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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 13-MAY-2002

SUBJECT: PP# 2E6407. **Clomazone (Command® 3ME) in/on Mint. Health Effects Division (HED) Risk Assessment.** PC Code 125401. DP Barcode: D280762. Case # 294738. Submission # S609875.

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TO: Shaja Brothers/Robert Forrest, PM Team 5
Registration Division (RD) (7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The 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 proposed use of clomazone (2-(2-Chlorophenyl)methyl-4,4-dimethyl-3-isoxazolidinone) on mint.

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, the residue chemistry data review was provided by George F. Kramer (RAB1), the occupational/residential exposure assessment by Mark Dow (RAB1), the dietary risk assessment by Sarah Levy (RAB1), the hazard characterization by Jessica Kidwell (RAB1) and the drinking water assessment by James Breithaupt of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration

Provided that a revised Section F is submitted, HED concludes that there are no residue chemistry or toxicology data requirements that would preclude the establishment of a conditional registration and permanent tolerances for residues of clomazone *per se* in/on the following raw agricultural commodities (RACs):

Peppermint, tops ..... 0.05 ppm
Spearmint, tops ..... 0.05 ppm

HED recommends that conversion of the conditional registration of Command® 3ME to unconditional registration may be considered upon submission of the following data:

1) Toxicology

- 28-day dermal toxicity study in rats using the technical grade active ingredient (TGAI) (OPPTS Guideline No. 870.3200). A 28-day dermal toxicity study was submitted to the Agency. Provided that this study meets the requirements of OPPTS Guideline No. 870.3200, this data gap will be considered fulfilled.

- 28-day inhalation toxicity study. The protocol for the existing 90-day inhalation toxicity study (OPPTS Guideline No. 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days. An inhalation waiver requested by the registrant was denied by HED (Memo, J. Whalen, 2/6/02; D276335). Since Command 3 ME is a microencapsulated product, a waiver might be justified if FMC can demonstrate that its product is not biologically available for inhalation during mixing/loading or application.

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 (trade name Command® 3 ME) used to control annual grasses and broadleaf weeds. Interregional Research Project No. 4 (IR-4) and FMC Corporation requests the establishment of permanent tolerances for residues of clomazone in/on:

Mint (stem and leaves)	0.05 ppm

Permanent tolerances are established under 40 CFR §180.448(a) for residues of clomazone in/on vegetable, tuberous and corm, except potato, subgroup at 0.05 ppm; sugarcane at 0.05 ppm; vegetable, cucurbit, group at 0.05 ppm; rice, grain at 0.02 ppm; and rice, straw at 0.02 ppm. Permanent tolerances for residues of clomazone have also been established in 40 CFR §180.425(a) in/on soybeans, cottonseed, peas (succulent), sweet potatoes, snap beans and peppers at 0.05 ppm and on pumpkins, squash, cucumber and cabbage at 0.1 ppm.

Hazard Assessment

Clomazone has low acute toxicity (Category III and IV) via the oral, dermal and inhalation routes. It is non-irritating to the eyes and mildly irritating to the skin. It is not a skin sensitizer. No systemic toxicity was observed at the highest dose tested (HDT) 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. Increased liver weights were seen in the subchronic rat study. There was no evidence of neurotoxicity in either the chronic or subchronic studies. Clomazone is not a carcinogen in either the rat or mouse. There is no concern for mutagenicity at this time.

There is no quantitative or qualitative evidence of susceptibility of rat 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.

Dose Response Assessment

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 (UF) 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. The Food Quality Protection Act (FQPA) Safety Factor (SF) of 1X is applicable for acute dietary risk assessment. Thus, the acute population adjusted dose (aPAD), which is a modification of the acute reference dose to include the FQPA SF, 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/carcinogenicity 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 ((HDT) from the 2-year chronic toxicity/carcinogenicity rat study was selected. An 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 cRfD. In the combined toxicity/carcinogenicity study, there were no compound related effects observed. Despite the absence of systemic toxicity at this dose, the Hazard Identification Assessment Review Committee (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. 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 in NOAELs 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 SF of 1X is applicable for chronic dietary risk assessment. Thus, the chronic population adjusted dose (cPAD), which is a modification of the chronic reference dose to include the FQPA SF, 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 2-year combined chronic toxicity/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 in the 2-year rat study was 84.4 mg/kg/day (HDT) since 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 Exposure Estimates

Due to the proposed use patterns, HED believes that the most highly exposed pesticide handler activities are likely to be for a mixer/loader using liquid open pour techniques and an applicator using open-cab, ground-boom machinery. In this review, these activities are assessed at the maximum rate of application (0.5 lb a.i./A). Based upon the proposed use pattern, HED assumes that application will most likely be by private (i.e., grower) applicators. Further, it is expected that exposures will be short-term (1-30 days).

