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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: May15, 2000

MEMORANDUM

Subject: **PP#7F04924.** Human Health Risk Assessment for the Use of the New Active Ingredient, Clodinafop-propargyl, on Wheat.

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Trade Name	Discover™		
EPA File Symbol	100-ONT		

From: Anna Lowit, Risk Assessor 5/15/00
Nancy Dodd, Chemist 5/15/00
Stanley Gross, Toxicologist 5/15/00
Kelly O'Rourke, Occupational Exposure 5/15/00
Registration Action Branch 3
Health Effects Division (7509C)

Through: Steve Dapson, Branch Senior Scientist
Registration Action Branch 3
Health Effects Division (7509C)
05/15/2000

To: Susan Stanton/Joanne Miller
PM Team 23
Registration Division (7505C)

The Health Effects Division (HED) has conducted a human health risk assessment for the new active ingredient, clodinafop-propargyl, for the purpose of making a tolerance eligibility decision to establish the wheat use requested by Novartis, the petitioner. Novartis has submitted a petition (PP#7F04924) proposing to establish permanent tolerances for combined residues of clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) in/on wheat. Clodinafop-propargyl is the active ingredient in the proposed formulation, Discover™ Herbicide. HED is recommending for the establishment of **a time-limited**

registration, conditional upon submission of data/information to satisfy the outstanding deficiences for the active ingredient, clodinafop-propargyl, and the formulation, Discover™. Tolerances for the combined residues of clodinafop-propargyl and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid) will be proposed in/on the following commodities: wheat grain, forage, and hay at 0.10 ppm and wheat straw at 0.50 ppm.

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1.0 EXECUTIVE SUMMARY

♦ **For a LIST of the ATTACHMENTS to this review, see Section 7.0.**

Clodinafop-propargyl is a new active ingredient which currently has no registered food or non-food uses in the U.S. This active ingredient belongs to the oxyphenoxy acid ester class of herbicides; this class of herbicides also includes the active ingredients fluazifop-butyl, fenoxaprop-ethyl, diclofop methyl, quizalofop-ethyl, and haloxyfop-methyl. The subject petition proposes **the first food use** for this active ingredient. There are no proposed non-food uses. Canada has recently reviewed a petition for clodinafop-propargyl on wheat. At this time, Canada has a default MRL of 0.1 mg/kg for clodinafop-propargyl on wheat. A Mexican limit exists for clodinafop-propargyl on wheat at 0.050 ppm. There are no Codex tolerances for clodinafop-propargyl on wheat.

Novartis Crop Protection, Inc. (formerly Ciba Crop Protection), the petitioner, has submitted a petition for the establishment of permanent tolerances for residues of clodinafop-propargyl (also referred to as CGA-184927; CGA-184927 is the "R" isomer) in/on wheat. The petitioner is also requesting Section 3 registration for the end-use product Discover™ Herbicide (EPA File Symbol 100-ONT), which contains the herbicide clodinafop-propargyl. The product is formulated as an emulsifiable concentrate which contains 22.3% clodinafop-propargyl and 77.7% inerts. Specifically, the petitioner proposed the establishment of tolerances for residues of the herbicide clodinafop-propargyl (propanoic acid, 2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester; CGA-184927) in or on wheat grain at 0.02 ppm and wheat straw at 0.05 ppm. HED is recommending for the establishment of **time-limited registrations, conditional upon submission of data/information to satisfy the outstanding deficiences** for the active ingredient, clodinafop-propargyl, and the formulation, Discover™. Tolerances for the combined residues of clodinafop-propargyl and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid) will be proposed in/on the following commodities:

wheat, grain..... 0.10 ppm
wheat, forage..... 0.10 ppm
wheat, hay..... 0.10 ppm
wheat, straw..... 0.50 ppm.

