) Since an oral route was used, 100% dermal and inhalation absorption factors was used for route-to-route extrapolation. However, since the uses under consideration in the current risk assessment do not include long-term dermal and inhalation exposure, long-term dermal and inhalation risk assessments were not performed.

MOE for Occupational/Residential Risk Assessments: The level of concern for MOEs for

dermal and inhalation occupational exposure risk assessment is 100. For short- and intermediate-term occupational exposure, route-to-route extrapolation was followed: the inhalation (using 100% absorption) and dermal (using 100% absorption) exposures were converted to equivalent oral doses, combined, and then compared to their respective oral NOAELs since both the dermal and inhalation endpoints were based on oral equivalents.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 3.

Table 3. Summary of Toxicological Doses and Endpoints for Use in Human Risk Assessment for Clomazone

EXPOSURE SCENARIO	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary females 13-50 years of age	Developmental NOAEL= 100 mg/kg/day UF = 100 **Acute RfD = 1.0 mg/kg/day**	FQPA SF = 1X **aPAD = acute RfD / FQPA SF =1.0 mg/kg/day**	Developmental rat Developmental LOAEL = 300 mg/kg/day, based on delayed ossification
Acute Dietary general population including infants and children	A dose and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure (dose). A risk assessment is not required for this population subgroup.		

EXPOSURE SCENARIO	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Chronic Dietary <u>all populations</u>	NOAEL = 84.4 mg/kg/day UF = 100 **Chronic RfD = 0.84 mg/kg/day**	FQPA SF = 1X **cPAD = <u>cRfD</u> = FQPA SF** **0.84 mg/kg/day**	Two year rat feeding study LOAEL > 84.4 mg/kg/day (highest dose tested) 90-day oral rat LOAEL = 319.3 mg/kg/day based on based on decreased body weight, body weight gains, food consumption and increased absolute and relative liver weights in females and increased absolute liver weights in males 2-Gen Repro. LOAEL = 100 mg/kg/day based on statistically significantly decreased body wt. & body wt. gain during pre-mating, and decreased body wt. during gestation & lactation M & F. In addition decreased food consumption in females and hydro-nephritic kidneys in males.
Oral, Short-term (1-7 days) (Residential)	No residential uses. An endpoint was not proposed/selected.		
Oral, Intermediate-term (1 week - several months) (Residential)	No residential uses. An endpoint was not proposed/selected.		
Dermal[a] and Inhalation[b], Short-Term (1-7 days) (Occupational/ Residential)	Maternal NOAEL= 100 mg/kg/day	LOC for MOE = 100	Developmental rat study Maternal LOAEL = 300 mg/kg/day, based on chromorhinorrhea and abdominogenital staining

EXPOSURE SCENARIO	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Dermal[a] and Inhalation[b], Intermediate-term (1week - several months) and Long-Term (several months - lifetime) (Occupational/ Residential)	Oral NOAEL= 84.4 mg/kg/day	LOC for MOE = 100	Two year rat feeding study LOAEL > 84.4 mg/kg/day (highest dose tested) 90-day oral rat LOAEL = 319.3 mg/kg/day based on based on decreased body weight, body weight gains, food consumption and increased absolute and relative liver weights in females and increased absolute liver weights in males 2-Gen Repro. LOAEL = 100 mg/kg/day based on statistically significantly decreased body wt. and body wt. gain during pre-mating, and decreased body wt. during gestation & lactation M & F. In addition decreased food consumption in females and hydro-nephritic kidneys in males.

UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern

[a] Since an oral NOAEL was selected, an dermal absorption factor of 100% (default value) should be used in route-to-route extrapolation.

[b] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

4.0. EXPOSURE ASSESSMENT

4.1. Summary of Proposed Uses

Rice: For use on rice, Command 3ME, a microencapsulated formulation, (EPA Registration #279-3158) is applied at a rate of 0.4 to 0.6 lb a.i./A (depending on soil texture) in a minimum of 10 to 40 gallons of water per acre. A single broadcast application is specified from 14 days prior to planting until 7 days after planting, but prior to weed emergence The label prohibits use of this product in California, use in conjunction with aquaculture and use with water-seeded rice. The re-use of water containing clomazone

residues for irrigating crops not registered for use with clomazone is also restricted. A 65-day preharvest interval (PHI) is proposed. HED notes that this PHI is significantly shorter than the minimum PHI represented in the crop field trials (100 days). The PHI should be revised to reflect these data. Alternatively, the petitioner may choose to omit a numerical PHI from the label as the application and harvest times are controlled by the growth stages of the rice. **A revised Command 3ME label is required.**

Tanier, cassava, yams, and arracacha: For use on these crops, Command 4EC (EPA Registration #279-3053) is applied at a rate of 0.75 to 1.5 lb a.i./A in a minimum of 10 gallons of water per acre. A single broadcast application is specified for either preplant incorporated or to the soil post-planting prior to crop emergence. A 125-day PHI is proposed.

Cucurbit vegetables: For use on these crops, Command 4EC is applied at a maximum rate of 1.0 lb a.i./A (pumpkins and winter squash) or 0.5 (all other cucurbits) lb a.i./A in a minimum of 10 gallons of water per acre. A single broadcast application is specified for prior to crop seeding.

Adequate rotational crop guidelines are included in the labels for Command 3ME and Command 4EC. These guidelines state that the primary crops cotton, peas, peppers, pumpkins, soybeans and tobacco may be rotated at anytime. After nine months, the following crops may be rotated:

Cotton	Dry beans	Sweet potatoes
Corn	Peanuts	Tomatoes (transplanted)
- field	Potatoes	Cucurbits
- pop	Rice	Sugar beets
- seed	Snap beans	
- sweet	Sorghum	

After 12-16 months, all crops may be rotated. The label also includes the statement "do not graze or harvest for food or feed cover crops planted less than nine months after Command 3ME treatment."

4.2. Dietary Exposure

4.2.1. Food Exposure

4.2.1.a. Nature of the Residue

Plants: Based on metabolism studies on soybeans (PP#4G2987, L. Propst, 4/17/84; summarized in PP#4F3128, J. Worthington, 9/24/84), corn (PP#0G3919, J. Garbus, Ph.D., 11/8/91), cotton (PP#2F4077, R.W. Cook, 10/28/92), sweet potatoes (PP#8E3628, M. J.

Nelson, 4/22/92), tomatoes and bell peppers (PP#9E3778, F. D. Griffith, 8/6/90) and alfalfa (PP#8E3608, A. Smith, 3/15/88), HED concludes that the nature of the residue in plants is adequately understood. The major metabolite was 2-chlorobenzyl alcohol. The postulated major route of metabolism of clomazone in plants is hydroxylation of the methylene bridge carbon of clomazone to form the carbinolamide; decomposition of the unstable intermediate the carbinolamide to form the isoxazolidinone moiety and 2-chlorobenzaldehyde. 2-chlorobenzaldehyde reduces to the alcohol or is oxidized to the carboxylic acid. The alcohol, the carboxylic acid, and the isoxazolidinone metabolites form glycosides and/or amino acid conjugates. Minor pathways include hydroxylation of clomazone to form monohydroxylated and possibly dihydroxylated metabolites. Based on low levels of these metabolites found in crops, the residue of concern for regulatory and risk assessment purposes in plants is clomazone *per se* (PP#8E3628, M. J. Nelson, 4/22/92).

Livestock: Based on the low TRR levels observed in a goat metabolism study, HED previously concluded that the nature of the residue in ruminants is adequately understood and the residue of concern is parent clomazone *per se* (7/26/89, F. D. Griffith, PP0G3919).

Based on the low TRR levels observed in a poultry metabolism study, HED previously concluded that for regulatory purposes, clomazone *per se* is the residue of concern (11/8/91, J. Garbus, PP0G3919).

The residue of concern for regulatory and risk assessment purposes in ruminants and poultry is clomazone *per se.*

4.2.1.b. Residue Analytical Methods

Adequate enforcement methods are available for the determination of the residues of clomazone in plants. Briefly, samples are acid hydrolyzed, hexane extracted, Na_2CO_3 washed, and cleaned-up with a Florisil® column. The resulting samples are analyzed by gas chromatography (GC) using a nitrogen phosphorus detector (NPD) or mass spectrometer (MS). The limit of quantitation (LOQ) for this method is 0.05 ppm. A confirmatory procedure (GC/MS-SIM) is available (Method I, PAM II).

4.2.1.c. Multiresidue Method

Clomazone is adequately recovered (>80%) using the published PAM I multiresidue methods (Pestrak, 1990).

4.2.1.d. Crop Field Trials

Rice: A total of 18 field trials were performed; 13 in EPA Region IV, 2 in EPA Region V and 3 in EPA Region VI (Memo Mark Perry, 1/29/98; D242601). The states represented in

this study comprise 85% of the U.S. rice production. Each trial was divided into a single untreated control plot and 3 treatment plots which received applications at different growing periods. Command 3ME was applied to one plot at pre-plant (incorporated), a second plot at pre-emergence and a third plot at early post-emergence. Applications to the treated plots were made by backpack or tractor-mounted broadcast spray at the maximum label rate of 0.6 lb a.i./acre. Samples of rice grain and rice straw were collected at normal harvest, from 100 to 209 days after application. The data collection method was adequately validated. Clomazone residues resulting from microencapsulated, pre-emergent applications were not detected in any samples for either study at or above the LOD (0.01 ppm) or LOQ (0.02 ppm).

Tanier, cassava, yams, and arracacha: The proposed directions for use of clomazone on tanier, cassava, yams, and arracacha are the same as those already specified for sweet potatoes on the Command 4 EC label. Tanier, cassava, yams, and arracacha are members of Crop Subgroup 1-D (Tuberous and corm vegetables), for which sweet potato is the representative commodity. IR-4 has proposed to establish tolerances for tanier, cassava, yams, and arracacha based on the existing data on sweet potatoes. No new data were submitted with this petition. As a tolerance is established on sweet potatoes at 0.05 ppm, additional data are not required for tanier, cassava, yams, and arracacha (Memo, George Kramer, 9/7/00; D268283). However, it is preferable to set a crop group tolerance rather than tolerances on the individual commodities. A tolerance of 0.05 ppm should be proposed for residues of clomazone in/on the "Vegetable, tuberous and corm, except potato, subgroup." **A revised Section F is required.**

Cucurbit vegetables: Muskmelon field trials were performed in TX, SC, MI and CA; watermelon trials, in TX, SC, GA, WA, FL and CA (Memo Mark Perry, 10/24/97; D238491). Command 4EC was applied pre-plant (incorporated) at rates of 0.25 lb a.i./acre or 0.5 lb a.i./acre (1X). Samples of melon were collected at normal harvest, from 50 to 112 days after application. Clomazone residues resulting from pre-emergent applications were not detected in any samples for either study at or above the LOQ (0.05 ppm). Muskmelons and watermelon are commodities within the cucurbit vegetables crop group (Crop Group 9), the representative commodities of which are cucumber, summer squash, and muskmelon. Tolerances of 0.1 ppm already exist (40 CFR 180.425) for residues of clomazone in/on cucumber and summer squash, both of which are also commodities within crop group 9. As adequate residue data are now available for all of the representative commodities of the cucurbit vegetables crop group, a crop group tolerance is appropriate. However, clomazone residues were <0.05 ppm in all of the representative commodities (Memos M. Perry, 10/24/97; D238491 & M. J. Nelson 4/15/95; D204737). The appropriate tolerance level is thus 0.05 ppm. Also, the correct commodity definition is "Vegetable, cucurbit, group." **A revised Section F is required.**

4.2.1.e. Processed Food/Feed

Rice: Command 4EC was applied pre-emergent to a single plot at the exaggerated rate of 1.25 lb a.i./acre (2X). The trial was performed in EPA Region IV (Louisiana). Rice was grown under normal agricultural practices and sampled at the normal harvest time. The samples were frozen and a grain subsample was sent to TX A&M U. for processing into polished rice, hulls, bran and grain dust. At an exaggerated application rate of 1.25 lb a.i./acre, no clomazone residues were detected in any samples. However, HED generally require that the processing study be performed at a rate of ≥5X if there is a potential for concentration in the processed commodities of >5X (the maximum theoretical concentration factor for rice bran = 7.7X). Given that residues were <0.01 ppm (LOD) at 2X, HED considers it unlikely that quantifiable residues (>LOQ, 0.02 ppm) would be present at a 5X rate. This processing study is thus acceptable. Therefore, a tolerance on polished rice is not required. **A revised Section F, in which the polished rice tolerance is deleted, should be submitted.**

4.2.1.f. Meat, Milk, Poultry, Eggs

The use of treated rice grain, straw, hulls and bran as livestock feed/feedstuff will not result in detectable residues of clomazone in milk, meat, poultry or eggs (Memo, Mark Perry, 1/29/98; D242601). This conclusion is supported by a ruminant metabolism study which demonstrated that 5 ppm clomazone in the livestock diet resulted in 2 to 9 ppb in milk, and 0.03 to 0.05 ppm in the liver and kidney tissue (Memo Joel Garbus, 11/8/91; PP#0G3919). Similarly, high clomazone doses in poultry also yielded low levels in tissue and eggs (Memo Joel Garbus, 11/8/91; PP#0G3919). Since, under the proposed use, clomazone is not detectable in livestock feed/feedstuff (<0.05 ppm) and it is transferred to meat, milk, poultry and eggs at a low level, no detectable residues are expected in meat, milk, poultry and eggs (40 CFR 180.6(a)(3)- "no reasonable expectation of finite residues") (Memo Mark Perry, 1/29/98; D242601). Note that should additional uses increase the dietary burden, the need for livestock tolerances will be reevaluated.

4.2.1.g. Confined Accumulation in Rotational Crops

The minimum plantback interval, 9 months, has been approved by EFED (Memo Carolyn Offutt, 7/2/85). This restriction was based on low levels of organosoluble residues (<0.02 ppm) observed at the 10-month interval in the confined rotational crop study conducted at an application rate of 2 lbs a.i./A EFED (Memo Samuel Creeger, 8/27/85).

4.2.1.h. International Harmonization of Tolerances

There is neither a Codex proposal, nor Canadian or Mexican limits for residues of clomazone in/on the subject crops. Therefore, a compatibility issue is not relevant to the proposed tolerance. A copy of the International Residue Limit Status (IRLS) sheet is

attached (Attachment 3).

4.2.2. Dietary Exposure and Risk Analyses

HED conducts dietary (food only) risk assessments using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic exposure/risk assessment, or be used with a residue distribution in a probabilistic type risk assessment. Acute exposure estimates are expressed in mg/kg bw/day and as a percent of the aPAD. For chronic risk assessments, residue estimates for foods or food-forms of interest are multiplied by the average consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD.

4.2.2.a. Acute Dietary Exposure Analysis

A Tier 1 acute analysis was performed for females 13-50 years old using existing and recommended tolerance level residues, 100% CT information, and DEEM™ default processing factors (Attachment 4). The aPAD for females 13-50 years old is 1.0 mg/kg/day. The acute dietary exposure estimate at the 95th percentile for females 13-50 years old is presented in Table 4.

Table 4. Summary of Results from Acute DEEM ™ Analysis of Clomazone at the 95th Percentile

Subgroup	95th Percentile	
	Exposure (mg/kg/day)	% aPAD
Females (13-50 years old)	0.000265	<1

The acute exposure estimate for females 13-50 years old accounted for <1% of the aPAD at the 95th percentile. For acute dietary risk estimates, HED's level of concern is >100% aPAD. The results of the acute analysis indicate that the acute dietary risk estimates for females 13-50 years old (at the 95th percentile) associated with the existing and proposed uses of clomazone do not exceed HED's level of concern.

4.2.2.b. Chronic Dietary Exposure Analysis

A Tier 1 chronic analysis was performed for the general U.S. population and all population subgroups using existing and recommended tolerance level residues, 100% CT information, and DEEM™ default processing factors (Attachment 4). The cPAD for the

general U.S. population and all population subgroups is 0.84 mg/kg/day. Chronic dietary exposure estimates for the U.S. population and other representative population subgroups (i.e., children, infants, females, and males) are presented in Table 5.

Table 5. Summary of Results from Chronic DEEM ™ Analysis of Clomazone.