Chemical-specific data were not available with which to assess pesticide handler exposure. Therefore, surrogate data from studies in the Pesticide Handler Exposure Database (PHED) Version 1.1 (August 1998) Surrogate Exposure Guide were used to estimate mixer/loader and applicator exposure. The proposed label directs pesticide handlers to wear long-sleeved shirt, long pants, waterproof gloves, shoes plus socks. It is HED policy to present estimates of exposures and risks with a single layer of work clothing (i.e., long pants, long-sleeved shirt, shoes plus socks) and **with or without** protective gloves. The estimated short- and intermediate-term MOEs are ≥100 **provided that mixer loaders wear protective gloves.** Therefore, with the use of protective gloves, the risks are below HED's level of concern.

There is potential for post-application exposure from the proposed new uses. Post-application exposure is expected to be of a short-term duration. There are no chemical-specific data available to determine the potential risks from post-application activities associated with the proposed use of clomazone. To estimate post-application risk to agricultural workers, a screening-level assessment was done for irrigation activities, scouting and hand weeding. HED believes this assessment presents estimates of most highly exposed agricultural workers performing post-application agricultural activities. The calculated MOEs are ≥100 for activities related to the proposed use on mint. This assessment demonstrates that potential post-application exposures for workers contacting clomazone treated surfaces are not expected to exceed HED's level of concern.

Residential Exposure Estimates

There are no proposed or registered residential uses for clomazone; therefore, this assessment is not required.

Dietary Exposure Estimates

Tier 1, conservative acute and chronic analyses were performed using existing and proposed tolerance level residues, 100% crop treated (CT) information, and Dietary Exposure Evaluation Model (DEEM™) default processing factors for all processed commodities. 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 general 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 Screening Concentration in Ground Water (SCI-GROW2), 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 Generic Estimated Environmental Concentration (GENEEC) and GENEECX. For surface water, the maximum acute EEC was 95 ppb and the chronic (56-day) EEC was 68 ppb. HED interim policy (HED SOP 99.5) 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 Scenarios and Risk Conclusions

Aggregate exposure risk assessments were performed only for the following: acute aggregate exposure (food + drinking water) and chronic (non-cancer) 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. Since HED does not have ground and/or surface water monitoring data to calculate a quantitative aggregate exposure, drinking water levels of comparison (DWLOCs) were calculated. 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. The EECs generated by EFED are less than HED's DWLOCs for all aggregate exposure scenarios. Thus, all aggregate risk estimates are below HED's level of concern.

Recommendation for Tolerances and Registration

Provided that a revised Section F is submitted, HED concludes that there are no residue chemistry or toxicology data requirements that would preclude the establishment of a conditional registration and permanent tolerances for residues of clomazone *per se* in/on the following RACs:

Peppermint, tops ..... 0.05 ppm
Spearmint, tops ..... 0.05 ppm

HED recommends that conversion of the conditional registration of Command® 3ME to unconditional registration may be considered upon submission of the following data:

Toxicology:

- 28-day dermal toxicity study in rats using the TGAI (OPPTS Guideline No. 870.3200). A 28-day dermal toxicity study was submitted to the Agency. Provided that this study meets the requirements of OPPTS Guideline No. 870.3200, this data gap will be considered fulfilled.

- 28-day inhalation toxicity study. The protocol for the existing 90-day inhalation toxicity study (OPPTS Guideline No. 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days. An inhalation waiver requested by the registrant was denied by HED (Memo, J. Whalen, 2/6/02; D276335).