For <u>wheat</u>, Discover™ Herbicide is to be applied broadcast by ground or air to all types of spring and winter wheat (including Durum) grown in Montana, Minnesota, North Dakota, and South Dakota. Discover™ Herbicide is to be applied postemergence to wheat from the 2-leaf stage to emergence of the 4th tiller at the rate of 3.2 - 4.0 fl oz Discover™ Herbicide/A (0.05-0.06 lb ai/A). Livestock grazing or foraging of feed should not be done in treated areas for a minimum of 7 days following application. Hay should not be fed for 30 days following application. Wheat (grain and straw) should not be harvested for 60 days following application. Only one application per crop season is proposed. Note: HED is recommending that the Section B/label be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section

B/label is made, the proposed use of clodinafop-propargyl on wheat will be adequately described.

Although additional toxicity studies are being required, the toxicity database for clodinafop-propargyl is considered adequate for risk assessment purposes. The toxicity data indicates that clodinafop-propargyl (CGA 184927) has low acute oral, dermal, and inhalation toxicity (Acute Toxicity Category III). It is slightly irritating to eyes and is not a skin irritant. However, it is a skin sensitizer. Clodinafop-propargyl has been classified as "likely to be carcinogenic to humans," causes developmental toxicity in the rat, and caused fetotoxicity in a 2-year reproductive toxicity in the rat. The primary target organ is the liver for dogs, mice, and rats in subchronic and chronic studies. Liver toxicity was evidenced by increased liver weight, elevated liver enzyme activities and abnormal histopathological findings. An increased incidence of hepatoma and hepatocellular carcinoma was observed at the high dose (29.6 mg/kg/day) in a mouse carcinogenicity study. For dogs only, skin lesions (e.g. pustules, erythema, and crusts) were observed in the subchronic and chronic dog studies. It was noted that the skin lesions were observed at doses as low as 50 ppm (1.73 mg/kg/day) in the subchronic feeding study while skin lesions were observed at higher doses (500 ppm or 15.2 mg/kg/day) in the one year feeding study.

On April 29, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of clodinafop-propargyl (CGA 184927), established Reference Doses (RfDs), selected toxicological endpoints for acute and chronic dietary as well as occupational and residential exposure risk assessments. **Data gaps for clodinafop-propargyl include toxicity studies for: acute neurotoxicity, subchronic neurotoxicity, developmental neurotoxicity and *in vitro* cytogenetics.**

Acute Dietary Exposure:

An acute reference dose (RfD) was selected for the subpopulation of *females 13-50 years old.* This acute RfD of **0.05 mg/kg/day** is based on the no-observed-adverse-effect-level (NOAEL) of 5 mg/kg/day selected from a developmental toxicity in rats (MRID no. 44399145) where an increased incidence of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal) were observed at 40 mg/kg/day (lowest-observed-adverse-effect-level; LOAEL). (The NOAEL of 5 mg/kg/day is divided by uncertainty factors (UF) for interspecies extrapolation (10x) and intraspecies variability (10x).) Based on the conservative assumption that developmental toxicity could occur following a single exposure to a pregnant female, this endpoint is appropriate for acute risk assessment for females 13-50.

An acute RfD for the *general U.S. population* was also selected by the HIARC. The acute RfD of **0.25 mg/kg/day** is based on a NOAEL of 25 mg/kg/day from a developmental toxicity study in rabbits (MRID no. 44399144) where maternal toxicity (increased mortality, clinical signs and body weight loss) was observed at 125 mg/kg/day. This study is suitable for the general population because mortality, clinical signs, and maternal body weight loss occurred on the first

measurement time point (day 2 after dosing). It is reasonable to assume that the adverse effects could occur after a single dose.

Chronic Dietary:
The HIARC selected a **chronic RfD of 0.0003 mg/kg/day** (NOAEL = 0.03 mg/kg/day; Uncertainty Factor = 100). This chronic RfD is based on a two year combined chronic/oncogenicity study in rats (MRID no. 44399147). In this study, the NOAEL of 0.03 mg/kg/day was based on observations of hepatocytic hypertrophy, chronic progressive nephropathy and tubular pigmentation at 0.3 mg/kg/day (LOAEL). The Uncertainty Factor accounts for both interspecies extrapolation (10X) and intraspecies variability (10X).

Short and Intermediate Term Dermal Endpoints:
Short- and intermediate-term dermal endpoints of 50 mg/kg/day (NOAEL) were selected from a 28-day dermal toxicity study (MRID no. 44399141) where dose-related increases in liver weights and clinical signs (piloerection and hunched posture) in male rats were observed at 200 mg/kg/day (LOAEL). This study is selected because its duration and route of exposure are appropriate for short- and intermediate-term dermal exposure.