Subgroups[a]	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.000099	<1
All Infants (< 1 year old)	0.000332	<1
Children 1-6 years old	0.000182	<1
Children 7-12 years old	0.000122	<1
Females 13-50 years old	0.000079	<1
Males 13-19 years old	0.000085	<1
Males 20+ years old	0.000080	<1
Seniors 55+ years old	0.000091	<1

[a]HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys, (e.g., nursing and non-nursing infants or Hispanics). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years).

The chronic exposure estimates for the general U.S. population and all population subgroups accounted for <1% of the cPAD. For chronic dietary risk estimates, HED's level of concern is >100% cPAD. The results of the chronic analysis indicate that the chronic dietary risk estimates for the general U.S. population and all population subgroups associated with the existing and proposed uses of clomazone do not exceed HED's level of concern.

4.2.3. Drinking Water

The HED Metabolism Assessment Review Committee (MARC) determined that both parent clomazone and its major environmental degradate FMC 65317 [N-[(2-chlorophenol)methyl]-3-hydroxy-2,2-dimethyl propanamide] should be included in a drinking water assessment (Memo, G. Kramer and J. Kidwell, October 2, 2000, D268905). Therefore, EFED provided environmental fate and drinking water assessments for both parent clomazone and FMC 65317 (Memo, J. Breithaupt, October 23, 2000, D269748; Memo, J. Breithaupt and M. Davy, May 31, 2000, DP Barcodes D173566, D249776, D249336, D261480, D259637, D248879, D254113, D249719, D238706, D259620, D259751, D259810, D262091, D263269). Since no monitoring data are available for clomazone, modeled concentrations were used. The EECs were based on the proposed uses of clomazone as specified on the Command 3ME® label.

4.2.3.a. Environmental Fate Assessment

Based on acceptable environmental fate studies and other information submitted to OPP, degradation and transport of clomazone residues from the site of application by volatility appear to be the principal routes of dissipation in the environment. Laboratory data indicate that clomazone is metabolized in soil under aerobic conditions and is potentially mobile to relatively mobile. Clomazone is stable to hydrolysis and to photolysis on soil, and essentially stable to photolysis in water (half-life of 87 days). The aerobic soil metabolism half-lives ranged from 128-173 days, with the primary degradate being CO_2 and bound residues. However, the anaerobic soil metabolism half-life was shorter at 13 days, with the primary degradate being FMC 65317. Clomazone is stable to anaerobic and aerobic aquatic metabolism with half-lives of 44 and 63 days, respectively. Clomazone is relatively mobile in soil and can be removed from soil by water. The primary anaerobic soil metabolite, FMC 65317, is also very mobile. In the field, half-lives for parent clomazone ranged from 16-139 days, with no evidence of leaching to lower soil depths.

4.2.3.b. Ground Water EEC

The predicted maximum ground water EEC for both parent clomazone and FMC 65317, using the Tier 1 screening model SCI-GROW2 [Screening Concentration in Ground Water], was 2.4 ppb which was considered as both an acute and chronic value for risk assessment purposes.

4.2.3.c. Surface Water EECs

The maximum acute and chronic surface water EECs for both parent clomazone and FMC 65317 were estimated by the Tier 1 screening model GENEEC (Generic Estimated Environmental Concentration) and GENEECX. For surface water, the maximum acute EEC was 95 ppb and the maximum chronic (56-day) EEC was 68 ppb. HED interim policy allows the 56-day GENEEC value to be divided by an adjustment factor of 3 to obtain a value for chronic risk assessment calculations. Therefore, a surface water value of 23 ppb was used for chronic risk assessment.

4.2.3.d. DWLOCs

A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

HED has calculated DWLOCs for acute and chronic exposure to clomazone in surface and ground water (See Table 7). To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from DEEM™) was subtracted from the aPAD to obtain the acceptable acute exposure to clomazone in drinking water. To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM™) was subtracted from the cPAD to obtain the acceptable chronic exposure to clomazone in drinking water. DWLOCs were then calculated using the default body weights and drinking water consumption figures listed in Table 6 below.

Table 6. Default Body Weight and Drinking Water Consumption Figures

DEEM Population	Body Weights (kg)	Drinking Water Consumption (liters/day)
U.S. Population/48 States	70	2
Females 13-50 years old	60	2
Infants/children	10	1

Calculation for acute and chronic exposures:

$$DWLOC\ (\mu g/L) = \frac{water\ exposure\ (mg/kg/day)\ x\ body\ weight\ (kg)}{consumption\ (L/day)\ x\ 0.001\ mg/\mu g}$$

The DWLOCs for the acute and chronic scenarios are listed in Table 7.

Table 7. DWLOCs

Scenario/Population Subgroup	DWLOC (ppb)
Acute	
Females 13-50 years old	30,000
Chronic	
U.S. Population (total)	29,000
All Infants (< 1 year old)	8400
Children 1-6 years old	8400
Children 7-12 years old	8400
Females 13-50 years old	25,000
Males 13-19 years old	29,000
Males 20+ years old	29,000

Scenario/Population Subgroup	DWLOC (ppb)
Seniors 55+ years old	29,000

4.3. Occupational/Residential Exposure

4.3.1. Summary of Use Patterns and Formulations

The assessment addresses the registration of the active ingredient clomazone on rice, cucurbits, and root crops. For these actions, two formulations will be used for control of broadleaf weeds and grasses. The Command 3 ME (31.4% clomazone) formulation will be used on dry-seeded rice crops while Command EC (46.7% clomazone) will be used on cucurbits and root crops. A single ground application will be made at a maximum of 1.5 lbs ai/Acre on root crops, 1.0 lbs ai/Acre on cucurbits, and 0.6 lbs ai/Acre on rice. The proposed label suggests that application to root crops and cucurbits be made before or after plant and can be soil incorporated. Applications to rice may take place prior to crop emergence or in the early post-emergent (1-2 leaf) stage of growth. The PHIs are 125 days and 65 days for root crops and rice, respectively. No PHI is listed for cucurbits. Table 8 summarizes the use pattern of clomazone for the proposed uses. Currently there are no registered or proposed residential uses of clomazone.

Table 8. Use Pattern Summary of Clomazone on Root crops, Cucurbits, and Rice

Crops	cucurbits	root crops-tanier, cassava, yams, arracacha	dry-seeded rice
Formulation	Command 4EC (emulsifiable concentrate)		Command 3ME (micro encapsulated)
Pests	broadleaf weeds and grasses		
Application methods	groundboom sprayer		
Maximum application rate (AR)	1.0 lbs ai/Acre	1.5 lb a.i/Acre	0.6 lbs ai/Acre
Maximum number of applications	1		
Manufacturer	FMC		

4.3.2. Occupational Exposure Assessment

Mixer/Loader/Applicator Exposure Assessment

Based on use patterns, short-term exposures are expected for private applicators (farmers treating their own crops). Both short- and intermediate-term dermal exposures are expected for commercial applicators. Since clomazone is applied once per year, long-term exposures from the proposed uses are not expected.

In the absence of chemical specific data, handler exposures addressing mixer/loaders and applicators have been assessed using data available in the Pesticide Handlers Exposure Database (PHED Ver 1.1, 1998) Surrogate Exposure Guide. As established on the label, the unit exposure corresponding to the 'single layer, gloves' scenarios was used. PHED does not contain exposure scenarios for the ME formulation. The best available surrogate exposure data for the ME formulation is the liquid mixer/loader and applicator scenarios from PHED. These data were used to represent both the EC and ME formulations.

Table 9 lists the worker exposure and risk assessment for the proposed uses of clomazone. Exposure calculations were done only for root crops and rice. Since ground applications of Command EC may be made to both root crops and cucurbits and cucurbits have a lower application rate than root crops, exposure calculations were done only for root crops. The exposure estimates for root crops are expected to represent a high-end exposure scenario for the proposed uses for both crop groups.

Table 9: Exposure and Risk Estimates for Workers Handling Clomazone EC Formulation

Exposure Scenario	Unit Exposure[a] mg/lb ai dermal/inhalation		AR (lbs ai/A)	Acres/ Day[b]	Average Daily Dose[c](mg/kg/day) short/intermediate		Combined MOE[d]	
							Short	Intermediate
rice crops								
Open mixing- liquid	dermal	0.023	0.6	200	0.05	0.04	2100	2000
	inhalation	0.0012			0.002	0.002		
Groundboom-open cab	dermal	0.014			0.03	0.02	3400	3300
	inhalation	0.00074			0.001	0.001		
Mixer/loader/ applicator (MLAP) Groundboom- open pour, open cab	dermal	0.057			0.11	0.10	860	840
	inhalation	0.0013			0.003	0.002		
root crops								
Open mixing- liquid	dermal	0.023	1.5	80	0.05	0.04	2100	2000
	inhalation	0.0012			0.002	0.002		
Groundboom-open cab	dermal	0.014			0.03	0.02	3400	3300
	inhalation	0.00074			0.001	0.001		
Mixer/loader/ applicator (MLAP) Groundboom- open pour, open cab	dermal	0.057			0.11	0.10	860	840
	inhalation	0.0013			0.003	0.002		

[a] Source: Pesticide Handlers Exposure Database (PHED) V1.1, Surrogate Exposure Table. HIGH Confidence Data. PPE = single layer + gloves.

[b] Acreage obtained from Standard Daily Area Treated, Exposure Sac, 7/5/00.

[c] ADD = Unit exposure(ug/lb ai) x AR x Acres/Day x 1/BW (60 kg used for short-term and 70 kg used for intermediate-term) x %Dermal Absorption (100% for dermal and inhalation routes)

[d] Combined MOE =NOAEL/Total Exposure; short-term dermal and inhalation NOAEL = 100 mg/kg/day(Developmental rat study); intermediate-term dermal and inhalation NOAEL = 84.4 mg/kg/day(2-year rat feeding study). *The level of concern is for MOEs below 100.*

The MOEs are 840 and greater for all handling activities for the proposed uses of clomazone. Since HED's level of concern for clomazone is for MOEs below 100, exposure to handlers do not exceed the level of concern.

Post-Application Exposure Assessment

For the proposed uses on cucurbits and root crops, clomazone may be applied pre-emergent, and may be soil incorporated. Therefore, minimal potential for post-application exposure is expected for the proposed uses on root crop and cucurbits.

For the proposed use on rice, clomazone may be applied pre-emergent or in the early post-

emergent stage of growth. According to the label, Command ME will not be applied to water-seeded rice or rice planted in sand or sandy loam soil. The label also states that planting may occur up to 7 days after application and lists a PHI of 65 days. For these reasons, the greatest potential for post-application exposures is expected during planting. Dryland rice is mechanically seeded with a grain drill, flooded, and drained. Then, once the rice has emerged, it is flooded again in increments as the rice grows. Once the crop has been flooded, essentially no activities resulting in dermal exposure occur. Rice is harvested mechanically (Personal Communication, C.Cook, Biological and Economic Analysis Division, to M.Dow, HED).

Due to the method and timing of applications and typical cultural practices for these crops, low potential for post-application exposure is expected for the proposed uses of clomazone. HED has determined that a specific postapplication exposure assessment is not necessary for these scenarios. This determination is based on the following: (1) routine hand labor activities that involve significant contact with the treated soil/planting medium are not required, or are not required for several weeks or months after the application, and (2) reentry activities that may be necessary are likely to result in relatively low levels of dermal exposure because contact with the treated medium is minimal or infrequent (ExpoSac Policy #008, 3/1/99).

Therefore, in lieu of estimating a specific REI, HED recommends a 12-hour REI that follows the Worker Protection Standard (WPS) criteria on setting REIs based on the acute toxicity of the active ingredient. This will provide some measure of protection to workers who re-enter treated areas for non-routine activities which may result in contact with treated surfaces (ExpoSac Policy #008, 3/1/99). Since no potentially significant post-application exposure is expected, this exposure assessment was not conducted.

REI

Clomazone is in toxicity category III for the dermal and ocular routes of exposure. Based on the WPS, an REI of 12 hours is sufficient to protect workers performing re-entry activities for the proposed use of clomazone.

Incident Reports

An updated review of clomazone poisoning incident reports shows that relatively few incidents of illness have been reported due to clomazone (Memo, J. Blondell and M. Spann, September 27, 2000, D268806). The emulsifiable concentrate formulation does have a potential for health effects to the skin or eyes if not protected. None of the four exposures reported for the microencapsulated formulation had symptoms that were likely to be related to their exposures.

4.4 Non-occupational Off-Target Exposure

This assessment for clomazone reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-*

Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment* presented at the September 1999 meeting of the FIFRA Scientific Advisory Panel (SAP). The Agency is, however, currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; exposures to farm worker children; and exposures to children in schools.

5.0. AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for the following: acute aggregate exposure (food + drinking water) and chronic aggregate exposure (food + drinking water). Short- and intermediate-term and cancer aggregate risk assessments were not performed because there are no registered or proposed residential non-food uses and clomazone is not carcinogenic, respectively.

5.1. Acute Aggregate Risk (food + drinking water)

Acute aggregate risk estimates are below HED's level of concern. A Tier 1 acute dietary exposure analysis for clomazone was performed using existing and proposed tolerance level residues, 100% CT for all commodities, and DEEM™ default processing factors. The acute analysis was performed for females 13-50 years old. The acute dietary exposure estimate (food only) for this population subgroup was <1% of the aPAD at the 95th percentile. Thus, the acute dietary risk associated with the existing and proposed uses of clomazone does not exceed HED's level of concern (>100% aPAD). The surface and ground water EECs were used to compare against the back-calculated DWLOC for aggregate risk assessment. For ground and surface water, the EECs for clomazone are less than HED's DWLOC for clomazone in drinking water as a contribution to acute aggregate exposure (Table 10). Therefore, HED concludes with reasonable certainty that residues of clomazone in drinking water do not contribute significantly to the acute aggregate human health risk at the present time.

Table 10. Acute Aggregate Exposure

Scenario/Population Subgroup	aPAD, mg/kg/day	Dietary Exposure, mg/kg/day	Allowable Drinking Water Exposure[1], mg/kg/day	DWLOC, ppb	Surface Water, ppb	Ground Water, ppb
Females 13-50 yrs old	1	0.000265	1	30,000	95	2.4

[1]Allowable Drinking Water Exposure (mg/kg/day) = aPAD (mg/kg/day) - Dietary Exposure from DEEM (mg/kg/day)

5.2. Chronic Aggregate Risk (food + drinking water)

Chronic aggregate risk estimates are below HED's level of concern. A Tier 1 chronic dietary exposure analysis for clomazone was performed using existing and proposed tolerance level residues, 100% CT for all commodities, and DEEM™ default processing factors. The chronic analysis applied to the U.S. population and all population subgroups. The chronic dietary exposure estimates (food only) for the general U.S. population and all population subgroups were <1% of the cPAD. Thus, the chronic dietary risk associated with the proposed uses of clomazone does not exceed HED's level of concern (>100% cPAD). The surface and ground water EECs were used to compare against back-calculated DWLOCs for aggregate risk assessments. For ground and surface water, the EECs for clomazone are less than HED's DWLOCs for clomazone in drinking water as a contribution to chronic aggregate exposure (Table 11). Therefore, HED concludes with reasonable certainty that residues of clomazone in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time.

Table 11. Chronic Aggregate Exposures

Scenario/ Population Subgroup	cPAD, mg/kg/day	Dietary Exposure, mg/kg/day	Allowable Drinking Water Exposure[1], mg/kg/day	DWLOC, ppb	Surface Water, ppb	Ground Water, ppb
U.S. Population	0.84	0.000099	0.84	29,000	23	2.4
All infants (< 1 year old)	0.84	0.000332	0.84	8400	23	2.4
Children (1-6 years old)	0.84	0.000182	0.84	8400	23	2.4
Children (7-12 years old)	0.84	0.000122	0.84	8400	23	2.4
Females (13-50 years old)	0.84	0.000079	0.84	25,000	23	2.4
Males (13-19 years old)	0.84	0.000085	0.84	29,000	23	2.4
Males (20+ years old)	0.84	0.000080	0.84	29,000	23	2.4

Seniors (55+ years old)	0.84	0.000091	0.84	29,000	23	2.4

[1]Allowable Drinking Water Exposure (mg/kg/day) = cPAD (mg/kg/day) - Chronic Dietary Exposure from DEEM (mg/kg/day)

6.0. DATA GAPS

6.1 Chemistry

- Revised label for Command 3ME.