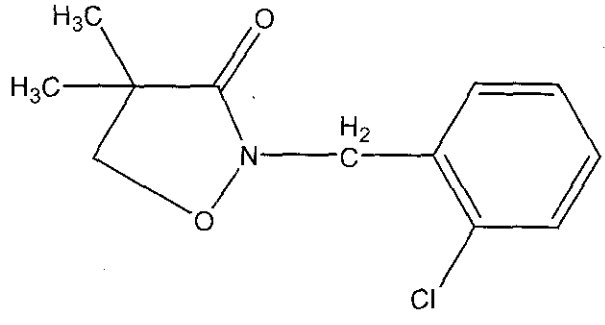
Note to RD: Although the carcinogenicity study in the mouse, which is graded unacceptable/guideline, is not considered a data gap for the current use pattern, a new carcinogenicity study in the mouse is required if additional requests for new uses will increase dietary and/or worker exposure.

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

A complete hazard characterization is presented in the Section 3 risk assessment for the use of clomazone in/on sugarcane (Memo, Kidwell *et. al.*, 2/13/01; D259635). For purposes of clarity, the dose response assessment is summarized below.

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); and 2) 28-day inhalation toxicity study (OPPTS Guideline No. 870.3465) (See Section 6 "Data Gaps" for further explanation).

3.1 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 UF 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 SF 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 cRfD of 0.84 mg/kg/day was determined on the basis of a 2-year combined toxicity/carcinogenicity 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 (HDT) from the 2-year chronic toxicity/carcinogenicity rat study was selected. An 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/carcinogenicity 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 toxicity 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. 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 in NOAELs 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 SF of 1X is applicable for chronic dietary risk assessment. Thus, the 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 HDT, 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 increase dietary and/or worker exposure, a new study will be required.**] Further, there are 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 2-year combined chronic toxicity/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 in the 2-year rat study was 84.4 mg/kg/day (HDT) since 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 the same endpoint.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 1.

Table 1. 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 toxicity 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.		
Chronic Dietary all populations	NOAEL = 84.4 mg/kg/day UF = 100 **Chronic RfD = 0.84 mg/kg/day**	FQPA SF = 1X **cPAD = cRfD / FQPA SF =** **0.84 mg/kg/day**	Two year combined toxicity/carcinogenicity rat LOAEL > 84.4 mg/kg/day (HDT) 90-Day oral toxicity 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-Generation reproduction toxicity rat 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)[C] (Residential)	No residential uses. An endpoint was not proposed/selected.		
Oral, Intermediate-term (1 week - several months)[C] (Residential)	No residential uses. An endpoint was not proposed/selected.		

EXPOSURE SCENARIO	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Dermal[a] and Inhalation[b], Short-Term (1-7 days)[C] (Occupational/ Residential)	Maternal NOAEL= 100 mg/kg/day	LOC for MOE = 100	Developmental toxicity rat Maternal LOAEL = 300 mg/kg/day, based on chromorhinorrhea and abdominogenital staining.
Dermal[a] and Inhalation[b], Intermediate-term (1week - several months)[C] and Long-Term (several months - lifetime)[C] (Occupational/ Residential)	Oral NOAEL= 84.4 mg/kg/day	LOC for MOE = 100	Two year combined toxicity/carcinogenicity rat LOAEL > 84.4 mg/kg/day (HDT) 90-day oral toxicity 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-Generation reproduction toxicity rat 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.

[C] HED has revised the definitions used in its human health risk assessments to describe occupational and residential exposure durations (Memo, M. Stasikowski, 04-JUN-2001, "Changes in the Definition of Exposure Durations for Occupational/Residential Risk Assessments Performed in the Health Effects Division"). The new exposure durations are as follows: 1) short-term, defined as lasting from 1 day to 1 month; 2) intermediate-term, defined as lasting from 1 to 6 months; 3) long-term, defined as lasting longer than 6 months. The toxicity endpoints originally selected for the short- (1-7 days) and intermediate-term (1 week to several months) incidental oral and the short- (1-7 days), intermediate- (1 week - several months) and long-term (several months - lifetime) dermal and inhalation endpoints are also applicable for the new exposure duration definitions for these routes of exposure.