Short-Term Inhalation Risk Assessment:
A short-term inhalation endpoint of 5 mg/kg/day (NOAEL) was selected from a developmental toxicity study in rats (MRID no. 44399145) where increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal) were observed at 40 mg/kg/day (LOAEL). Only an acute inhalation toxicity study has been submitted to the Agency. There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database. Consequently, the oral values should be used for inhalation exposure risk assessment; route-to-route extrapolation has been performed assuming 100% absorption.

Intermediate-Term Inhalation Risk Assessment:
A intermediate-term inhalation endpoint of 0.9 mg/kg/day (NOAEL) was selected from a subchronic oral toxicity in rats (MRID no. 44399132) where increases in liver weights and enzyme activity were observed in males at 8.2 mg/kg/day (LOAEL). Only an acute inhalation toxicity study has been submitted to the Agency. There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database. Consequently, the oral values should be used for inhalation exposure risk assessment; route-to-route extrapolation has been performed assuming 100% absorption.

Long-Term Dermal and Inhalation Risk Assessments:
Based on the proposed use patterns, no long-term dermal or inhalation exposure is expected to occur. Therefore, no endpoints were selected.

For short term aggregate exposure risk assessment, oral and dermal exposures could not be combined due to differences in the toxicological endpoints via these routes. For intermediate-term aggregate exposure risk assessment, oral and dermal exposures have been combined since

increased liver weights were observed via both of these routes. Oral and inhalation exposure have been combined since inhalation exposure is corrected to oral equivalent doses. Based on the current use pattern, long-term aggregate exposure risk assessment is not required. A MOE of 100 is required for occupational exposure risk assessment.

In accordance with the EPA *Proposed EPA Weight-of-the-Evidence Categories*, August 1999, the Cancer Assessment Review Committee (CARC) classified clodinafop-propargyl (CGA 184927) as **"likely to be carcinogenic to humans"** by the oral route based on the occurrence of prostate tumors in male rats, ovarian tumors in female rats and liver tumors in both sexes of mice, as well as blood vessel tumors in female mice. For the quantification of human cancer risk, the CARC recommended a linear low-dose extrapolation approach based on the most potent of these tumor types. This approach is supported by possible genotoxic potential and the lack of confirmation of the mode of action of clodinafop-propargyl.. The most potent unit risk, **Q_1^*(mg/kg/day)$^{-1}$**, of those calculated for clodinafop-propargyl is that for male mouse liver benign hepatoma and/or carcinoma combined tumor rates at **0.129 (mg/kg/day)$^{-1}$** in human equivalents.

The HED FQPA Safety Factor Committee met on March 6, 2000 and again on March 20, 2000 to evaluate the hazard and exposure data for clodinafop-propargyl and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be retained at *up to* 10x in assessing the risk posed by this chemical. The FQPA SFC concluded that the FQPA safety factor be **retained at *up to* 10x** because: the toxicology database for clodinafop-propargyl is incomplete; there is quantitative and qualitative evidence of increased susceptibility; and there is evidence of potential endocrine disruption.

When assessing acute dietary exposure, the safety factor is **retained at 10x for the females 13-50** population subgroup. The calculated population adjusted dose for acute exposure (aPAD) for females 13-50 years old is 0.05 mg/kg/day/10x = **0.005 mg/kg/day.** The safety factor is **reduced to 3x for the infants and children** population subgroups. The calculated population adjusted dose for acute exposure (aPAD) for infants and children is 0.25 mg/kg/day/3x = **0.083 mg/kg/day.** The calculated population adjusted dose for acute exposure (aPAD) for all other subpopulations is 0.25 mg/kg/day/1x = **0.25 mg/kg/day.** When assessing the chronic dietary exposure, the safety factor should be **retained at 10x for all population subgroups**. The calculated population adjusted dose for chronic exposure (cPAD) for all other subpopulations is 0.0003 mg/kg/day/10x = **0.00003 mg/kg/day.**

The submitted product chemistry data for the technical grade of the active ingredient (TGAI) were reviewed by Registration Division (Memo, 9/23/99, Shyam Mathur, D255798). No additional data are required.