6.2. Toxicology

- 21-day dermal toxicity study in rats using the technical grade active ingredient (TGAI) (OPPTS 870.3200) (data gap).

- 28-day inhalation toxicity study. This study was requested by HIARC for further characterization of inhalation risk assessments. Due to the potential for inhalation exposure, there is concern for toxicity by the inhalation route. The 28-day inhalation toxicity study would give a dose and endpoint examined via the route of exposure of concern (i.e., route specific study) and thus would avoid using an oral study and route-to-route extrapolation. The protocol for the existing 90-day inhalation toxicity study (OPPTS 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.

- Although the carcinogenicity study in the mouse, which is graded Unacceptable/guideline, is **not** considered a data gap for the current use pattern, a new carcinogenicity study in the mouse is required if additional requests for new uses will increase dietary and/or worker exposure.

Attachment 1: Hazard Identification Assessment Review Committee Report
Attachment 2: FQPA Safety Factor Committee Report
Attachment 3: IRLS Form
Attachment 4: Dietary Exposure Analyses
Attachment 5: Drinking Water Assessment for Clomazone
Attachment 6: Incident Report

cc (with attachments): J. Kidwell (RAB1), D. Vogel (RAB1), J. Rowell (RAB1), G. Kramer (RAB1)
RDI: RAB1 Toxicologists (9/12/00), RAB1 Chemists (9/12/00), Team (9/12/00), Branch (9/20/00), G. Herndon, Acting BSS (10/26/00)
J. Kidwell:806S:CM#2:(703)305-7472:7509C:RAB1

ATTACHMENT 1 - Hazard Identification Assessment Review Committee Report
(*Available Electronically*)

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

014299

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: August 14, 2000

MEMORANDUM

SUBJECT: ***CLOMAZONE*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Guruva B. Reddy 8/15/00
Registration Action Branch 1
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 8/28/00
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: George Kramer, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 125401

On August 10, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for CLOMAZONE with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to CLOMAZONE was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were: Bill Burnam, Elizabeth Doyle, Pamela Hurley, Tina Levine, Elizabeth Mendez, David Nixon, Ayaad Assaad, Jonathan Chen and Jess Rowland.

Member(s) in absentia: Yung Yang

Data evaluation prepared by: Guruva B. Reddy, Registration Action Branch 1

Also in attendance were: Karen Whitby, Marion Copley, and P.V. Shah from HED

Data Evaluation / Report Presentation

Guruva B. Reddy
Toxicologist

1. INTRODUCTION

On August 10, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for CLOMAZONE with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to CLOMAZONE was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

2. HAZARD IDENTIFICATION

2.1.1 Acute Reference Dose (RfD)

For Females 13 - 50

Study: Developmental Toxicity Rat Guideline #:83-3

MRID No.: 00150291

Executive Summary: : One-hundred assumed pregnant Sprague-Dawley rats were divided into four groups of 25 and orally gavaged with either 100, 300 or 600 mg/kg of test material from days 6-15 of gestation. One additional group served a vehicle control group and received only corn oil. Dams were sacrificed on day 20 of gestation and necropsied. Half the viable fetuses were examined for skeletal effects using a modification of the Wilson technique and half examined for visceral effects. Standard statistical analysis were conducted on 13 of 15 parameters covering both dams and fetuses. (MRID No.00150291).

There were no compound related deaths. Non-treatment related deaths were associated with esophageal or lung puncture during the administration of compound. **Clinical signs** were observed only in dams receiving 300 and 600 mg/kg/d. Signs seen at 300 mg/kg/d consisted of chromorhinorrhea and/or abdominogenital staining in 4/24 dams. Signs seen at 600 mg/kg in 23/23 dams were abdominogenital staining, decreased locomotion and/or chromorhinorrhea. **Body weight gain** in dams was decreased, but not statistically significant, at 600 mg/kg/d on days 6-15 [-5.7%], 15-20 [-9.0%] and 0-20 [-7.2%]. **Food consumption** in dams at 600 mg/kg/d was however, meaningfully decreased only on days 6-13. [-12 %; $p < 0.05$]. **Fetal body weights** were decreased only for females at 600 mg/kg/d [-6.6%; $p < 0.05$] with male body weights [-3.3%] and total live fetal body weights [-5.0%] being generally comparable to controls and not statistically significant. **Minor malformation** of the thoracic vertebrae was statistically significant at 600 mg/kg when reported on a fetal incidence basis . **Indications of delayed ossification** in the form of either partial ossification or the absence of the following bones were reported as

statistically significant either on a litter or a fetal basis at 300 or 600 mg/kg: manubrium, sternebrae 3-4, xiphoid, caudal vertebrae, and meta-carpals. The fetal/litter incidences for sternebrae 3-4, at 300 and 600 mg/kg/day were 2.8%/17.4% and 4.7%/22.7%, respectively, compared to 0%/0% in the controls. Normal variations were reported for sternebrae 2 and 5 at 300 and 600 mg/kg.

All other reported values for both dams and fetuses were comparable to controls.

The maternal NOAEL is 100 mg/kg. The maternal LOAEL is 300 mg/kg based on chromorhinorrhea and/or abdominogenital staining. The developmental NOAEL is 100 mg/kg. The developmental LOAEL is 300 mg/kg based on indications of delayed ossification in the form of either partial ossification or the absence of the manubrium, sternebrae 3-4, xiphoid, caudal vertebrae, and meta-carpals.

This developmental toxicity study in the rat is classified **ACCEPTABLE/Guideline** and satisfies the guideline requirement for a developmental toxicity study in the rat (§83-3).

Dose and Endpoint for Establishing Acute RfD: **The developmental NOAEL is 100 mg/kg. The developmental LOAEL is 300 mg/kg based on indications of delayed ossification in the form of either partial ossification or the absence of the manubrium, sternebrae 3-4, xiphoid, caudal vertebrae, and meta-carpals.**

Uncertainty Factor(s): 100

Comments about Study/Endpoint/Uncertainty Factor(s): The skeletal malformations are presumed to occur after a single exposure (dose) and thus were considered to be appropriate for this (acute) risk assessment. This dose/endpoint is applicable only to females 13 - 50.

Acute RfD =	100.0 mg/kg (NOAEL) / 100 (UF)	=	**1.0 mg/kg**

2.1.2 General population (including infants and children).

A dose and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure (dose). This risk assessment is not required for this population subgroup.

2.2 Chronic Reference Dose (RfD)

Studies: Combined Chronic/Carcinogenicity in Rat
90-Day Oral - Rat (MRID 00132586)
2-Generation Reproduction - Rat (MRID 00151108)

Guideline #: 870.4300, 83-5

MRID No.: 00132586

Executive Summary: In a chronic toxicity/oncogenicity study (MRID 00132586), FMC 57020 Technical (Reference E1756-146) was administered to 5 groups of 120 CD (Sprague-Dawley) outbred albino rats/sex for a period of up to 24 months in the diet at concentrations of 0, 20, 100, 500, 1000, or 2000 ppm. These dietary levels resulted in mean doses of 0, 0.9, 4.3, 21.5, 42.9, or 84.8 mg/kg/day (males), and 0, 1.1, 5.5, 27.8, 56.5, or 112.9 mg/kg/day (females). After 15 weeks of treatment, 20 rats/sex/group were chosen for hematology, urinalysis, and gross pathology to satisfy the requirements for the subchronic portion of the study; these results are discussed in a separate DER. During the chronic phase of the study, 10 randomly selected rats/sex/group were sacrificed at 6, 12, and 18 months for blood and histopathological evaluations. At the final 24-month sacrifice, 10 rats/sex/group were bled for hematological analysis and a complete histopathological evaluation was performed on all rats.

Survival was not affected by the test substance in any of the treated groups compared to either of the control groups. No treatment-related clinical signs or alterations of body weight, food consumption, hematology or urinalysis parameters were observed.

During the first year of treatment, males and females fed 1000 or 2000 ppm had slightly elevated total cholesterol plasma levels. Since this effect did not continue into the second year of treatment, the toxicological relevance of these alterations remains unclear.

At the 3-month sacrifice slight liver enlargement ($p < 0.05$, liver weight and ratio to body weight) was evident among male and female rats treated with 2000 ppm and in females treated with 2000 ppm at the final 24-month sacrifice. Clear liver effects were seen at 4000 and 8000 ppm. At other interim sacrifice time points, no significant differences were observed.

Histopathological analysis of the livers of treated males and females revealed increased incidences of hepatocytomegaly. These increases achieved statistical significance at various time points of sacrifice, but generally were not dose-related and often were more profound in the mid-dose groups. Therefore, the toxicological significance of this finding in this dose range remains obscured.

The no-observed-adverse-effect level (NOAEL) is > 2000 ppm for males (84.4 mg/kg/day) and females (112.9 mg/kg/day) in this study. A lowest-observed-

adverse-effect level (LOAEL) was not identified.

The administration of FMC 57020 Technical for up to 104 weeks did not result in a statistically significant increase in the incidence of neoplastic lesions. Dosing was not considered adequate based on the lack of a toxic effect on the animals.

This chronic study in rats is classified as **Acceptable/Guideline** and satisfy the Subdivision F guideline requirements for a chronic toxicity study in rats [870.4100 (83-1)].

The oncogenicity phase of study in rats is classified as **Acceptable/Guideline** and does satisfy the Subdivision F guideline requirements for a combined chronic toxicity/oncogenicity study in rats [870.4200 (83-2)], since body weight decrement and hepatotoxicity were observed at 4000 and 8000 ppm in a subchronic phase of this study.

Dose and Endpoint for Establishing Chronic RfD: 84.4 mg/kg/day is the highest dose tested and there were no compound related effects observed.

Uncertainty Factor(s): 100 (10 for intraspecies extrapolation; 10 for interspecies variations)

Comments about Study/Endpoint/Uncertainty Factor(s): No treatment-related effects were observed at the highest dose tested (2000 ppm; 84.4 mg/kg/day). Inspite of the absence of systemic toxicity at this dose, the HIARC concluded that this dose was adequate to assess the chronic toxicity and carcinogenicity in rats. This conclusion was based on the results obtained in the 90-day oral toxicity and the two generation reproduction study in rats. In the 90-day study, the LOAEL was 4000 ppm (319 mg/kg/day) and the NOAEL was 2000 ppm (160 mg/kg/day) based on statistically significant decrease in body weight and body weight gain in female rats.

In the two generation reproduction study, the LOAEL was 2000 ppm (100 mg/kg/day) and the NOAEL was 1000 ppm (50 mg/kg/day).

Even though the NOAEL (50 mg/kg/day) is lower in the two generation reproduction study, the HIARC selected the NOAEL (84.4 mg/kg/day) from the 2-year rat study, since the difference is due to differences in the calculated food intake (mg/kg/day) between these two studies. The 2-year rat study used actual consumption data, whereas the two generation study used the standard food conversion values.

Chronic RfD =	$\frac{\text{84.4 mg/kg/day (NOAEL)}}{\text{100 (UF)}}$ =	**0.84 mg/kg/day**

2.3 Occupational/Residential Exposure

No registered residential use for this herbicide.

2.3.1 Dermal Absorption

Proposed Study: None Guideline #:

MRID No.: None

Executive Summary: None

Proposed Percentage (%) Dermal Absorption: 100% (default value)

Comments about Dermal Absorption: No dermal absorption studies are available and no dermal absorption values can be estimated from the available data base as there are no two studies in the same species with the same or similar endpoints nor is there any dermal study on the technical material alone. Only, a 21-day dermal toxicity study (MRID 40279601) in rabbit with a formulation is available in the data base. This study was not utilized for dermal risk assessment, because the test material was mixture of clomazone and treflon plus (34.55% + 26.24%).

2.3.4 Short-term Dermal (1 - 7 days) Exposure

Study: Developmental toxicity in the rat Guideline #:83-3

MRID No.: 00150291

Executive Summary: Same as acute RfD.

Dose and Endpoint: Maternal NOAEL 100 mg/kg/day, based on chromorhinorrhea and/or abdominal staining.

Comments about Study/Endpoint: The 21 day dermal study done with the mixture is not appropriate. Therefore, an oral NOAEL was selected. The maternal NOAEL would be protective of developmental concerns. Since an oral route was used, 100% absorption factor should be used to route-to-route extrapolation.

2.3.5 Intermediate-term Dermal (1-Week to Several Months)

Studies: Combined Chronic/Carcinogenicity in Rat Guideline #: 83-5

90-day Oral - Rat (MRID 00132586)
2-generation Reproduction - Rat (MRID 00151108)

MRID No.: 00132586

Executive Summary: Same as for chronic RfD.

Dose and Endpoint: 84.4 mg/kg/day is the highest dose tested and there were no compound related effects observed.

Comments about Study/Endpoint: See chronic RfD. Use 100% dermal absorption.

2.3.6 Long-term Dermal (Several Months to Lifetime)

Studies: Combined Chronic Feeding/Carcinogenicity Rat § 83-5
90-day Oral - Rat (MRID 00132586)
2-generation Reproduction - Rat (MRID 00151108)

MRID No.: 0132586

Executive Summary: See summary of chronic RfD.

Dose and Endpoint: 84.4 mg/kg/day is the highest dose tested and there were no compound related effects observed.

Comments about Study/Endpoint: See chronic RfD.

2.3.6 Inhalation Exposure

When route-to-route extrapolations is recommended: 1) **convert** the inhalation exposure (µg/lb a.i) and the dermal exposure (mg/lb a.i) to oral equivalent doses (mg/kg); 2) **combine** the converted oral equivalent doses to get a combined dose for total (dermal + inhalation) exposure; and 3) this combined dose should then be **compared** with the oral NOEL to calculate the Margins of Exposure.

Step I: **Convert** the inhalation and dermal exposures to oral equivalent doses (mg/kg) as follows:

a. unit inhalation exposure (µg/lb ai) x absorption rate (100% default) x application rate (lb ai/acre) x acres treated x 1 mg/1000 µg/kg ÷ body weight (70 kg or 60 kg for

developmental endpoints)

b. unit dermal exposure (mg/lb ai) x absorption rate (% recommended or 100% default) x application rate (lb ai/acre) x acres treated ÷ body weight (70 kg or 60 kg for developmental endpoints)

Step II: **Combine** the converted oral equivalent doses to obtain total exposure via these routes (inhalation and dermal).

Step III: **Compare** the combined dose to the oral NOELs for the appropriate exposure period (i.e., Short-, Intermediate-, or Long-Term).

2.3.6.1 Short-term Inhalation Exposure: Maternal NOAEL 100 mg/kg/day

2.3.6.2 Intermediate-term Inhalation Exposure: 84.4 mg/kg/day

2.3.6.3 Long-term Inhalation Exposure: 84.4 mg/kg/day

2.3.6 Margin of Exposure for Occupational/Residential Risk Assessments

The acceptable MOEs for occupational risk assessment are 100. There are no registered residential uses at the present time.

2.4 Recommendation for Aggregate Exposure Risk Assessments

There are no residential uses. Aggregate food and water only.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No.: 00132586

Discussion of Tumor Data: The Toxicology Branch Peer Review Group (Ted Farber, Reto Engler, Robert Zendzian, Bill Burnam and Bert Litt met on December 21, 1984; HED Doc. No. 004173) discussed the histopathology findings in the chronic feeding carcinogenicity study in the rat. The group unanimously agreed that no dose response relationship was observed for the tumors and the adequate dose spread was employed in this study. Further, the historical control data submitted indicate a high degree of variability in the incidence of these types of tumors, and that the low incidence observed in the concurrent controls was within the range of variability. Based on these facts, the

committee concluded that the incidence of pheochromocytoma and hepatocellular adenoma observed in this study do not represent a oncogenic potential.

Adequacy of the Dose Levels Tested: No treatment-related effects were observed at the highest dose tested (2000 ppm; 84.4 mg/kg/day). Inspite of the absence of systemic toxicity at this dose, the HIARC concluded that this dose was adequate to assess the chronic toxicity and carcinogenicity in rats. This conclusion was based on the results obtained in the 90-day oral toxicity and the two generation reproduction study in rats. In the 90-day study, the LOAEL was 4000 ppm (319 mg/kg/day) and the NOAEL was 2000 ppm (160 mg/kg/day) based on statistically significant decrease in body weight and body weight gain in female rats.