3.2 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 has 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.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Proposed Uses

Table 2. Summary of Directions for Use of Clomazone.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)
preemergent, broadcast ground application	Command® 3ME [279-3158]	0.50	1	0.50	Numerical PHI not required for preemergent application

HED concludes that the proposed use is adequate. The use pattern of the submitted crop field trials matches that specified on the Section 3 label.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Residue chemistry data pertaining to the proposed use of clomazone on mint were submitted and reviewed by HED (Memo, G. Kramer, 4/12/02, D280851).

Background

Command® 3ME is a herbicide for control of annual grasses and broadleaf weeds. This product

is a microencapsulated formulation containing 31.4% clomazone and is labeled for preemergent or early post-emergent use. IR-4 and FMC Corporation requests the establishment of permanent tolerances for residues of clomazone in/on:

Mint (stem and leaves)	0.05 ppm

Permanent tolerances are established under 40 CFR §180.448(a) for residues of clomazone in/on vegetable, tuberous and corm, except potato, subgroup at 0.05 ppm; sugarcane at 0.05 ppm; vegetable, cucurbit, group at 0.05 ppm; rice, grain at 0.02 ppm; and rice, straw at 0.02 ppm. Permanent tolerances for residues of clomazone have also been established in 40 CFR §180.425(a) in/on soybeans, cottonseed, peas (succulent), sweet potatoes, snap beans and peppers at 0.05 ppm and on pumpkins, squash, cucumber and cabbage at 0.1 ppm.

Nature of the Residue

Plants: HED concludes that the nature of the residue in plants is adequately understood 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). 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: As there are no livestock feed items currently associated with mint, issues pertaining to the nature of the residue in livestock are not germane to this petition.

Residue Analytical Methods

Adequate analytical 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/mass selective detector (GC/MSD) or GC/electron capture detection (ECD). The limit of quantitation (LOQ) for this method is 0.05 ppm. A confirmatory procedure (GC/MS-SIM) is available as Method I in Pesticide Analytical Method Volume II (PAM II).

Mint samples were analyzed for clomazone residues using the FMC Method No. ACG 124, which is virtually the same as the PAM-II enforcement method. Validation data indicate that this

method is adequate. A LOQ of 0.05 ppm was established for mint foliage and oil.

Multiresidue Method (MRM)

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

Crop Field Trials

In five trials conducted in WI (2) and WA (3), a single application of clomazone (Command® 3ME) at 0.5-1.0 lb ai/A/ (1x-2x) was made to dormant mint plants. Mature stem and leaf samples were harvested by hand 84-139 days after application. Clomazone residues were <0.05 ppm in/on all samples. HED concludes that the geographic representation and the number of field trials conducted on mint are adequate to support a tolerance petition for mint. Based on the concurrent method recoveries, the GC method (Method No. ACG 124) is adequate for collecting data on residues of clomazone in/on mint stem and leaf. Adequate sample calculations and chromatograms were submitted.

Table 3. Tolerance Summary for Clomazone (40 CFR §180.448(a))

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
Mint (stem & leaves)	0.05	0.05	Peppermint, tops Spearmint, tops

A revised Section F should be submitted with the correct commodity definition.

Processed Food/Feed

In two trials conducted in WI and WA, a single application of clomazone (Command® 3ME) at 1.0 lb ai/A/ was made to dormant mint plants. Mature stem and leaf samples were harvested by hand 84-139 days after application. The mint stem and leaf samples were processed into oil by distillation. Quantifiable residues were found in neither the control or treated mint leaf and oil samples. Based on these results, residues of clomazone do not appear to concentrate in mint oil; therefore, a separate tolerance for residues of clomazone in mint oil is not required.

Meat, Milk, Poultry, Eggs (MMPE)

As there are no livestock feed items currently associated with mint, issues pertaining to the magnitude of the residue in livestock are not germane to this petition.

Confined and Field Accumulation in Rotational Crops

As mint is a perennial crop, confined and field rotational crop studies are not required to support the subject petition.

International Harmonization of Tolerances

There is neither a Codex proposal, nor Canadian or Mexican maximum residue limits (MRLs) for residues of clomazone in/on mint. Therefore, a compatibility issue is not relevant to the proposed tolerance.

4.2.2 Dietary Exposure Analyses

HED conducts dietary (food only) risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's 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. 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.