HED has evaluated the residue chemistry database from residue field trials and processing studies. There are residue chemistry data gaps. Provided that revised Sections B (proposed label) and F (tolerance proposal) are submitted and the analytical method validation by

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ACL/BEAD is successful, the residue chemistry data gaps do not preclude the establishment of a time-limited registration.

The following residue chemistry issues remain to be resolved or deficiencies exist concerning the following topics:

1. Proposed Use/Revised Section B/label
2. Nature of the Residue in Wheat
3. Nature of the Residue in Ruminants
4. Nature of the Residue in Poultry
5. Plant Analytical Methods
6. Multiresidue Methods
7. Storage Stability
8. Magnitude of the Residue in Wheat
9. Magnitude of the Residue in Processed Food/Feed
10. Rotational Crop Data
11. Revised Section F

Although the noted residue chemistry issues exist, this assessment is considered conservative and health protective. Except for the submission of revised Sections B and F and the availability of adequate EPA method validations, noted issues will not preclude the establishment of a time-limited registration.

The HED Metabolism Assessment Review Committee (MARC) has determined (2/15/00) for this time-limited registration that the residues of concern for risk assessment and tolerance setting purposes in the primary crop are the parent and the acid metabolite [(R) (2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid; CGA-193469]. Transfer of finite residues of clodinafop-propargyl and its acid metabolite to meat, milk, poultry, and eggs is not expected (40 CFR §180.6(a)(3) category). The petitioner has proposed high performance liquid chromatography (HPLC) methods with UV-detection (REM 138.01 for parent and REM 138.06 for the acid metabolite) for enforcement of the tolerances on wheat. The HPLC/UV method REM 138.10 was used to collect the residue/processing data on CGA-193469 in wheat in the US. Successful independent laboratory method validations, indicating adequate recovery of residues, were conducted for methods REM 138.01 and REM 138.06 on wheat grain, forage, and straw. The limits of quantitation of the method REM 138.01 for parent (CGA-184927) are 0.02 ppm for grain and 0.05 ppm for wheat forage, hay, and straw. The limit of quantitation of the method REM 138.06 for the acid metabolite (CGA-193469) is 0.05 ppm for wheat grain, forage, hay, and straw. The limits of quantitation of the method REM 138.10 for CGA-193469 are 0.02 ppm for wheat grain and 0.05 ppm for forage, hay, and straw. An EPA (ACL/BEAD) method validation of methods REM 138.01, REM 138.06, and REM 138.10 has been requested and is now underway. The validation by ACL/BEAD must be successfully completed prior to the establishment of the proposed tolerances.

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Occupational exposure is expected from the use of clodinafop-propargyl. The dermal toxicity endpoint (NOAEL = 50 mg/kg/day) was chosen for both short-and intermediate-term occupational exposure, based on the results of a 28-day dermal toxicity study in rats. The effects seen were increased liver weight and clinical signs (piloerection and hunched posture) in males. There were no inhalation toxicity studies available for risk assessment. For short-term inhalation toxicity, the inhalation exposure is converted to an oral-equivalent dose (100% absorption) and compared to the oral endpoint (NOAEL = 5 mg/kg/day) from a developmental study in rats. This endpoint is applicable to females 13+ years old, and therefore uses a 60-kg body weight in the calculations. For intermediate-term inhalation toxicity, the inhalation exposure is converted to an oral-equivalent dose and compared to the oral endpoint (NOAEL = 0.9 mg/kg/day) from a subchronic oral toxicity study in rats. These calculations result in Margins of Exposure (MOEs) which are compared to the target MOE of 100 to determine any risk concerns. Please note that for intermediate-term exposures, similar effects (increased liver weight) were observed in the studies selected for the intermediate-term dermal and inhalation endpoints; therefore, the intermediate-term dermal and inhalation MOEs were combined into a Total MOE for comparison to the target MOE of 100.