3.2 Carcinogenicity Study in Mice

MRID No.: 00132585; 00132587; 00144244

Discussion of Tumor Data: The Toxicology Branch Peer Review Group consisting of Drs.Ted Farber , Reto Engler, Robert Zendzian, and Messrs. Bill Burnam and Bert Litt met on December 21, 1984 to discuss the histopathology findings in the chronic feeding carcinogenicity study in the mouse. Histopathololgy examination of the individual animal liver data of both males and females in the 24 month feeding/oncogenicity study in mice (FMC Study No. A81-651; Toxicogenics Study No.410-0817) demonstrated a non-statistical increase in hepatocellular adenomas and hepatocellular carcinomas separately and when combined in males. The Branch Peer Review Group unanimously agreed that no carcinogenic potential was demonstrated in the mouse.

Adequacy of the Dose Levels Tested: Systemic toxicity was not observed at the highest dose tested. The HIARC classified this study as **Unacceptable/guideline**; however, the committee considered that the data were adequate to assess the carcinogenicity in mice. A new mouse study is not required for the current use pattern; however, if any petitions for new uses will increase dietary and/or worker exposure, a new study will be required.

3.3 Classification of Carcinogenic Potential

The HIARC classified clomazone as a "not likely human carcinogen" based on the lack of carcinogenic response in rats and mice and the lack of mutagenic concern. Further, there is no data in the literature or SAR information to indicate carcinogenic potential (Yintak Woo personal communication, August 14, 2000).

4 MUTAGENICITY

1) In a reverse gene mutation assay in bacteria (MRID 00117413), five histidine

auxotrophic (*his*$^-$) strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA 1537, TA1538) were exposed to test article (Lot No. E-1382-95) dissolved in dimethylsulfoxide (DMSO) at five concentrations ranging between 6 and 600 μg per plate, both in the presence and absence of a mammalian metabolic system prepared as microsomes from livers (S9) of male Sprague-Dawley rats pretreated with Aroclor 1254. After 48 hours incubation, histidine prototrophic colonies (*his*$^+$) were counted. In addition to cultures treated with DMSO (solvent control) other cultures were exposed to specific strain and activation mutagens to serve as positive controls.

FMC 57020 was assayed up to cytotoxic concentrations, 600 μg/plate, causing inhibition of background lawn of growth and decreased revertant colonies, but **in no instance did it cause an appreciable increase in the number of revertants above solvent levels, in either the presence or absence of metabolic activation.**

This study is classified as **unacceptable** and **does not satisfy** the requirement for FIFRA Test Guideline

2) In a reverse gene mutation assay in bacteria (MRID 00133221), five histidine auxotrophic (*his*$^-$) strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, TA100) were exposed to the test material (Lot No. 249-1) dissolved in dimethylsulfoxide (DMSO) at five concentrations ranging from 0.04 to 4.0 μL per plate, and revertants to histidine prototrophy (*his*$^+$) counted following 48 hours incubation. Additional cultures of bacteria were exposed to the solvent (DMSO) and strain specific mutagens, but only in the absence of metabolic activation; only strains TA98 and TA100 were exposed to a specific mutagen in the presence of S9 metabolic activation prepared from Sprague-Dawley rat liver induced with Aroclor 1254.

Cultures were assayed up to a cytotoxic concentration, 4.0 μL/plate +/-S9, but **no appreciable increase in the number of revertants was recorded for any of the tester strains assayed.**

This study is classified as **unacceptable** in satisfying the requirement for reverse mutation in bacteria (FIFRA Test Guideline 84-2), because of two major deficiencies:

i. Although considered not mutagenic in the absence of S9 activation and activated TA98 and TA100 cultures, the study lacks data for activated TA1535, TA1537 and TA1538 cultures assayed in the presence of S9 activation.

ii. Without the provision of % of purity of the a.i., there is no indication of how much test material was administered to the cultures.

3) In a reverse gene mutation assay in bacteria (MRID 00142238), five histidine auxotrophic (*his*$^-$) strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537

and TA1538) were exposed to test article. Lot No. E3175-104-6, > 98% (dissolved in dimethylsulfoxide, DMSO) at five concentrations ranging from 17 to 680 μg/plate, both in the absence and presence of liver microsomal enzymes (S9) prepared from male Sprague-Dawley rats pretreated with Aroclor 1254. In addition to cultures treated with the DMSO (vehicle control), others were exposed to strain and activation specific mutagens, to serve as positive controls. Following 48 hours incubation, revertants to histidine prototrophy (*his*$^+$) were counted in treated cultures and compared to vehicle controls.

The test article was assayed up to cytotoxic doses (thinning of bacterial background lawn at 680 μg/plate +S9) and produced a dose-responsive increased number of revertants (twice background and above) but in treated TA100 cultures only, beginning at a nontoxic dose of 340 μg/plate and above, both ± S9. **Thus under conditions of this assay, FMC 65361, Lot No. E3175-104-6 caused a positive mutagenic response in tester strain TA100 both in the absence and presence of microsomal activation.** All positive control cultures responded appropriately with large increase in revertants.

This study is classified as **acceptable** and satisfies the requirement for FIFRA Test guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

4) In a reverse gene mutation assay in bacteria (MRID 00142242), histidine auxotrophic (*his*$^-$) strains TA1535, TA1537, TA1538, TA100 and TA98 of *Salmonella typhimurium* were exposed to test article (Lot No. 2383-65) dissolved in dimethylsulfoxide (DMSO) at five concentrations ranging from 185.2 to 15,000 per plate (at sequentially triple steps), both in the presence and absence of mammalian metabolic activation [source and characterization not provided]. After two days incubation at 37 degrees C, the study was terminated and the number of revertant colonies to histidine prototrophy (*his*$^+$) counted. In addition to DMSO (solvent controls), additional cultures were treated with specific strain and activation mutagens, to serve as positive controls.

In the absence of any recorded cytotoxicity [i.e., none was measured], significant increases in revertants over solvent controls were recorded in TA1535 and TA100, ranging from a doubling to a 3.5-fold increase in non-activated and activated cultures, but at no other concentration or strain. The investigators concluded that "under the conditions of this assay, the mutagenic potential, if any, of the test material could not be fully characterized."[1]

We agree, which classifies this study as **unacceptable** and not fully satisfying the FIFRA

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[1]However, the positive response in base-substitution strains TA1535 and TA100 at doses of 5000 and higher is consistent with results from another report from another laboratory, MRID 00142243.

Test guideline for reverse gene mutation data. Additionally the mammalian metabolic activation system was not characterized.

5) In a reverse gene mutation assay in bacteria (MRID 00142243) five histidine auxtrophic strains (*his*$^-$) of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) were exposed to test article (Lot No. E-2383-139A) dissolved in dimethylsulfoxide (DMSO) at five concentrations ranging from 100 to 10,000 μg/plate, both in the presence and absence of S9 homogenate mammalian metabolic activation prepared from liver microsomal enzymes from male Sprague-Dawley rats pretreated with Aroclor 1254. Additional cultures were exposed to test article vehicle DMSO, as solvent control, and further cultures were treated with specific strain and activation mutagens, to serve as positive controls. Following 48 hours incubation at 37 degrees C, revertant colonies in tester strains were counted and compared to vehicle control counts.

In the absence of reported cytotoxicity, **the test article increased (more than doubling) the frequency of histidine prototrophy (*his*$^+$) in both base substitution strains TA1535 and TA100 under both non-activation and activation (±S9) cultures in a dose-responsive manner at 5000 and 10,000 μg/plate, i.e., a positive response.**[2]

This study is classified as **acceptable** and satisfies the requirement for FIFRA Test Guideline 84-2 for **in vitro** mutagenicity (bacterial reverse gene mutation) data.

6) In a reverse gene mutation in bacteria (MRID 00142244), five histidine auxotrophic (*his*$^-$) strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) were exposed to test article, Lot No. E3175-140-1, > 98% (dissolved in dimethylsulfoxide, (DMSO) at five concentrations ranging from 100 to 10,000 μg/plate in the presence of a liver microsome (S9) preparation derived from male Sprague-Dawley rats induced with Aroclor 1254; but from 50 to 5000 μg/plate in its absence (-S9). In addition to cultures treated with the vehicle (DMSO), other cultures were exposed to specific strain and activation mutagens, to serve as positive controls. After 48 hours incubation, revertant colonies to histidine prototrophy (*his*$^+$) were counted and compared to DMSO controls.

FMC 22896 was tested up to the HDT (10,000 μplate) without cytotoxicity under activation conditions (+S9), but induced a large dose-responsive increased number of histidine prototrophic colonies (*his*$^+$) from 500 μg/plate and above, up to 26.9 x background at the HDT in activated TA 100 cultures. A lesser dose-responsive increase in prototrophy over background (2.2 to 3.0-fold increase at 1250 to 5000 μg/plate) was

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[2]This positive response in base-substitution TA1535 and TA100 strains at doses of 5000 and higher is consistent with the results of a previous report from another laboratory, MRID 00142242.

also recorded in activated TA1535 colonies. In nonactivated cultures, cytotoxicity (diminishing of bacterial background lawn) was seen in all strains at ≥ 2500 μg/plate. Moderate dose-responsive increases in revertants were recorded in both nonactivated TA100 and TA1535 cultures, beginning at 1250 μg/plate, the lowest effective dose. All positive controls responded appropriately with large increases over background (vehicle controls). The remaining strains, with/without activation, did not respond to the test article. **Thus, FMC 22896, Lot No. E2175-140-1, was positive for mutagenicity in the base substitution strains TA100 and TA1535 in the absence of overt cytotoxicity.**

This study is classified as **acceptable** and satisfies the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

7) In a reverse gene mutation assay in bacteria (MRID 00150292), five histidine auxotrophic (*his*$^-$) strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) were exposed to test article (Lot No. E3376-112, 93.4% a.i.) dissolved in dimethylsulfoxide (DMSO) at five concentrations ranging from 50 to 5000 μg per plate, both in the presence and absence of mammalian metabolic activation provided by microsomes of livers (S9) from male Sprague-Dawley rats pretreated with Aroclor 1254. In addition to DMSO (solvent controls), additional cultures were treated with strain and activation specific mutagens to serve as positive controls. The number of revertant colonies (*his*$^-$) was counted after 48 hours incubation.

The test article was assayed up to cytotoxic concentrations (5000 μg/plate), but **in no instance were appreciably increased number of revertants to histidine prototrophy (*his*$^+$) found in any of the tester strains, either in the presence or absence of metabolic activation.**

This study is classified as **acceptable** and **does satisfy** the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

8) In a reverse gene mutation assay in bacteria (MRID 40123605), five histidine auxotrophic (*his*$^-$) mutant strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA1538) were exposed to FMC 57091, Lot No. E1202-44, dissolved in water, at five concentrations ranging from 136 to 13,594 μg/plate, both in the absence and presence of mammalian metabolic activation prepared as S9 microsomes of rat liver from male Sprague-Dawley rats induced by Aroclor 1254. In addition to cultures exposed to water (as vehicle control), other cultures were treated with specific strain and activation mutagens to serve as positive controls. After incubation at 37 degrees C for 48 hours, the numbers of revertant colonies to histidine prototrophy (*his*$^+$) was compared to water controls.

In the absence of any recorded cytotoxicity up to the HDT (13,594 μg/plate), **the test article did not induce any significant increases in the number of revertants per plate**

in any of the tester strain cultures with/without metabolic activation by Aroclor 1254 induced rat liver microsomes (S9).

This study is classified as **unacceptable** and does not satisfy the requirement for FIFRA Test Guideline 84-2 for *in vitro* mutagenicity (bacterial reverse gene mutation) data, because no purity information was provided. It can be upgraded upon receipt of the purity information.

9) In a mammalian forward cell gene mutation assay (MRID 00144186), cultures of Chinese hamster ovary cells (CHO-K_1-BH_4) were exposed to test article, (88.8%, Lot No. 1756-146) dissolved in dimethylsulfoxide (DMSO), at four concentrations (200, 300, 500, 600 μg/mL), both in the presence or absence of mammalian metabolic activation provided by microsomes from livers (S9) of Fischer-344 rats induced with Aroclor 1254. After 5 hours incubation, cultures were refed with untreated culture medium for 18-24 hours, then subcultured for 9 days at 2-3 days intervals (expression period), followed by incubation for 11 days in thioguanine (TG) supplemented culture medium to determine TG-resistant (selection of presumably mutant phenotype) colonies. In addition to cultures treated with DMSO (solvent negative controls), other CHO cultures were treated with ethylmethanesulfonate (EMS) or benzo(a)pyrene (BaP), to serve as positive controls for nonactivated and S9-activated series, respectively. The entire assay was repeated twice due to stated "contamination of cultures and poor positive response in the positive control doses" of the first assay.

Clomazone was tested up to a dose (an HDT of 600 μg/mL) producing moderate cytotoxicity (average cloning efficiency, CE of 42%) in nonactivated cultures, but a lesser degree of cytotoxicity ($\geq$ 44% CE) in activated cultures. In preliminary toxicity testing, 1281 μg/mL was lethal to cultures with/without +S9. At 600 μg/mL, the number of presumed mutants was 76.2 /10^6 clonable survivors -S9 compared to 25.8/10^6 survivors for DMSO negative controls; values comparable to DMSO were obtained at all other doses. In activated (+S9) cultures, only at 500 μg/mL was the frequency of mutants increased over DMSO controls (55.1/10^6 survivors *versus* 21.2/10^6 survivors in DMSO cultures. Hence, the fold increase in mutation frequency was 2.9x without S9 (600 μg/mL -S9) and 2.6 x (500 μg/mL +S9). Thus, **a weak degree of mutagenicity was recorded at the HDT in nonactivated cultures; and close to the HDT in activated cultures, contrary to the conclusions of negative mutagenicity recorded by the investigators.** The positive controls responded appropriately.

This study is classified as **unacceptable** in satisfying FIFRA Testing Guideline for *in vitro* forward mutation data, since it is inconclusive and requires retesting at a narrower range of concentration between the HDT and lethal dose to define more exactly mutagen response above the doses tested herein.

10) In a mammalian cell gene mutation assay (MRID 00144187) cultures of Chinese

hamster ovary (CHO-K_1BH_4) cells were exposed to test article, Lot No. E3175-104-5, 98% (dissolved in acetone) at four dose levels: 400, 500, 600 and 700 μg/mL in non-activated cultures; 500, 600, 700, and 800 μg/mL in the presence of S9 mammalian metabolic activation provided by liver homogenates of Fischer 344 rats induced by Aroclor 1254. After 5 hours incubation in treatment medium followed by 18 - 24 hours in fresh (non-treatment) medium, cells were subcultured for 8 days (expression period), followed by subculturing for 12 days in fresh medium containing 10 μM thioguanine (TG), which selects for TG-resistant cells, presumably mutant colonies for the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus. Additional cultures were exposed to the solvent (acetone, as control), while others were treated with the mutagens, ethylmethanesulfonate (EMS) and benzo(a)pyrene (BaP) [both dissolved in dimethylsulfoxide (DMSO)] to serve as positive controls for the non-activated and activated series, respectively.

The test article was assayed up to the limit of solubility (700 - 800 μg/mL), at which doses cloning efficiency (a measure of cytotoxicity) was reduced by more than 40% in both activated and non-activated cultures. **At no dose did the test article induce a significant increase in presumed mutant colonies over control.** In contrast, both mutagen treated cultures responded appropriately with large increases in mutant colonies.

This study is classified as **acceptable** and satisfies the FIFRA Test Guideline for mammalian cell mutation data.

11) In an unscheduled DNA synthesis (UDS) assay (MRID 00133223), primary rat hepatocyte cultures from normal adult Sprague-Dawley rats were exposed for 18 hours to test article, (88.8%, Lot. No. E1756-146-20, dissolved in ethanol) at five dose levels ranging from 0.001 to 0.10 μL/mL, and prepared on coverslips attached to slides cell side up. The slides were coated with Kodak NTB emulsion and stored at refrigerator temperatures for 10 days, following which they were developed in Kodak D-19, fixed, stained in hematoxylin-sodium acetate-eosin and mounted. In addition to cultures treated with solvent (acting as control), others were exposed to a known mutagen, 2-acetylaminofluorene (AAF), also dissolved in ethanol to serve as positive control. UDS was measured as the number of net nuclear counts of silver grains.