4.2.2.1 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 (Memo, S. Levy, 4/26/02, D282390). 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	<1.0

The acute exposure estimate for females 13-50 years old accounts 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.

4.2.2.2 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. 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	<1.0
All Infants (< 1 year old)	0.000332	<1.0
Children 1-6 years old	0.000182	<1.0
Children 7-12 years old	0.000122	<1.0
Females 13-50 years old	0.000079	<1.0
Males 13-19 years old	0.000085	<1.0
Males 20+ years old	0.000080	<1.0
Seniors 55+ years old	0.000091	<1.0

[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). 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 old).

The chronic exposure estimates for the general U.S. population and all population subgroups accounted for <1.0% 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.

4.3 Water Exposure/Risk Pathway

The HED Metabolism Assessment Review Committee (MARC) determined that both parent clomazone and its major environmental degradate, FMC 65317, 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). 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® 3 ME label (maximum application rate = 1.25 lb ai/A).

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

Surface Water: The maximum acute and chronic surface water EECs for both parent clomazone and FMC 65317 were estimated by the Tier 1 screening models GENEEC 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 (HED SOP 99.5) 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.

4.4 Residential Exposure/Risk Pathway

There are no proposed or registered residential uses for clomazone; therefore, this assessment is not required.

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

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. Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. 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.

To calculate the chronic DWLOCs, the chronic dietary food estimates (from DEEM™) were subtracted from the cPAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70kg/2L (adult male and US Population), 60 kg/2L (adult female), and 10kg/1L (infant & children).

DWLOCs are compared to EECs for a pesticide in surface water and ground water. If the DWLOCs are greater than the EECs, HED concludes with reasonable certainty that estimates of aggregate risks are below HED's level of concern.

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 for all processed commodities. The acute analysis was performed for 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 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 6). 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 6. 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	0.000265	1.0	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 (non-cancer) 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 7). 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 7. 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 CUMULATIVE RISK

The FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject

pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this tolerance action for clomazone because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of clomazone. For purposes of this tolerance action, EPA has assumed that clomazone does not have 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. If HED identifies other substances that share a common mechanism of toxicity with clomazone, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at: http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf

In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity" (64 FR 5795-5796, February 5, 1999).

7.0 OCCUPATIONAL EXPOSURE

7.1 Summary of Proposed New Use Patterns and Formulations

IR-4 and FMC Corporation have submitted an application to amend the currently registered product COMMAND® 3 ME (EPA Reg. No. 279-3158) by the addition of the new crop use mint. COMMAND® 3 ME is a 3.0 lb a.i./gallon liquid, microencapsulated herbicide containing the active ingredient clomazone. See Table 8 for a summary of the proposed new use practice.

Table 8. Summary of Proposed New Use of Clomazone on Mint	
Formulation	3.0 lb a.i./gallon liquid
Use Site	Mint
Method of Application	Ground
Pest	Grass and Broadleaf Weed Species
Maximum Application Rate	0.5 lb a.i./A
Frequency/Timing	one application per year **prior** to mint emergence
PHI	None stated on label
Restricted Entry Interval (REI)	12 hours per registered label
Manufacturer	FMC Corporation

7.2 Handler Exposure

Due to the proposed use patterns, HED believes that the most highly exposed pesticide handler activities are likely to be for a mixer/loader using liquid open pour techniques and an applicator using open-cab, ground-boom machinery. It is possible that private (i.e., grower) pesticide handlers may perform both tasks; i.e., mixing/loading and then applying. The HED Science Advisory Council for Exposure (ExpoSAC) Policy 12 (29 March, 2000) directs that although the same individual may perform both tasks, they shall be assessed separately. "By separating the two job functions, HED determines the most appropriate levels of personal protection equipment (PPE) for each aspect of the job without requiring the applicator to wear unnecessary PPE that may be required for the mixer/loaders (i.e., chemical resistant gloves may only be necessary during the pouring of a liquid formulation)."

In this review, these activities are assessed at the maximum rate of application (0.5 lb a.i./A). Based upon the proposed use pattern, HED assumes that application will most likely be by private (i.e., grower) applicators. Further, it is expected that exposures will be short-term (1-30 days). Even if commercial applicators are involved, exposures are not likely to exceed short-term. However, in the unlikely event that intermediate-term exposures might occur, estimates of risk for intermediate-term exposures are presented.