To quantify cancer risk, the Q_1* of 0.129 mg/kg/day^{-1} (calculated based on male mouse liver benign hepatoma and/or carcinoma combined tumor rates) is multiplied by the estimated doses from occupational exposure. Dermal doses are first adjusted for dermal absorption (i.e., 2.5%) because the Q_1* is based on an oral study, while inhalation doses are assumed to be 100% absorbed. Cancer risks for handlers and reentry workers that exceed 10^{-4} are indicative of concern, and require measures such as additional PPE or engineering controls to mitigate exposure, with the goal of achieving a risk level of 10^{-6} or less.

There are no residential uses registered for clodinafop-propargyl.

Chemical-specific handler exposure data were submitted in support of this Section 3 registration. Two of these submissions (MRID#s 443992-33 and -34) were surrogate exposure assessments for aerial applicators and groundboom mixer/loaders, based on an analysis of Pesticide Handlers Exposure Database (PHED) data sets. However, HED performed its own analysis of these scenarios using the PHED Surrogate Table for unit exposure values.

Data from the submission on Field Operator Exposure for mixing/loading and applying using groundboom sprayer (MRID# 443992-35) were used in this assessment; the approach taken is in harmony with the Canadian risk assessment for Horizon™.

Handlers of clodinafop-propargyl (Discover™) were assessed for exposure during open mixing/loading to support aerial and groundboom application, using PHED unit exposure values. Aerial and groundboom operators, as well as flaggers for aerial application, were assessed separately, using PHED unit exposure values for closed cockpit, open-cab tractor, and baseline clothing, respectively. Also, handlers who mix, load and apply by groundboom were assessed together, using unit exposure values obtained from a registrant-sponsored study. The MOEs, under all the above circumstances, range from **5.2×10^2 to 5.9×10^5 for handlers. These MOEs**

are greater than the target (100) and do not exceed HED's level of concern. The cancer risks range from **2.3 x 10^{-7} to 2.1 x 10^{-6}**, which also do not exceed HED's level of concern.

The proposed label for Discover™ has a 12-hour restricted entry interval (REI). The technical material has a Toxicity Category IV for Acute Inhalation and Primary Skin Irritation; all other acute effects are Category III. Per the Worker Protection Standard (WPS), a 12-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours is in compliance with the WPS.

Postapplication risk assessment uses the same dermal toxicity endpoints and Q_1* as for handlers above. No inhalation exposure scenarios were identified for postapplication activities because once sprays and dusts settle, inhalation exposure is not expected; therefore, this postapplication route of exposure was not assessed. Postapplication risks were assessed for workers entering wheat fields to scout and irrigate. Wheat is assumed to be mechanically harvested. The Agency acknowledges that there is some potential for exposure during harvesting because individuals engaged in fully mechanized activities have short-term excursions from the protected area for various reasons (e.g., unclogging machinery or equipment inspection for breakage). In these cases, the WPS § 170.112(c) Exception for short-term activities applies. Because the application being made relatively early in the growth cycle (i.e., 1 to 6 leaf stage on main stem), dislodgeable residues are expected to be significantly reduced by the time of harvest, due to degradation, growth of the plant, and absorption by the plant material. The MOE resulting from postapplication exposure is 3,100 as early as the day of application. **This MOE is greater than the target (100) and does not exceed HED's level of concern.** The cancer risk on the day of application is **9.9 x 10^{-7}**, which also does not exceed HED's level of concern.

For dietary exposure three different aPADs apply to different population subgroups: 1) females 13-50, 0.005 mg/kg/day, 2) infants and children, 0.0.083 mg/kg/day, 3) general population, 0.25 mg/kg/day. The acute food only risk estimate associated with clodinafop-propargyl use on wheat is below HED's level of concern (100% aPAD) for all population groups. Based on tolerance level residues and assuming 100% crop treated, the 95th percentile of exposure is predicted to be up to **7.5%** of the aPAD for **nursing females ages 13-50 years old**, the most highly exposed subgroup of females of childbearing age. The aPAD for infants and children is calculated to be 0.083 mg/kg/day. Based on the food only exposure assessment, at the 95th percentile of exposure the highest exposed subgroup of infants and children is **children 1-6** years old which utilizes up to **1.0% of the aPAD.** The aPAD for the general population and subgroups not included in females 13-50 years old and infants and children is calculated to be 0.25 mg/kg/day. Based on the food only exposure assessment, at the 95th percentile of exposure, the **total U.S. population** in addition to all **male only** subgroups are exposed to **< 1.0% of the aPAD**.