Clomazone was tested up to cytotoxicity (relative toxicity at 0.10 μL/mL was 88.6%), but **in no cultures treated with test article was a significant increase in mean net nuclear counts indicative of UDS recorded.**

This study is classified as **acceptable** in satisfying the FIFRA Testing guideline for other genotoxicity (UDS) data.

12) In an *in vivo* cytogenetic assay (MRID 00133222), male Sprague-Dawley rats (5/dose) were administered test article, (88.8%, Lot No. E1756-146-20 dissolved in corn

oil) at oral (gavage) doses of 200, 667 and 2000 mg/kg/day for five consecutive days. Two to four hours after the last dose, the animals were injected i.p. with the mitotic arresting alkaloid, colchicine. Two hour following that, bone marrow cells were collected from both femurs and prepared for microscopic examination of structural and numerical chromosome aberrations. In addition to a group of animals treated orally with the vehicle (corn oil, solvent control), a fifth group was injected i.p. once with the clastogen, triethylmelamine (TEM) one day prior to sacrifice at a dose level of 0.5 mg/kg. A model chromosome number and mitotic index was recorded for each animal, as well as total number and types of aberration and percentage of damaged cells in the total population of cells examined for each treatment group. Chi-square analysis, using a 2x2 contingency table was used to ascertain significance differences between number of cells with aberrations in the treatment and control groups; the severity of damage within the cells was recorded as the number of aberrations per cell for each treatment group. The t-test was used to compare pairwise the number of aberrations per cell of each treatment group with that of the vehicle control group.

Clomazone was tested up to animal toxicity (mean body weight decrease in the HDT group of 10%; excess salivation at 2000 and 667 mg/kg/day/groups), but no effect on mitotic index in any group. **The incidence of aberrations, however, and the aberrations per cells were reported to be similar to vehicle control values, i.e., not significantly increased.** The TEM positive control responded with appropriately increased aberration (up to 16%). Thus, the investigators concluded that the test article was negative (not clastogenic) in this *in vivo* cytogenetic assay.

We agree with the investigators that the assay is **acceptable** from a regulatory standpoint (animals were tested up to the limiting dose, 2000 mg/kg, producing animal toxicity, whereas higher doses, 3000 mg/kg/day resulted in death), despite certain minor deficiencies, as follows:

i. Only males were tested; females were not assayed. No evidence was presented, however, that a sex sensitivity exists with this compound.

ii. No evidence that test material or its metabolites reached the bone marrow from oral administration, even though mitotic index was affected at any oral treatment.

iii. The positive control, TEM, was given by a different route, injected i.p.

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base

The data base is adequate for FQPA considerations.

5.2 **Neurotoxicity Data**

Neurotoxicity data is not available nor is it required as the chemical is not a cholinesterase inhibitor and has shown no indications of central or peripheral nervous system effects in any other studies and does not appear to be structurally related to any other chemical that causes adverse nervous system effects

5.3 Developmental Toxicity

Executive Summary: **RATS** One-hundred assumed pregnant Sprague-Dawley rats were divided into four groups of 25 and orally gavaged with either 100, 300 or 600 mg/kg of test material from days 6-15 of gestation. One additional group served a vehicle control group and received only corn oil. Dams were sacrificed on day 20 of gestation and necropsied. Half the viable fetuses were examined for skeletal effects using a modification of the Wilson technique and half examined for visceral effects. Standard statistical analysis were conducted on 13 of 15 parameters covering both dams and fetuses. (MRID No.00150291).

There were no compound related deaths. Treatment related deaths were associated with esophageal or lung puncture during the administration of compound. **Clinical signs** were observed only in dams receiving 300 and 600 mg/kg/d. Signs seen at 300 mg/kg/d consisted of chromorhinorrhea and/or abdominogenital staining in 4/24 dams. Signs seen at 600 mg/kg in 23/23 dams were abdominogenital staining, decreased locomotion and/or chromorhinorrhea. **Body weight gain** in dams was decreased, but not statistically significant, at 600 mg/kg/d on days 6-15 [-5.7%], 15-20 [-9.0%] and 0-20 [-7.2%]. **Food consumption** in dams at 600 mg/kg/d was however, meaningfully decreased only on days 6-13. [-12 %; $p < 0.05$]. **Fetal body weights** were decreased only for females at 600 mg/kg/d [-6.6%; $p < 0.05$] with male body weights [-3.3%] and total live fetal body weights [-5.0%] being generally comparable to controls and not statistically significant. **Minor malformation** of the thoracic vertebrae was statistically significant at 600 mg/kg when reported on a fetal incidence basis.. **Indications of delayed ossification** in the form of either partial ossification or the absence of the following bones were reported as statistically significant either on a litter or a fetal basis at 300 or 600 mg/kg: manubrium, sternebrae 3-4, xiphoid, caudal vertebrae, and meta-carpals. Normal variations were reported for sternebrae 2 and 5 at 300 and 600 mg/kg.

All other reported values for both dams and fetuses were comparable to controls.

The maternal NOAEL is 100 mg/kg. The maternal LOAEL is 300 mg/kg based on chromorhinorrhea and/or abdominogenital staining. The developmental NOAEL is 100 mg/kg. The developmental LOAEL is 300 mg/kg based on indications of delayed ossification in the form of either partial ossification or the absence of the

manubrium, sternebrae 3-4, xiphoid, caudal vertebrae, and meta-carpals.

EXECUTIVE SUMMARY:**RABBITS** Four groups of assumed pregnant New Zealand white rabbits comprised of 18 animals per group were administered FMC 57020 in doses of either 30.0, 240.0 or 1000 mg/kg (reduced to 700 mg/kg on day 13-18 of gestation) from days 6-18 of gestation. An additional group served as control and received only the vehicle carboxy-methyl-cellulose. All animals were sacrificed on day 29 of gestation.

Compound related toxicity at the high dose tested (HDT; 1000/700 mg/kg) included 3 deaths, and 3 abortions all after day 18. [animals dying were not animals aborting]. Net body mean weight gain [i.e. maternal body weight at day 29 minus the weight of the gravid uterus] for controls and treated groups was +87; +160; -60 and -85 grams respectively with the HDT being statistically significant [-85 grams; $p<0.05$]. Mean weight of the gravid uteri were comparable between dose groups ranging from 340-361 grams. Mean maternal body weight gain for days 6-18 of gestation from controls to the HDT was +155; +219; +96 and -300 grams respectively. Ataxia was also reported for 2 animals in the HDT as well as red vaginal discharge in 4 rabbits 3 of which aborted. Decreased or no defecation was also observed at 1000/700 mg/kg more frequently than at the lower doses. No other significant toxicological effects were noted for dams at either 30.0 or 240 mg/kg.

Examination of fetal and litter data indicated no meaningful developmental toxicological effects for either mean fetal data at the time of laparotomy, or external, skeletal or visceral compound related effects at any dose level.

Maternal NOAEL is 240 mg/kg. The maternal LOAEL is 700 mg/kg based on the effects seen at 1000 mg/kg. (The assumption here is that the effects of maternal death, abortions, decreased body weight gain and deceased or no defecation may also have occurred at 700 mg/kg if the animals had been given this dose of 700 mg/kg during days 6-18).

Developmental NOAEL is 700 mg/kg. The developmental LOAEL is > 700 mg/kg since no higher dose was given for the days 13-18.

5.4 Reproductive Toxicity

EXECUTIVE SUMMARY:**RATS** Two hundred and fifty [250] male and female Charles River CD strain rats were randomly assigned into 5 groups of 25 males and 25 females per dose group and administered either 100; 1000; 2000 or 4000 ppm (equivalent to 5; 50; 100; or 200 mg/kg/d) of FMC 57020 in a standard dietary 2-generation reproduction study with one group serving as the control group.

There was no compound related mortality. Parental body weight in males during pre-

mating was comparable to controls whereas female body weight was statistically significantly lower [$p<0.05$-$p<0.01$] at 2000 and 4000 ppm as early as 2 and 5 weeks thru to copulation [8 and 11 weeks later]. Premating body weight gain was also lower [$p<0.01$] for females in both generations at 2000 ppm and 4000 ppm (26%;26% and 11%;13% respectively) Maternal body weight during periods of gestation (days 0-20) and lactation (days 0-21) were lower [$p<0.05$-0.01] at 2000 and 4000 ppm for all generation and litters.. Food consumption for treated males was generally comparable to controls during premating; however food consumption for F_0 and F_1 females was generally lower at 2000 and 4000 ppm with several occasions of statistical significance ($p<0.05$-$p<0.01$). The only clinically significant observation was noted in the 4000 ppm female groups of the F_0 and F1 generations and consisted of urine soaked and/or yellow-brown stained fur.

Reproductive performance was comparable for all generations when compared to controls with the exception of a statistically significant [$p<0.05$] but apparently aberrant decreased fertility value for the F_1b litter at 4000 ppm. Pup survival and pup body weight values were comparable to control values for all litters during lactation with the exception of a statistically significant decrease in pup body weight values at 2000 ppm and 4000 ppm for the F_2a and F_2b litters . Statistically significant increases were noted for liver to body weight ratios in both males and females of the F_0 generation at 4000 ppm and in liver to brain weight ratios for males at 4000 ppm. Statistically significant increases for liver to body weight ratios were also reported for F_1 males and females in the 4000 ppm groups and females in the 2000 ppm group. However, absolute weights were not increased and histopathology was not remarkable indicating that increases may be attributable to a combination of enzyme induction and/or decreased body weight. There was also an increased incidence of dilated and distended pelvis of the kidney in the F_1 males after the F_2b mating in the 2000 and 4000 ppm groups when compared to the control group [1/23; 2/24; 1/23; 6/24; 7/24 equal to 4%; 8%; 4%; 25% and 29% control to high dose respectively]. These effects were not seen after F_2a mating. This suggests that the effects occurred as adults but not <u>in utero</u> effect. Histopathology was conducted on the F_0 and F_1 parental animals from the control and the 4000 ppm group as well as 10 male and 10 female F1b and F2b progeny from the control and the 4000 ppm dose groups randomly chosen from those subjected to necropsy examination. Any progeny which exhibited grossly apparent developmental anomalies were subjected to gross pathologic study and tissues retained by the pathologist. Tissues and organs examined for histopathology included the ovaries (with corpus), prostate, seminal vesicles, testes (with epididymides), uteri, and vagina, and all other tissues and organs appearing abnormal. All kidneys from the F_1 parental generation were also examined microscopically as a result of the incidence of hydro-nephritic kidneys noted grossly. Malformations reported were either those commonly occurring, not statistically significant and/or not dose responsive. Observations such as short, kinked and hair like tail, macrophthalmia and anophthalmia were reported as common observations. Limb abnormalities (i.e. 1 pup in the 1000 ppm group and 1 in the 4000 ppm group) and the absence of the anal opening (1 pup in the

4000 ppm group) raised concerns of teratogenicity. [NOTE: the absence of these effects in the rat teratology resulted in the rat teratology study being audited and re-examined by outside experts].

Parental NOAEL is 1000 ppm equivalent to 50 mg/kg/d.

Parental LOAEL is 2000 ppm equivalent to 100 mg/kg/d based on statistically significant decreases in premating body weight and body weight gain, statistically significant decreases in body weight during gestation and lactation, a statistically significant decrease in food consumption in females and hydro-nephritic kidneys in males.

Offspring NOAEL is 1000 ppm (50 mg/kg/d).

Offspring LOAEL is 2000 ppm (100 mg/kg/d) based on a decreased body weight in F2a and F2b litters.

5.5 Additional Information from Literature Sources (if available)

none

5.6 Determination of Susceptibility

There is no *quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to in utero exposure in developmental studies. There was an indication of qualitative susceptibility in the rat developmental study based on the presence of delayed ossification in the fetuses; however, the HIARC concluded that the fetal effects were no more severe than the maternal effects because:*

- *there is no dose response relationship for delayed ossification (i.e., absence of increased incidence with increase in dose);*
- *low fetal/litter incidences;*
- *delayed ossifications were not considered to be severe; and*
- *no visceral or skeletal malformations were seen.*

5.7 Recommendation for a Developmental Neurotoxicity Study

5.7.1 Evidence that suggests requiring a Developmental Neurotoxicity study:

none

5.7.2 Evidence that **does not** support the need for a Developmental Neurotoxicity study:

(1) there is no obvious indication in any of the studies that the compound induces central nervous system or peripheral nervous system effects.
(2) there is no evidence in the rabbit or the rat developmental study of increased susceptibility to the in utero exposure of fetuses
(3) there is no readily available evidence that the test chemical is related to any other chemical that is known to cause effects on the nervous system.

6. HAZARD CHARACTERIZATION

Clomazone has low acute toxicity (Category III and IV) via oral, dermal and inhalation routes. It is non-irritating to the eye and mildly irritating to the skin. It is not a skin sensitizer. The primary target organ for clomazone in the rat and dog studies is the liver. It is not a carcinogen in both the rat and mouse. The available genetic toxicology studies indicate that clomazone is not mutagenic in bacteria (*Salmonella typhimurium*) or induce chromosomal aberrations in rat bone marrow. Similarly, clomazone did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocyte. Based on the results of acceptable studies, there is no concern for mutagenicity at this time. No systemic toxicity was observed at the highest dose tested in the 2-year rat, mouse oncogenicity and chronic dog studies. The doses ranged from 84.8 mg/kg/day for the 2-year rat study to 1038 mg/kg/day for the chronic dog study. There was no evidence of neurotoxicity in chronic and subchronic studies.

There is no quantitative or qualitative evidence of susceptibility of rats or rabbit fetuses to in utero exposure in available developmental studies.
In the 2-generation reproduction study, no qualitative or quantitative evidence of increased susceptibility was observed.

In a metabolism study in rat, Clomazone is absorbed from the digestive tract and extensively metabolized by the liver and excreted in the urine and feces within 24 hours. Sixteen metabolites including the parent compound were identified; and the predominant route of excretion was in urine. A total of 75 - 85% of the administered dose was recovered for all routes and doses, except the single high dose females which accounted for 48% which was explained as fecal excretion was suppressed in these females. The total recovery after 48 hours was generally comparable between all groups and sexes and ranged from 91 - 100%. The quantities of metabolites varied with the dose regimen, sex, and route of administration but were the same qualitatively both in the urine and the feces in all groups.

7 DATA GAPS :

i) 21-Day dermal rat - need study for dermal risk assessment.
ii) 28-Day inhalation - need study for inhalation risk assessment

8 ACUTE TOXICITY

Acute Toxicity of Clomazone

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	00117121	LD_{50} = 2077.0 mg/kg ♂ 1369.0 mg/kg ♀	3
81-2	Acute Dermal	00117122	LD_{50} > 2000.0 mg/kg	3
81-3	Acute Inhalation	00117123	LC_{50} = 6.52 mg/L ♂ 4.23 mg/L ♀	4
81-4	Primary Eye Irritation	00117124	almost non-irritating at 1 hour in washed and unwashed eyes	3
81-5	Primary Skin Irritation	00117125	minimally irritating at 24 and 72 hours	3
81-6	Dermal Sensitization	00117126	non-sensitizer	
81-8	Acute Neurotoxicity	not required	not applicable	

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 100 UF = 100	LOAEL = 300 mg/kg/day, based on delayed ossification	Developmental rat
	Acute RfD = 1.0 mg/kg/day		
Chronic Dietary	NOAEL = 84.4 UF = 100	LOAEL > 84.4 mg/kg/day LOAEL = 319.3 mg/kg/day LOAEL = 100 mg/kg/day	Two year rat feeding study 90-day oral rat 2-Gen Repro.
	Chronic RfD = 0.84 mg/kg/day		
Incidental Oral, Short-Term	NOAEL=	No residential uses	
Incidental Oral, Intermediate-Term	NOAEL=	No residential uses	
Dermal, Short-Term[a]	Maternal NOAEL= 100	LOAEL = 300 mg/kg/day, based chromorhinorrhea and/or abdominal staining	Developmental rat
Dermal, Intermediate- and Long-Term[a]	NOAEL= 84.4	LOAEL > 84.4 mg/kg/day	Two year rat feeding study
Inhalation, Short-Term[b]	NOAEL= 100	LOAEL = 300 mg/kg/day, based on delayed ossification	Developmental rat
Inhalation, Intermediate- and Long-Term[b]	NOAEL= 84.4	LOAEL > 84.4 mg/kg/day	Two year rat feeding study

(a) = Since an oral NOAEL was selected, an dermal absorption factor of 100% of oral absorption (default value) should be used in route-to-route extrapolation.