Chemical-specific data were not available with which to assess pesticide handler exposure. Therefore, surrogate data from studies in the PHED Version 1.1 (August 1998) Surrogate Exposure Guide were used to estimate mixer/loader and applicator exposure. The proposed label directs pesticide handlers to wear long-sleeved shirt, long pants, waterproof gloves, shoes plus socks. It is HED policy to present estimates of exposures and risks with a single layer of work clothing (i.e., long pants, long-sleeved shirt, shoes plus socks) and **with or without** protective gloves. See Table 9 for estimates of exposure and risk to pesticide handlers.

Table 9. Estimated Exposures and Risks to Pesticide Handlers Applying Clomazone to Mint

Unit Exposure[1] mg a.i./lb handled	Applic Rate[2] lb a.i./A	Units Treated[3]	Avg. Daily Dose[4] mg a.i./kg bw/day	Short term NOAEL[5] mg a.i./kg bw/day	Interm term NOAEL[6] mg a.i./kg bw/day	MOE[7]	
						Short-term	Intermed.-term
Mixer/Loader - Using Liquid - Open Pour							
DermNG 2.9 HC DermWG 0.023 HC Inhalat 0.0012 HC	0.5	200A	4.1 0.033 $1.7x10^{-3}$	100	84.4	Derm NG 24 Derm WG 2900	Derm NG 20 Derm WG 2400
Applicator - Groundboom - Open Cab							
DermNG 0.014 HC DermWG 0.014 MC Inhalat. 0.00074 HC	0.5	200 A	0.02 0.02 $1.1x10^{-3}$	100	84.4	Derm NG 4800 Derm WG 4800	Derm NG 4000 DermWG 4000

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database PHED Surrogate Exposure Guide version 1.1; August 1998; DermNG = Dermal Unit Exposure with a single layer of work clothing (long pants, long-sleeved shirt, shoes plus socks) No Gloves; DermWG = single layer work clothing **with gloves;** Inhalat. = Inhalation unit exposure. HC = high confidence data; MC = medium confidence data; LC = low confidence data
2. Application Rate from proposed labeling from IR-4 P.R. No. 06680, Clomazone/Mint, Volume I Page 24.
3. Acres Treated are derived from ExpoSAC Pol. No. 9.1. Rev. 25 SEPT 2001. 1992 Census of Agriculture indicates the "average farm size" for mint in ID IN OR and WI is 176 A.
4. Average Daily Dose (ADD) = Unit Exposure * Application Rate * Units Treated ÷ 70 kg body weight. (Dermal and Inhalation exposures assume 100% absorption; HIARC HED Doc. No. 014299).
5. Short term NOAEL (1-30 days) = No Observed Adverse Effect Level; Short-term dermal and inhalation = 100 mg a.i./kg bw/day maternal effects from developmental rat study.
6. Intermediate term NOAEL (1-3 months) = No Observed Adverse Effect Level; Intermediate-term dermal and inhalation = 84.4 mg a.i./kg bw/day from two year rat feeding study.
7. MOE = NOAEL ÷ ADD. ADD = short term dermal + short term inhalation and intermediate term dermal + intermediate term inhalation.

A MOE of 100 is adequate to protect pesticide handlers. The estimated short- and intermediate-term MOEs are ≥100 **provided that mixer loaders wear protective gloves.** Therefore, with the use of protective gloves, the risks do not exceed HED's level of concern.

7.2 Post-Application Worker Exposure

Since clomazone may be applied up to 30 days **prior** to crop emergence, post-application exposure to agricultural workers is not expected to be significant. Typical agricultural practices used to grow mint are essentially mechanical.

However, the ExpoSAC Policy Number 003.1 (Revised 7 August 2000) and amended by "*ExpoSAC meeting Notes - 9/13/01"* lists a number of possible post-application agricultural activities for the proposed use that might result in post-application, "re-entry" exposure. For the very early season stages of a mint crop, these are: irrigation activities, scouting and hand weeding. These activities are reported as having transfer coefficients (TC) of 100 cm^2/hr of

foliar pesticide dislodgeable residue. HED expects that these are short-term (1-30 days) activities. Although considered unlikely to occur, intermediate-term exposures and risks have been calculated and presented.