The Environmental Fate and Effects Division (EFED) provided HED with estimated environmental concentrations (EECs) of both clodinafop-propargyl and the major degradate, CGA-196469 {(R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)} using available models for ground water (SCI-GROW) and surface water (PRZM/EXAMS with index reservoir and percent crop area adjustment). The EECs provided by EFED for assessing acute

aggregate dietary risk are **5.0 x 10^{-6} μg/L and 0.044 μg/L** (in ground water, based on SCI-GROW for clodinafop-propargyl and CGA-193469, respectively) and **0.23 μg/L and 1.10 μg/L** (in surface water, 1 in 10 year peak value based on PRZM/EXAMS for clodinafop-propargyl and CGA-193469, respectively). The back-calculated DWLOCs for assessing acute aggregate dietary risk **range from 1.4 x 10^2 μg/L to 8.7 x 10^3 μg/L** for women of childbearing age (13-50 years old) and the general U.S. population. DWLOCs for assessing acute aggregate dietary risk are in excess of EECs for acute exposure.

The chronic (non-cancer) food risk estimate associated with clodinafop-propargyl use in/on wheat is below HED's level of concern (100% of cPAD). The cPAD for applicable to all subgroups of U.S. populations is 0.00003 mg/kg/day. The Tier 3 analysis was performed using the residues of 0.07 ppm for wheat and assuming 4% crop treated. This value arises from the sum of the limit of quantitation (LOQ) of the clodinofop-propargyl (0.02 ppm) plus the LOQ of the metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid) in/on wheat grain (0.05 ppm). For this chronic DEEM run, HED is not rounding up to 0.10 ppm, as done for establishment of the tolerance. It is important to note that the residue value (0.07 ppm) is still *very* conservative and health protective. The most highly exposed subgroup, **children 1-6 years old** utilize up to **32% of the cPAD.** The **total U.S. population** utilizes up to **14% of the cPAD**.

The EECs provided by EFED for assessing chronic aggregate dietary risk are **5.0 x 10^{-6} μL and 0.044 μL** (in ground water, based on SCI-GROW for clodinafop-propargyl and CGA-193469, respectively) and **0.0017 μL and 0.11 μL** (in surface water, based on the 1 in 10 year annual mean PRZM/EXAMS for clodinafop-propargyl and CGA-193469, respectively). The back-calculated DWLOCs for assessing chronic aggregate dietary risk **range from 0.21 μL** for the most highly exposed population subgroup **(children 1-6 years old)** to **0.91 μL** for the **total U.S. Population**. DWLOCs for assessing chronic aggregate dietary risk are greater than EECs for chronic exposure.

In the estimation of lifetime cancer risk from dietary exposure scenarios, the DWLOC values are greater than or equal to the modeled EEC values reported by EFED. The largest EEC value is for the surface water chronic exposure to CGA-193469 **(0.11 μg/L).** The Tier 3 DEEM™ analysis using the conservative residue values of 0.07 ppm for wheat and assuming 4% crop treated estimates that chronic exposure to the U.S. population will be 0.000004 mg/kg/day. Applying the Q_1* value of 0.129 $(mg/kg/day)^{-1}$ results in a food only risk for cancer of **5.3×10^{-7}** which is below HED's level of concern (**10^{-6}**). Following an aggregate dietary (food + water) assessment for lifetime cancer risk, the resulting DWLOC is **0.13 μg/L.** This cancer DWLOC is *slightly greater than* the EEC for chronic exposure to CGA-193469 in surface water. Because the models used to obtain the EECs for clodinafop-propargyl and CGA-193469 are highly conservative screening models not designed specifically for estimating concentrations in drinking water and because of the conversative nature of the food exposure assessment (anticipated residues at LOQ for parent + metabolite), HED believes this aggregate cancer dietary assessment will not underestimate exposure and that chronic dietary exposure from clodinafop-propargyl

residues in food and drinking water **will not exceed HED's level of concern for lifetime cancer risk.**