(b) = Since an oral NOAEL was selected, an inhalation absorption factor of 100% of oral absorption (default value) should be used in route-to-route extrapolation.

ATTACHMENT 2 - FQPA Safety Factor Committee Report (*Available Electronically*)

HED DOC. NO. 014327

September 19, 2000

MEMORANDUM

SUBJECT: *CLOMAZONE* - Report of the FQPA Safety Factor Committee

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: George Kramer, Risk Assessor
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 125401

The FQPA Safety Factor Committee evaluated the available hazard and exposure data for clomazone on August 28, 2000 and made the recommendation for the FQPA safety factor to be used in human health risk assessments (as required by Food Quality Protection Act of August 3, 1996). The committee concluded that the FQPA safety factor could be removed (1x) in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

(*Correspondence:* P.V. Shah to B. Tarplee dated August 23, 2000)

A. Adequacy of the Toxicology Database

The toxicology data base for clomazone is complete. There are adequate studies for evaluating susceptibility following pre- and postnatal exposure including rat and rabbit developmental studies, and a 2-generation rat reproduction study in rats.

B. Determination of Susceptibility

There is no evidence of increased susceptibility of fetuses to *in utero* exposure to clomazone in the developmental toxicity studies in rats and rabbits. There is also no evidence of increased susceptibility of offspring observed in the two-generation reproduction study in rats.

Although developmental and maternal effects occurred at the same dose in the prenatal developmental study in rats, the HIARC concluded that there was no qualitative increase in susceptibility (Refer to HED Doc. No. 014299 for complete report of the HIARC).

C. Requirement of a Developmental Neurotoxicity Study

The HIARC concluded that a developmental neurotoxicity study with clomazone is not required (Refer to HED Doc. No. 014299 for complete report of the HIARC).

II. EXPOSURE ASSESSMENTS

A. Dietary Food Exposure Considerations

(*Correspondence:* P.V. Shah to B. Tarplee dated August 23, 2000)

Clomazone is a broad spectrum herbicide used to control annual grasses and broadleaf weeds. Tolerances have been established (40 CFR §180.425) for residues of clomazone [(2-(2-chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone)], in or on a variety of raw agricultural commodities including snap beans, cottonseed, soybeans, peppers, sweet potatoes, and peas (succulent) at 0.05 ppm and pumpkins, winter and summer squash, cucumbers, and cabbage at 0.1 ppm. Residues in meat, milk, poultry and, eggs are not expected.

There are no monitoring data or percent crop treated information available for clomazone. Field trial data are available including data for the proposed uses: rice; processed rice; and root vegetables. No clomazone residues were detected above the limit of quantification (LOQ) in any of the samples.

The HED Dietary Exposure Evaluation Model (DEEM) will be used to assess the risk from chronic dietary exposure to residues in food resulting from the use of clomazone (no dose and/or endpoint was selected to assess acute dietary exposure). The chronic analysis for dietary exposure to clomazone is expected to assume tolerance level residues and 100 percent crop treated (%CT) for the proposed commodities and all other commodities with tolerances for residues of clomazone in order to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and subgroups of interest.

The Committee recognizes that further refinement to the dietary food exposure analyses may be required as the risk assessment is developed. Therefore, provided the final dietary food exposure assessment includes all metabolic residues of concern and does not underestimate the potential risk for infants and children, the safety factor recommendations of this Committee stand.

B. Dietary Drinking Water Exposure Considerations
(*Correspondence:* J. Breithaupt to B. Tarplee dated August 23, 2000)

The environmental fate database is adequate to characterize drinking water exposure for parent clomazone. In summary, the data indicate that clomazone is relatively mobile and persistent. There is one significant environmental degradate, FMC 65317. The HED Metabolism Assessment Review Committee (MARC) concluded that the parent compound and its major environmental degradate (FMC 65317) need to be included in the drinking water risk assessment.

No monitoring data are available for clomazone. The Generic Estimated Environmental Concentration (GENEEC) model was used to estimate surface water concentrations for clomazone. The SCI-GROW model was run to estimate the ground water concentrations due to possible leaching.

NOTE: According to the HED risk assessor, the estimated environmental concentrations for surface and ground water (previously provided by EFED for the parent compound only) will be adjusted upwards by 100X in order to account for residues of FMC 65317 in the drinking water risk assessment.

The Committee recognizes that further refinement to the dietary drinking water exposure analyses may be required as the risk assessment is developed. Therefore, provided the final dietary drinking water exposure assessment includes all environmental degradates of toxicological concern and does not underestimate the potential risk for infants and children, the safety factor recommendations of this Committee stand.

C. Residential Exposure Considerations
(*Correspondence:* P.V. Shah to B. Tarplee dated August 23, 2000)

There are currently no residential uses of clomazone.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

A. Recommendation of the Factor

The Committee recommended that the FQPA safety factor be **removed (1x).**

B. Rationale for Removing the FQPA Safety Factor

The Committee concluded that the safety factor could be removed for clomazone because:

1. There is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure;
2. A developmental neurotoxicity study is **not** required; and
3. The dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children (there are currently no registered residential uses).

ATTACHMENT 3 - Codex Form

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name: 2-(2-chlorophenyl) methyl-4,4-dimethyl-3-isoxazolidinone	Common Name: clomazone	☒ Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date: 9/5/00

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested	Petition Number: 00LA0024, 8F4985, 9E06063, & 6F4738. DP Barcode: D268283 Other Identifier:
Residue definition:N/A	Reviewer/Branch: G.F. Kramer
	Residue definition: parent only

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Tanier, cassava, yams, & arracacha	0.05
		rice	0.05
		cucurbit vegetables	0.10
		sugarcane	0.05

Limits for Canada	Limits for Mexico
☐ No Limits X No Limits for the crops requested	☐ No Limits ☐ No Limits for the crops requested
Residue definition: 2-(2-chlorobenzyl)-4,4-dimethyl-1,2-oxazolidin-3-one	Residue definition:clomazone

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
		sugar cane	0.050

Notes/Special Instructions:.

Rev 1998

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ATTACHMENT 4 - Dietary Exposure Analyses (*Available Electronically*)

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 14-SEP-2000

SUBJECT: **Clomazone - Acute and Chronic Dietary Exposure Analyses.**
PP#s: 00LA0024, 9E6063, 7F4896, and 7E4865. Chemical: 125401.
DP Barcode: D268388. Case: 289118. Submission: S568659. 40 §CFR 180.425.

FROM: Jennifer E. Rowell, Chemist
Registration Action Branch 1 (RAB1)
Health Effects Division (HED) (7509C)

THROUGH: Christina Swartz, Chemist
Doug Dotson, Chemist
Dietary Exposure Science Advisory Council (DE SAC)

G. Jeffrey Herndon, Acting Branch Senior Scientist
RAB1/HED (7509C)

TO: Jessica Kidwell, Environmental Protection Specialist
RAB1/HED (7509C)

Action Requested

Provide estimates of the acute and chronic dietary exposures and associated risks for the herbicide clomazone resulting from the existing and proposed uses (PP# 00LA0024, 9E6063, 7F4896, and 7E4865).

Executive Summary

Conservative, deterministic acute and chronic dietary exposure analyses for clomazone were performed using the Dietary Exposure Evaluation Model (DEEM™). For all commodities, tolerance level residues were used and 100% crop treated (CT) was assumed. The acute analysis was conducted for females 13-50 years old. At the 95th percentile, the acute dietary exposure estimate for females 13-50 years old accounted for <1% of the acute Population Adjusted Dose

(aPAD). The chronic analysis was conducted for the general U.S. population and all population subgroups. The chronic exposure estimates for the general U.S. population and all population subgroups accounted for <1% of the chronic Population Adjusted Dose (cPAD). **The results of the analyses indicate that the acute and chronic dietary risk estimates associated with the existing and proposed uses of clomazone do not exceed HED's level of concern for the U.S. population and all population subgroups.**

Toxicological Endpoints

On August 10, 2000, the HED Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for clomazone with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to clomazone was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 (HED Doc. No. 014299, G. Reddy, 8/14/00). A summary of the doses and toxicological endpoints chosen by HIARC is listed in Table 1.

Cancer

The HIARC classified clomazone as a "not likely human carcinogen" based on the lack of carcinogenic response in rats and mice and the lack of mutagenic concern. Further, there are no data in the literature or SAR information to indicate carcinogenic potential (Yintak Woo, personal communication, August 14, 2000) (HED Doc. No. 014299, G. Reddy, 8/14/00).

FQPA Recommendation

The HED FQPA Safety Factor Committee (SFC) evaluated the available hazard and exposure data for clomazone on August 28, 2000 and made the recommendation for the FQPA safety factor to be used in human health risk assessments (as required by FQPA of August 3, 1996). The Committee concluded that the 10x FQPA safety factor should be reduced to 1x in assessing the risk posed by this chemical (Memo in progress, B. Tarplee).

The aPAD and cPAD are modifications of the acute and chronic RfDs to accommodate the FQPA safety factor. The aPAD is equal to the acute RfD divided by the FQPA safety factor, and the cPAD is equal to the chronic RfD divided by the FQPA safety factor. As the FQPA SFC recommended that the 10x FQPA safety factor be reduced to 1x, the acute and chronic RfDs and the aPAD and cPAD are equivalent. The aPAD for females 13-50 years old is 1.0 mg/kg/day (RfD of 1.0 mg/kg/day ÷ 1x safety factor). The cPAD for the U.S. population and all population subgroups is 0.84 mg/kg/day (RfD of 0.84 mg/kg/day ÷ 1x FQPA safety factor).

Table 1. Summary of Doses and Toxicological Endpoint Selections for Clomazone.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (females 13-50 years old)	NOAEL= 100 UF = 100 FQPA SF = 1	LOAEL = 300 mg/kg/day, based on delayed ossification	Developmental rat
		Acute RfD [a] = aPAD [b] = 1.0 mg/kg/day	
Chronic Dietary	NOAEL = 84.4 UF = 100 FQPA SF = 1	LOAEL > 84.4 mg/kg/day LOAEL = 319.3 mg/kg/day LOAEL = 100 mg/kg/day	Two year rat feeding study 90-day oral rat 2-Gen Repro.
		Chronic RfD [a] = cPAD [b] = 0.84 mg/kg/day	

a. $\text{RfD} = \text{NOAEL} / \text{UF}$

b. $\text{aPAD or cPAD} = \text{(acute or chronic) RfD} / \text{FQPA Safety Factor}$

Residues of Concern

The nature of the residue in plants and livestock is adequately understood. The residue of concern is clomazone *per se* [as specified in 40 §CFR 180.425].

Residue Information

Permanent tolerances are currently established for residues of the herbicide clomazone in/on the following raw agricultural commodities (RACs): beans, snap (0.05 ppm); cabbage (0.1 ppm); cotton, seed (0.05 ppm); cucumbers (0.1 ppm); peas (succulent) (0.05 ppm); peppers (0.05 ppm); pumpkins (0.1 ppm); soybeans (0.05 ppm); squash, summer (0.1 ppm); squash, winter (0.1 ppm); and sweet potatoes (0.05 ppm). In addition, time-limited tolerances are established for clomazone residues in/on watermelon at 0.01 ppm (expiration date 5/30/01); and rice, grain (0.1 ppm) and rice, straw (0.01 ppm) (expiration date 12/31/01). The proposed uses for clomazone and corresponding tolerance levels for residues of clomazone are listed in Table 2.

Table 2: Proposed Uses for Clomazone.

RAC(s)	Tolerance	PP#
Tanier	0.05	9E6063
Cassava	0.05	
Yams	0.05	
Arracacha	0.05	
Rice	0.05	7F4896
Cucurbit Vegetables	0.10	7E4865

RAC(s)	Tolerance	PP#
Sugarcane	0.05	00LA0024

For all RACs, existing and proposed tolerance level residues were used and 100% CT was assumed. As residues in meat, milk, poultry, and eggs are not expected, these commodities were not included in the assessment. DEEM ™ default concentration factors were used for all RACs. A summary of the residue information used in the acute and chronic analyses is attached (Attachment 1).

Consumption Data

HED conducts dietary risk assessments using DEEM™, which incorporates consumption data generated in USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, one-day consumption data are summed and a food consumption distribution is calculated for each population subgroup of interest. The consumption distribution can be multiplied by a residue point estimate for a deterministic exposure/risk assessment, or be used with a residue distribution in a probabilistic type risk assessment. Acute exposure estimates are expressed in mg/kg bw/day and as a percent of the aPAD. For chronic risk assessments, residue estimates for foods or food-forms of interest are multiplied by the average consumption estimate of each food/food-form of each population subgroup. Chronic exposure estimates are expressed in mg/kg bw/day and as a percent of the cPAD.

Dietary Exposure Assessment

Acute Dietary Exposure Analysis

The acute analysis was performed for females 13-50 years old. The aPAD for females 13-50 years old is 1.0 mg/kg/day. The acute dietary exposure estimate at the 95th percentile for females 13-50 years old is presented in Table 3. A detailed listing of acute dietary exposure estimates is attached (Attachment 2).

Table 3. Summary of Results from Acute DEEM ™ Analyses of Clomazone at the 95th Percentile.

Subgroup	95th Percentile	
	Exposure (mg/kg/day)	% aPAD
Females (13-50 years)	0.000265	<1

Chronic Dietary Exposure Analysis

The chronic analysis was performed for the general U.S. population and all population subgroups. The cPAD for the general U.S. population and all population subgroups is 0.84 mg/kg/day. Chronic dietary exposure estimates for the U.S. population and other population subgroups (i.e.,

children, infants, females, and males) are presented in Table 4. A detailed listing of chronic dietary exposure estimates is attached (Attachment 3).

Table 4. Summary of Results from Chronic DEEM ™ Analysis of Clomazone.

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (total)	0.000099	<1
All Infants (< 1 year old)	0.000332	<1
Children 1-6 years old	0.000182	<1
Children 7-12 years old	0.000122	<1
Females 13-50 years old	0.000079	<1
Males 13-19 years old	0.000085	<1
Males 20+ years old	0.000080	<1
Seniors 55+ years old	0.000091	<1

Conclusions

The acute exposure estimates for females 13-50 years old accounted for <1% of the aPAD at the 95th percentile. For acute dietary risk estimates, HED's level of concern is >100% aPAD. The results of the acute analysis indicate that the acute dietary risk estimates for females 13-50 years old (at the 95th percentile) associated with the existing and proposed uses of clomazone do not exceed HED's level of concern.

The chronic exposure estimates for the general U.S. population and all population subgroups accounted for <1% of the cPAD. For chronic dietary risk estimates, HED's level of concern is >100% cPAD. The results of the chronic analysis indicate that the chronic dietary risk estimates for the general U.S. population and all population subgroups associated with the existing and proposed uses of clomazone do not exceed HED's level of concern.

Attachments

Attachment 1: Clomazone Residue File for Acute and Chronic DEEM™ Analyses.
Attachment 2: Clomazone Acute DEEM™ Analysis (Females 13-50 years old) (J. Rowell, 9/7/00).
Attachment 3: Clomazone Chronic DEEM™ Analysis (J. Rowell, 9/7/00).

cc (w/ Attachments): M.Sahafeyen (CEB1); Tobi Colvin-Snyder (RD-7505C)
RDI: DE SAC [Swartz (9/10/00), Dotson (9/11/00)]; G. Herndon (9/14/00)
J.Rowell:806W:CM#2:(703)305-5564: 7509C:RAB1

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Attachment 1: Clomazone Residue File for Acute and Chronic DEEM Analyses.