The TCs discussed in this assessment are from an interim transfer coefficient policy developed by HED's ExpoSAC using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database (policy # 3.1). It is the intention of HED's ExpoSAC that this policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature. Using a TC of 100 cm^2/hr and assuming application was at the maximum rate of 0.5 lb a.i./A and that re-entry occurred on the day of treatment, post-application exposure may be estimated using the following convention.

$PDR_t = DFR_t * CF1 * Tc * ET$ where:

PDR_t = potential dose rate on day "t" (mg/day)
DFR_t = dislodgeable foliar residue on day "t" (ug/cm^2)
CF1 = weighted unit conversion factor changing μg to mg (0.001 mg/μg)
TC = transfer coefficient (cm^2/hr) 100
ET = Exposure Time (hr/day) 8

where
$DFR_t = (AR * F) * (1 - D)^t * CF2 * CF3$ where:

AR = application rate (lb a.i./ft^2 or lb a.i./Acre) (0.5 lb a.i./A)
F = fraction of a.i. retained on foliage (unitless = 20%)
D = fraction of residue that dissipates daily (unitless) (10%)
t = postapplication day on which exposure is being assessed
CF2= conversion factor lb a.i. to μg for DFR (4.54×10^8 μg/lb)
CF3 = conversion factor to convert surface area units (ft^2) in application rate to cm^2 for DFR value (1.08×10^{-3} ft^2/cm^2 or 2.47×10^{-8} acre/cm^2 if rate is per acre).

The Potential Dose $Rate_t$ is then normalized to the body weight (bw) of a worker, 70 kg for an average male or 60 kg for female. The result is expressed as mg a.i./kg bw/day. The bw used in calculation is determined by the toxicological endpoint identified. For this assessment, 70 kg bw is used to calculate MOE.

The DFR_t is calculated as:

0.5 lb a.i./A * 0.2 * $(1 - D)^0$ * 4.54×10^8 μg/lb * 2.47×10^{-8}A/cm^2 = 1.12 μg a.i./cm^2 and

PDR_t = 1.12 μg a.i./cm^2 * 0.001 mg/μg * 100 cm^2/hr * 8 hr/day = 0.897 mg/day

assuming 100% dermal absorption and normalized to 70 mg bw = 0.0128 mg a.i./kg bw/day.

MOE = NOAEL ÷ Dose, therefore:

100 mg a.i./kg bw/day = **7800 for short-term;**
0.0128 mg a.i./kg bw/day

84.4 mg a.i./kg bw/day = **6600 for intermediate-term.**
0.0128 mg a.i./kg bw/day

Since the MOEs are ≥100, these estimated risks are not of concern to HED.

7.3 Restricted Entry Interval

The interim WPS REI of 12 hours, based on Toxicity Category III for primary eye irritation, primary skin irritation, and acute dermal, is sufficient to protect workers.

7.4 Incident Reports

In the previous risk assessment by J. Kidwell, *et al.* (Memo 13-FEB-2001, D259635), it was reported that: "An updated review of clomazone poisoning incident reports show that relatively few incidents of illness have been reported due to clomazone (Memo, J. Blondell and M. Spann, 27-SEP-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." OPP's Pesticide Incident Data System was accessed on 17-APR-2002. There appear to be additional incident reports since the review by Kidwell *et al.* The additional reports are of "unknown certainty."

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Chemistry

- Revised Section F.

8.2 Toxicology

- 28-day dermal toxicity study in rats using the TGAI (OPPTS 870.3200) (data gap). A 28-day dermal toxicity study was submitted to the Agency. Provided that this study meets the requirements of OPPTS Guideline No. 870.3200, this data gap will be considered fulfilled.

- 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 is needed to characterize the direct effects of clomazone on the pulmonary system and any systemic effects via 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. An inhalation waiver requested by the registrant was denied by HED (Memo, J. Whalen, 2/6/02; D276335). Since Command 3 ME is a microencapsulated product, a waiver might be justified if FMC can demonstrate that its product is not biologically available for inhalation during mixing/loading or application.

- 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.

8.3 Occupational Exposure

- None

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