Filename: C:\MyFiles\DEEM\Clomazone\125401.rs7 Chemical: Clomazone
RfD(Chronic): .84 mg/kg bw/day NOEL(Chronic): 84 mg/kg bw/day
RfD(Acute): 1 mg/kg bw/day NOEL(Acute): 100 mg/kg bw/day
Date created/last modified: 09-07-2000/13:49:50/8 Program ver. 7.075
Comment: Section 3: PP#s 9E6063, 7F4896, and 7E4865. Section 18: 00LA0024. Requestor: J. Kidwell. 10x FQPA SF reduced to 1x, therefore RfDs and PADs are equivalent.

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
203	1CD	Artichokes-jerusalem	0.050000	1.000	1.000	PP#9E6063
497	9B	Balsam pear	0.100000	1.000	1.000	PP#7E4865
234	6A	Beans-succulent-green	0.050000	1.000	1.000	PP#5E4521
152	9B	Bitter melon	0.100000	1.000	1.000	PP#7E4865
170	5A	Cabbage-green and red	0.100000	1.000	1.000	PP#4E4311
383	5B	Cabbage-savoy	0.100000	1.000	1.000	PP#4E4311
143	9A	Casabas	0.100000	1.000	1.000	PP#7E4865
222	1CD	Cassava (yuca blanca)	0.050000	1.000	1.000	PP#9E6063
386	9B	Christophine	0.100000	1.000	1.000	PP#7E4865
291	O	Cottonseed-meal	0.050000	1.000	1.000	PP#2F4077
290	O	Cottonseed-oil	0.050000	1.000	1.000	PP#2F4077
144	9A	Crenshaws	0.100000	1.000	1.000	PP#7E4865
148	9B	Cucumbers	0.100000	1.000	1.000	PP#7E4865
124	1CD	Ginger	0.050000	1.000	1.000	PP#9E6063
141	9A	Melons-cantaloupes-juice	0.100000	1.000	1.000	PP#7E4865
142	9A	Melons-cantaloupes-pulp	0.100000	1.000	1.000	PP#7E4865
145	9A	Melons-honeydew	0.100000	1.000	1.000	PP#7E4865
146	9A	Melons-persian	0.100000	1.000	1.000	PP#7E4865
397	9B	Okra/chinese (luffa)	0.100000	1.000	1.000	PP#7E4865
241	6AB	Peas (garden)-green	0.050000	1.000	1.000	PP#8E3608
405	6B	Peas-succulent/blackeye/cowpea	0.050000	1.000	1.000	PP#8E3608
156	8	Peppers-chilli incl jalapeno	0.050000	1.000	1.000	PP#9E3778
157	8	Peppers-other	0.050000	1.000	1.000	PP#9E3778
155	8	Peppers-sweet(garden)	0.050000	1.000	1.000	PP#9E3778
149	9B	Pumpkin	0.100000	1.000	1.000	PP#7E4865
408	15	Rice-bran	0.050000	1.000	1.000	PP#7F4896
271	15	Rice-milled (white)	0.050000	1.000	1.000	PP#7F4896

270	15	Rice-rough (brown)	0.050000	1.000	1.000	PP#7F4896
303	6A	Soybean-other	0.050000	1.000	1.000	PP#4F3128
307	6A	Soybeans-flour (defatted)	0.050000	1.000	1.000	PP#4F3128
306	6A	Soybeans-flour (low fat)	0.050000	1.000	1.000	PP#4F3128
305	6A	Soybeans-flour (full fat)	0.050000	1.000	1.000	PP#4F3128
304	6A	Soybeans-mature seeds dry	0.050000	1.000	1.000	PP#4F3128
297	6A	Soybeans-oil	0.050000	1.000	1.000	PP#4F3128
482	O	Soybeans-protein isolate	0.050000	1.000	1.000	PP#4F3128
255	6A	Soybeans-sprouted seeds	0.050000	0.330	1.000	PP#4F3128
150	9B	Squash-summer	0.100000	1.000	1.000	PP#7E4865
415	9B	Squash-spaghetti	0.100000	1.000	1.000	PP#7E4865
151	9B	Squash-winter	0.100000	1.000	1.000	PP#7E4865
283	O	Sugar-cane	0.050000	1.000	1.000	PP#00L0024
284	O	Sugar-cane/molasses	0.050000	1.000	1.000	PP#00L0024
218	1CD	Sweet potatoes (incl yams)	0.050000	1.000	1.000	PP#9E6063
418	2	Sweet potatos-leaves	0.050000	1.000	1.000	PP#9E6063
201	1CD	Taro-root	0.050000	1.000	1.000	PP#9E6063
137	1CD	Turmeric	0.050000	1.000	1.000	PP#9E6063
147	9A	Watermelon	0.100000	1.000	1.000	PP#7E4865
436	9A	Watermelon-juice	0.100000	1.000	1.000	PP#7E4865
439	9B	Wintermelon	0.100000	1.000	1.000	PP#7E4865
221	1CD	Yam-bean tuber (jicama)	0.050000	1.000	1.000	PP#9E6063
224	1CD	Yautia (tanier)	0.050000	1.000	1.000	PP#9E6063

Attachment 2: Clomazone Acute DEEM™ Analysis (Females 13-50 years old) (J. Rowell, 9/7/00).

```
U.S. Environmental Protection Agency                                    Ver. 7.075
DEEM ACUTE analysis for CLOMAZONE                                   (1989-92 data)
Residue file: 125401.rs7                              Adjustment factor #2 NOT used.
Analysis Date: 09-07-2000/13:58:21    Residue file dated: 09-07-2000/13:56:05/8
NOEL (Acute) = 100.000000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "Section 3:  PP#s 9E6063, 7F4896, and 7E4865.  Section 18:  00LA0024.
Requestor: J. Kidwell. 10x FQPA SF reduced to 1x, therefore RfDs and PADs are
equivalent."
================================================================================

Summary calculations (per capita):

      95th Percentile              99th Percentile              99.9th Percentile
 Exposure  % aRfD     MOE     Exposure  % aRfD     MOE     Exposure  % aRfD     MOE
---------- ------- -------- ---------- ------- -------- ---------- ------- --------
Females 13+ (preg/not nursing):
  0.000291    0.03   343970    0.000676    0.07   148016    0.000915    0.09   109297
Females 13+ (nursing):
  0.000398    0.04   251023    0.000512    0.05   195500    0.000676    0.07   147823
Females 13-19 (not preg or nursing):
  0.000229    0.02   435896    0.000715    0.07   139945    0.001328    0.13    75308
Females 20+ (not preg or nursing):
  0.000313    0.03   319410    0.000570    0.06   175567    0.001160    0.12    86200
Females 13-50 yrs:
  0.000265    0.03   376685    0.000582    0.06   171745    0.001006    0.10    99448
```

Attachment 4: Clomazone Chronic DEEM™ Analysis (J. Rowell, 9/7/00).

U.S. Environmental Protection Agency Ver. 7.075
DEEM Chronic analysis for CLOMAZONE (1989-92 data)
Residue file name: C:\MyFiles\DEEM\Clomazone\125401.rs7 Adjustment factor #2 NOT used.
Analysis Date 09-07-2000/13:57:01 Residue file dated: 09-07-2000/13:56:05/8
Reference dose (RfD, Chronic) = .84 mg/kg bw/day
COMMENT 1: Section 3: PP#s 9E6063, 7F4896, and 7E4865. Section 18: 00LA0024.
Requestor: J. Kidwell. 10x FQPA SF reduced to 1x, therefore RfDs and PADs are equivalent.

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Population (total)	0.000099	0.0%
U.S. Population (spring season)	0.000098	0.0%
U.S. Population (summer season)	0.000122	0.0%
U.S. Population (autumn season)	0.000093	0.0%
U.S. Population (winter season)	0.000082	0.0%
Northeast region	0.000110	0.0%
Midwest region	0.000090	0.0%
Southern region	0.000100	0.0%
Western region	0.000096	0.0%
Hispanics	0.000109	0.0%
Non-hispanic whites	0.000095	0.0%
Non-hispanic blacks	0.000112	0.0%
Non-hisp/non-white/non-black	0.000133	0.0%
All infants (< 1 year)	0.000332	0.0%
Nursing infants	0.000056	0.0%
Non-nursing infants	0.000449	0.1%
Children 1-6 yrs	0.000182	0.0%
Children 7-12 yrs	0.000122	0.0%
Females 13-19 (not preg or nursing)	0.000081	0.0%
Females 20+ (not preg or nursing)	0.000084	0.0%
Females 13-50 yrs	0.000079	0.0%
Females 13+ (preg/not nursing)	0.000078	0.0%
Females 13+ (nursing)	0.000106	0.0%
Males 13-19 yrs	0.000085	0.0%
Males 20+ yrs	0.000080	0.0%
Seniors 55+	0.000091	0.0%
Pacific Region	0.000096	0.0%

80

ATTACHMENT 5: Drinking Water Assessment for Clomazone (*Available Electronically)*

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

PC Code: 125401 October 23, 2000

MEMORANDUM

SUBJECT: Water Memorandum for Clomazone Incorporating both Parent Clomazone and the Metabolite FMC 65,317 (DP Barcode D269748).

TO: Tobi Colvin-Snyder, PM #25
Registration Division (7505C)

FROM: James Breithaupt, Agronomist
Environmental Risk Branch II
Environmental Fate and Effects Division (7507C)

James Breithaupt 10-23-00

THRU: Tom Bailey, Chief
Environmental Risk Branch II,
Environmental Fate and Effects Division (7507C)

Tom A. Bailey 10-24-00

In the Section 3 document dated 6/2/2000, EFED provided drinking water estimates for parent clomazone only for the uses listed below. Since that time, the HED MARC has decided that both parent clomazone and the metabolite FMC 65,317 should be included in a drinking water assessment. As a result, EFED is now providing estimates of drinking water concentrations for both compounds in surface and ground water for the proposed new 3ME uses on rice and sugarcane, new 4EC uses on IR-4 crops (tanier, cassava, yams, sweet potato, arracacha), and the existing 3ME uses on cotton, pepper, soybeans, and sweet potatoes.

Since there are no available monitoring data for clomazone, the modeled concentrations should be used for the dietary exposure assessment. Table 1 presents the Tier 1 EEC's for **surface water** using GENEEC and GENEECX. **For surface water, the maximum acute concentration of 94.8 ppb and the maximum chronic (56-day) concentration of 68.1 ppb should be used.** Table 2 presents the Tier 1 acute and chronic **ground water** concentrations using the SCI-GROW2 model. For ground water, the maximum EEC of 2.4 ppb should be used for acute, chronic, and cancer assessment. These recommendations are based upon the proposed uses of clomazone as specified on the Command 3ME® label and contained in this memorandum.

Attachment 1 contains the GENEEC and GENEECX modeling outputs and Attachment 2 contains the SCI-GROW2 outputs.

Table 1.Tier I upper tenth percentile EEC's for Clomazone.

Crop	Maximum (g L^{-1})	4 Day (g L^{-1})	21 Day (g L^{-1})	56 Day (g L^{-1})
Sweet Potato, tanier, yams, and arracacha	54.0	52.8	47.1	38.1
Cotton	45.0	44.0	39.3	31.8
Sugarcane	36.0	44.0	39.3	31.8
Pepper	36.0	35.2	31.4	25.4
Soybeans	36.0	35.2	31.4	25.4
Rice (AR)*	81.3	69.6	70.1	58.4
Rice (LA)*	94.8	81.2	81.8	68.1
Rice (TX)*	94.8	81.2	81.8	68.1

* GENEECX uses different rainfall volumes for Arkansas compared to Louisiana and Texas (same for LA and TX).

Table 2. Acute and Chronic Concentrations of Parent Clomazone and Metabolites in Ground Water Using SCI-GROW.*

Crop	Acute (g L^{-1})	Chronic (g L^{-1})	Cancer (g L^{-1})
Sweet Potato, tanier, yams, and arracacha	2.4	2.4	2.4
Cotton	2.0	2.0	2.0
Sugarcane	2.0	2.0	2.0
Pepper	1.6	1.6	1.6
Soybeans	1.6	1.6	1.6

* SCI-GROW is not appropriate for rice since rice production requires a soil that can hold a flood. SCI-GROW assumes a soil that is vulnerable to leaching.

Aerobic aquatic metabolism data for clomazone were recently upgraded to acceptable with submission of additional data. Therefore, the 346-day aerobic aquatic metabolism half-life which was calculated by multiplying the aerobic soil metabolism half-life of 173 days by 2 was no longer used. Instead, EFED is now using a 63 day aerobic aquatic metabolism half-life, which is based on parent clomazone and the metabolite FMC 65,317. Table 3 below lists the GENEEC inputs for the terrestrial crops and Table 4 below lists the GENEECX inputs for clomazone used on rice. Table 5 below lists the SCI-GROW2 inputs for clomazone used on terrestrial crops. The comment column of each table lists the justification for each input.

Table 3. Surface Water Exposure Inputs for GENEEC for Clomazone for Sweet Potato, Sugarcane, Cotton, Soybeans, and Peppers.

MODEL INPUT VARIABLE	INPUT VALUE	COMMENTS
Application Rate (lbs ai/A)	1.50 (sweet potato, tanier, yams, and arracacha) 1.25 (Sugarcane, cotton, 1.0 (Soybeans, peppers	Proposed maximum rates from attached labels.
Maximum No. of Applications	1(Sugarcane)	Sugarcane–1 preemergence application/year in spring or fall Other crops–1 preemergence application/year
Application Interval (days)	N/A	
K_{oc}	152	for Cosad Sdy. Loam, the only available value, (MRID #44864488). Kd of 1.76/1.16 % OC. 1.16 % is the OC content of the Loring silt loam soil.
Aerobic Soil Metabolic Half-life (days)	173	Half-life of Clomazone from ACC# 072819
Is the pesticide wetted-in?	No	Proposed use information in summary document.
Depth of Incorporation (in.)	0 (not incorporated)	EFED recommends incorporation due to volatility characteristics of clomazone.
Spray Drift (%)	1(all crops)	Aerial or airblast = 5%; Ground = 1%; Granular = 0% Label does not allow for aerial or chemigation
Solubility (mg/L)	1,100	EFGWB One-liner database
Aerobic Aquatic Metabolic Half-life (days)	63	R^2=0.78, F=90, p=5.88e^{-10}, MRID 44348404
Photolysis Half-life (days)	87 days	MRID #44864488

Table 4. Surface Water Exposure Inputs for GENEECX for 3ME Clomazone on Dry-Seeded Rice.

MODEL INPUT VARIABLE	INPUT VALUE	COMMENTS
Choose Crop	B (rice)	Program allows several crops.
Choose Crop Production Method (A for dry-seeded), (B for water-seeded)	A (dry-seeded rice)	Program allows two different methods of rice production.
Length of time after planting but prior to flooding (days)	28	Program recommends using 28 days as a maximum.
State	A,C	Separate runs. Program assumes different storm volumes and runoff volumes for Arkansas, California, and Louisiana and Texas (LA and TX are same)
Application Rate (lbs ai/A)	0.6	Label #279-3158 allows 0.4-0.6 lbs ai/A
Maximum No. of Applications	1	Other crops–1 preemergence application/year
Application Interval (days)	N/A	
K_d	1.76	for Cosad Sdy. Loam, the only available value, (MRID #44864488). Koc of 152/1.16 %. 1.16 % is the OC content of the Loring silt loam soil.
Aerobic Soil Metabolic Half-life (days)	173	Half-life of Clomazone from ACC# 072819 (Ref 6)-1984
Method of Application (air, ground, or granular)	B (Ground)	Label #279-3158 allows only ground application of 3ME clomazone.
Depth of Incorporation (in.)	0 (not incorporated)	EFED recommends incorporation due to volatility characteristics of clomazone.
Water Solubility (mg/L)	1,100	EFGWB One-liner database
Aerobic Aquatic Metabolic Half-life (days)	63	R^2=0.78, F=90, p=5.88e^{-10}, MRID 44348404
Photolysis Half-life (days)	87 days	MRID #44864488
Dilution Factor	2	The model allows different dilution factors. EFED has used a dilution factor of 2 in previous assessments.

Limitations of This Analysis

There are certain limitations imposed when Tier I EEC's are used for drinking water exposure estimates. A single 10 hectare field with a 1 hectare pond does not reflect the dynamics in a watershed large enough to support a drinking water facility. A basin of this size would likely not be planted completely to a single crop nor be completely treated with a pesticide. Additionally, treatment with the pesticide would likely

occur over several days or weeks, rather than all on a single day. This would reduce the magnitude of the concentration peaks, but also make them broader, reducing the acute exposure but perhaps increasing the chronic exposure. The fact that the simulated pond has no outlet is also a limitation as water bodies in this size range would have at least some flow through (rivers) or turnover (reservoirs). In spite of these limitations, a Tier I EEC can provide a reasonable upper bound on the concentration found in drinking water if not an accurate assessment of the true concentration. The EEC'S have been calculated so that in any given year, there is a 10% probability that the maximum average concentration of that duration in that year will equal or exceed the EEC at the site. Risk assessment using Tier I values can capably be used as refined screens to demonstrate that the risk is below the level of concern.

Table 5. Ground Water Exposure Inputs for SCI-GROW2 for Parent Clomazone.

MODEL INPUT VARIABLE	INPUT VALUE	COMMENTS
Application Rate (lbs. ai/A)	1.50 (sweet potato, tanier, yams, and arracacha) 1.25 (Sugarcane, cotton, 1.0 (Soybeans, peppers	Proposed maximum rates from attached labels.
Maximum No. of Applications	1	Proposed maximum number of applications in summary document.
K_{oc}	152	for Cosad Sdy. Loam, the only available value, (MRID #4486-4488)
Aerobic Soil Metabolic Half-life (days)	173	Half-life of Clomazone from ACC# 072819 (Ref 6)-1984

Method for Estimating Concentrations in Ground Water

Results from the SCI-GROW2 (Screening Concentrations in Ground Water) model predict that the maximum chronic concentration of parent clomazone in shallow ground water is not expected to exceed 2.4 ug/L for the proposed maximum rate of 1 application at 1.5 lbs ai/A to sweet potato, tanier, yams, and arracacha.

The SCI-GROW2 model is a model for estimating maximum concentrations of pesticides in ground water. SCI-GROW2 provides a screening concentration, an estimate of likely ground water concentrations if the pesticide is used at the maximum allowed label rate in areas with ground water exceptionally vulnerable to contamination. In most cases, a majority of the use area will have ground water that is less vulnerable to contamination than the areas used to derive the SCI-GROW2 estimate.

The SCI-GROW2 model is based on scaled ground water concentration from ground water monitoring studies, environmental fate properties (aerobic soil half-lives and organic carbon partitioning coefficients- K_{oc}'s) and application rates. The model is based on permeable soils that are vulnerable to leaching and on shallow ground water (10-30 feet).

Attachment 1. GENEEC and GENEECX Runs for Total Toxic Clomazone (Parent and FMC 65,317).

GENEEC Runs

RUN No. 1 FOR clomazone INPUT VALUES

RATE (#/AC) ONE(MULT)	APPLICATIONS NO.-INTERVAL	SOIL KOC	SOLUBILITY (PPM)	% SPRAY DRIFT	INCORP DEPTH(IN)
1.500(1.500)	1 1	152.0	1100.0	1.0	.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
172.00	2	N/A	87.00-10674.90	63.00	62.63

GENERIC EECs (IN PPB)

PEAK GEEC	AVERAGE 4 DAY GEEC	AVERAGE 21 DAY GEEC	AVERAGE 56 DAY GEEC
53.93	52.82	47.13	38.10

RUN No. 2 FOR clomazone INPUT VALUES

RATE (#/AC) ONE(MULT)	APPLICATIONS NO.-INTERVAL	SOIL KOC	SOLUBILITY (PPM)	% SPRAY DRIFT	INCORP DEPTH(IN)
1.000(1.000)	1 1	152.0	1100.0	1.0	.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
172.00	2	N/A	87.00-10674.90	63.00	62.63

GENERIC EECs (IN PPB)

PEAK GEEC	AVERAGE 4 DAY GEEC	AVERAGE 21 DAY GEEC	AVERAGE 56 DAY GEEC
35.96	35.21	31.42	25.40

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RUN No. 3 FOR clomazone INPUT VALUES

RATE (#/AC) ONE(MULT)	APPLICATIONS NO.-INTERVAL	SOIL KOC	SOLUBILITY (PPM)	% SPRAY DRIFT	INCORP DEPTH(IN)
1.250(1.250)	1 1	152.0	1100.0	1.0	.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
172.00	2	N/A	87.00-10674.90	63.00	62.63

GENERIC EECs (IN PPB)

PEAK GEEC	AVERAGE 4 DAY GEEC	AVERAGE 21 DAY GEEC	AVERAGE 56 DAY GEEC
44.95	44.02	39.27	31.75

GENEECX Runs

RUN No. 1 FOR clomazone ON RICE IN ARK * INPUT VALUES *

RATE (#/AC) ONE(MULT)	APPLICATIONS NO.-INTERVAL	SOIL KD	SOLUBILITY (PPM)	SEEDING SCENARIO	INCORP DEPTH(IN)
0.600(0.600)	1 1	1.8	1100.0	A(DRY)	0.0

DRY AND FLOODED FIELD HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS BEFORE FLOODING	HYDROLYSIS (PADDY)	PHOTOLYSIS (PADDY-EFF)	METABOLIC (PADDY)	COMBINED (PADDY)
173.00	28	N/A	87.00-539.40	63.00	56.41

GENERIC EECs (IN PPB) (DILUTION FACTOR = 2.)

PEAK GEEC	AVERAGE 4 DAY GEEC	AVERAGE 21 DAY GEEC	AVERAGE 56 DAY GEEC
81.27	69.63	70.14	58.39

RUN No. 2 FOR clomazone ON RICE IN LA * INPUT VALUES *

RATE (#/AC) ONE(MULT)	APPLICATIONS NO.-INTERVAL	SOIL KD	SOLUBILITY (PPM)	SEEDING SCENARIO	INCORP DEPTH(IN)
0.600(0.600)	1 1	1.8	1100.0	A(DRY)	0.0

DRY AND FLOODED FIELD HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS BEFORE FLOODING	HYDROLYSIS (PADDY)	PHOTOLYSIS (PADDY-EFF)	METABOLIC (PADDY)	COMBINED (PADDY)
173.00	28	N/A	87.00-539.40	63.00	56.41

GENERIC EECs (IN PPB) (DILUTION FACTOR = 2.)

PEAK GEEC	AVERAGE 4 DAY GEEC	AVERAGE 21 DAY GEEC	AVERAGE 56 DAY GEEC
94.82	81.24	81.83	68.12

Attachment 2. SCI-GROW Runs for Total Toxic Clomazone

RUN No. 1 FOR clomazone INPUT VALUES

APPL (#/AC) RATE	APPL. NO.	URATE (#/AC/YR)	SOIL KOC	SOIL METABOLISM (DAYS) AEROBIC
1.500	1	1.500	152.0	173.0

GROUND-WATER SCREENING CONCENTRATIONS IN PPB

2.421292

A= 168.000 B= 157.000 C= 2.225 D= 2.196 RILP= 4.015
F= .208 G= 1.614 URATE= 1.500 GWSC= 2.421292

RUN No. 2 FOR clomazone INPUT VALUES

APPL (#/AC) RATE	APPL. NO.	URATE (#/AC/YR)	SOIL KOC	SOIL METABOLISM (DAYS) AEROBIC
1.000	1	1.000	152.0	173.0

GROUND-WATER SCREENING CONCENTRATIONS IN PPB

1.614194

A= 168.000 B= 157.000 C= 2.225 D= 2.196 RILP= 4.015
F= .208 G= 1.614 URATE= 1.000 GWSC= 1.614194

RUN No. 3 FOR clomazone INPUT VALUES

APPL (#/AC) RATE	APPL. NO.	URATE (#/AC/YR)	SOIL KOC	SOIL METABOLISM (DAYS) AEROBIC
1.250	1	1.250	152.0	173.0

GROUND-WATER SCREENING CONCENTRATIONS IN PPB

2.017743

A= 168.000 B= 157.000 C= 2.225 D= 2.196 RILP= 4.015
F= .208 G= 1.614 URATE= 1.250 GWSC= 2.017743

ATTACHMENT 6: Incident Report (*Available Electronically)*

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

September 27, 2000

MEMORANDUM

SUBJECT: Updated Review of Clomazone Incident Reports
DP Barcode D268806, Chemical #125401,

FROM: Jerome Blondell, Ph.D., Health Statistician
Chemistry and Exposure Branch 1
Health Effects Division (7509C)

Monica F. Spann, M.P.H., Environmental Health Scientist
Chemistry and Exposure Branch 1
Health Effects Division (7509C)

THRU: Francis Suhre, Senior Scientist
Chemistry and Exposure Branch 1
Health Effects Division (7509C)

TO: Tobi Colvin-Snyder
Special Review and Reregistration (7508C)

I. BACKGROUND

The following data bases have been consulted for the poisoning incident data on the active ingredient Clomazone (PC Code: 125401):

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested.

2) Poison Control Centers - as the result of Data-Call-Ins issued in 1993, OPP received data covering the years 1985 through 1992 for 28 organophosphate and carbamate chemicals. Subsequently EPA purchased Poison Control Center data on all pesticides for the years 1993-1998. Most of the national Poison Control Centers

(PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc.

3) California Department of Food and Agriculture (replaced by the Department of Pesticide Regulation in 1991) - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

II. INCIDENT DATA SYSTEM

Please note that the following cases from the IDS do not have documentation confirming exposure or health effects unless otherwise noted.

The following incidents involved exposure to **Command EC** formulations:

Incident#165-30
A pesticide incident occurred in 1992, when an individual mixed the product and it splashed into their eyes. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#165-44
A pesticide incident occurred in 1992, when three workers reported numbness. No further information on the disposition of the case was reported.

Incident#165-56
A pesticide incident occurred in 1992, when an individual splashed the product into their eyes. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#256-21

A pesticide incident occurred in 1992, when a spray hose broke and a mixer was sprayed with the product. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#577-1 and Incident#662-1 and 662-2

A pesticide incident occurred in 1993, when several residents reported sore throats, nausea, diarrhea, headaches, stomach cramps, numbness, severe bronchial infection, and tingling after they were exposed to spray drift. Medical records were obtained on this potential cluster of cases and EPA Regions were surveyed to find out if others had reported similar complaints. This review concluded:

> There appears to be no clear link between the symptoms reported in New Hampshire and other states and exposure to Command herbicide. Many of the symptoms are inconsistent with what is known about the toxicology of Command. Often the timing of symptoms was inconsistent with poisoning. Only rarely was medical or veterinary documentation obtained which would permit a proper assessment of the effects. In two cases the complaint of health effects was not made until 3 months after the exposure incident. The pattern of symptoms is not consistent with any particular disease endpoint or toxicological profile that would suggest poisoning by the herbicide Command.
>
> An additional health review will be provided of the medical records in the New Hampshire case by Dr. Sheldon Wagner, OPP's physician consultant. This review is attached. Dr. Wagner's conclusion was the same; that there is no causal connection that can be made with reported health complaints and exposure to Command. (Review of adverse health effects attributed to Command. Memorandum from Jerome Blondell to Karen Hicks, February 9, 1994).

Incident#582-37

A pesticide incident occurred in 1993, when a hose broke while an applicator, who was not wearing safety eyewear, sprayed the product that got into their eyes. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#843-6

In a lawsuit, the plaintiff alleged that exposure to clomazone caused respiratory effects.

Incident#844-20

A pesticide incident occurred in 1993, when the product was sprayed off target. Several people reported malaise. No further information on the disposition of the case was reported.

Incident#1170-1
In a lawsuit, the plaintiff alleged that exposure to clomazone caused acute bronchitis and conjunctivitis.

Incident#1179-57
A pesticide incident occurred in 1994, when a boy reported coughing several days after the product was applied nearby. No further information on the disposition of the case was reported.

Incident#1280-20
A pesticide incident occurred in 1994, when an individual reported burning and swollen eyes forty-five days after the product was applied near their home. Development or persistence of symptoms this long after applications is unlikely. No further information on the disposition of the case was reported.

Incident#2290-12
A pesticide incident occurred in 1995, when several workers, who wore personal protective equipment, reported a skin rash after they applied the product. No further information on the disposition of the case was reported.

Incident#2423-1
In a lawsuit, the plaintiff alleged that exposure to clomazone caused painful bowel dysfunction resulting in a permanent disability, tinnitus, and depression. Two other lawsuits, Incident#2423-2 and Incident#2423-3, did not specify any specific symptoms.

Incident#2423-4
In a lawsuit, the plaintiff alleged that exposure to clomazone caused respiratory problems and high temperatures.

Incident#2443-36
A pesticide incident occurred in 1995, when the product splashed into a worker's eyes during a spray operation. Specific symptoms were not mentioned. No further information on the disposition of the case was reported.

Incident#2443-59
A pesticide incident occurred in 1995, when an individual was exposed two years earlier to the product and other chemicals due to off target drift. The individual reported developing allergies subsequent to this exposure. No further information on the disposition of the case was reported.

Incident#3296-33
A pesticide incident occurred in 1995, when a child reported malaise six weeks after the product was applied near their home. It is very unlikely this child's symptoms could be related to the

exposure. No further information on the disposition of the case was reported.

Incident#3582-38
A pesticide incident occurred in 1996, when a man walked outside and smelled the product and reported malaise. No further information on the disposition of the case was reported.

Incident#4439-26
A pesticide incident occurred in 1996, when an individual reported headaches, a bitter taste in his mouth, and a severe upset stomach for a period of two and a half weeks after mixing the product with water. It is unlikely that these symptoms are related to the exposure. No further information on the disposition of the case was reported.

The following incidents involved exposure to **Command ME** formulations:

Incident#7546-51
A pesticide incident occurred in 1997, when a woman reported a sore throat and nasal discharge for a period of 23 days after a field was treated near her home. These symptoms appear to be unlikely to be related to the exposure. No further information on the disposition of the case was reported.

Incident#7546-55
A pesticide incident occurred in 1997, when an individual reported a sore throat two weeks after being exposed to spray drift. It is very unlikely that such symptoms are related to the exposure. No further information on the disposition of the case was reported.

Incident#7546-61
A pesticide incident occurred in 1997, when an individual reported malaise and biting of their tongue after being exposed to spray drift. No further information on the disposition of the case was reported.

None of the incidents reported for ME formulation are likely to be related to the exposure.

III. <u>POISON CONTROL CENTER DATA</u> - 1993-1998

A total of 38 cases of exposure to clomazone were reported to the nation's Poison Control Centers from 1993 through 1998. This number of cases is insufficient to warrant a detailed analysis of risk by age or occupational subgroups. However, the following

general observations can be made. The number of incidents occurring has declined quite markedly from a high of 18 incidents in 1993 to a range of 1 to 7 incidents per year for 1994-1998.

Of the 38 total reports, the majority (31 or 82%) were due to emulsifiable concentrates (EC) formulations. There were 3 cases reportedly involving the technical formulation, 3 involving a wettable powder (WP), and 1 case involving the micro-encapsulated (ME) formulation. For the 21 cases with medical outcome determined, 2 reported exposure without symptoms, 15 had a minor outcome (1 technical, 1 WP, and the rest EC), 2 moderate (both EC) and 2 major (both EC). No particular symptoms predominated among the minor effects. The two moderate case involved one case which reported ocular abrasion and a second case with gastrointestinal effects that were categorized as unknown if related to the exposure. The two major cases include a report of renal failure (unknown if related) and a report of second and/or third skin burns to the skin. The one case involving the ME formulation was not followed, but was judged a non-toxic exposure meaning that no symptoms were expected.

IV. CALIFORNIA DATA - 1982 THROUGH 1996 - No reported incidents.

V. NATIONAL PESTICIDE TELECOMMUNICATIONS NETWORK

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, clomazone was not reported to be involved in human incidents.

VI. CONCLUSIONS

Relatively few incidents of illness have been reported due to clomazone. The emulsifiable concentrate formulation does have a potential for health effects to the skin or eyes if not protected. None of the four exposures reported for the microencapsulated formulation had symptoms that were likely to be related to their exposures.

VII. RECOMMENDATIONS

No recommendations can be made based on the few incident reports available.

cc: Correspondence

Clomazone file (chemical no. 125401)
HED - George Herndon (7509C)