Based on the data gaps outlined in Section 6.0, HED is recommending for the establishment of *a time-limited registration, conditioned upon submission of data/information to satisfy the outstanding deficiences* for the combined residues of clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid) in/on the following commodities:

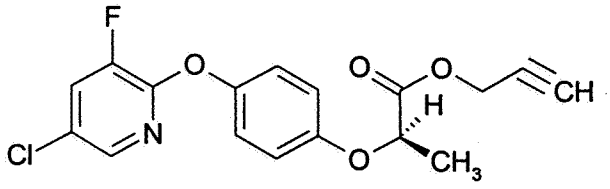
wheat, grain.....0.10 ppm
wheat, forage.....0.10 ppm
wheat, hay..... 0.10 ppm
wheat, straw..... 0.50 ppm.

Prior to the establishment of these tolerances, revised Sections B and F along with adequate validation of the proposed analytical enforcement methods are required.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Chemical Name:	propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester)
Chemical Group:	oxyphenoxy acid ester
Chemical Type:	herbicide (grass weeds)
CAS Registry No.:	105512-06-9 (R- isomer)
Common Name:	clodinafop-propargyl
Other Names:	CGA-184927
Trade Names:	Discover™ Herbicide
Empirical Formula:	$C_{17}H_{13}Cl_1F_1N_1O_4$
Molecular Weight:	349
Appearance:	cream-colored fine powder
Melting Point:	59.4 °C [PAI] (OECD Method No.102)
	48.2-57.1 °C [TGAI]
Vapor Pressure:	2.39×10^{-8} mm Hg at 25°C [PAI]
	(OECD Method No. 104, gas saturation)
Partition Coefficient:	log P_{ow} = 3.90 at 25 °C (octanol/water)
	(PAI; OECD Method No. 107, shake-flask)
Solubility in Water:	4.0 mg/L in water at pH 7, 25 °C (>99% PAI; OECD Method No. 105, shake-flask)
Toxic Impurities:	none at levels of concern

Chemical Structure:



clodinafop-propargyl
CGA-184927
("R" isomer)

3.0 HAZARD CHARACTERIZATION

- **References**:
  Attachment 1: Clodinafop-propargyl - Report of the Hazard Identification Assessment Review Committee (6/2/99, Y. Yang).

- Attachment 2: PP#7F04924 CLODINAFOP PROPARGYL (PC Code: 125203) Toxicology Disciplinary Chapter for Registration Support Document (S. Gross, 4/21/00).

- Attachment 3: Cancer Assessment Document: Evaluation of the carcinogenic potential of clodinafop-propargyl (CGA184927). (11/7/99, Y. Yang)

- Attachment 4: REVISED CGA 184927 (Clodinafop-Propargyl) Quantitative Risk Assessment (Q_1^*) Based On Tif:RAIf(SPF) Albino Rat and Tif:MAGf(SPF) Albino Mouse Chronic Dietary Studies With $^3/_4$'s Interspecies Scaling Factor. (3/2/00, L. Brunsman).

- Attachment 5: Clodinafop-propargyl (CGA 184927): Assessment of Mode of Action on Liver Carcinogenicity. (9/21/99, Y. Yang)

- Attachment 6: CLODINAFOP-PROPARGYL: Report of the FQPA Safety Factor Committee. (4/4/00, B. Tarplee)

3.1 Hazard Profile

3.1.1 Acute Toxicity

The toxicity data indicated that clodinafop-propargyl (CGA 184927) has low acute oral, dermal, and inhalation toxicity (Acute Toxicity Category III). It is slightly irritating to eyes and is not a skin irritant. However, it is a skin sensitizer.

Table 1. Acute Toxicity Data on Clodinafop-propargyl				
GDLN	Study Type	MRID	Results	Tox. Cat.
81-1	Acute Oral- Rat	44399124	LD_{50} =1392(♂)/2271(♀) mg/kg	3
81-2	Acute Dermal -Rabbit -Rat	44399125	LD_{50} > 2000 mg/kg (rat or rabbit)	3
81-3	Acute Inhalation-Rat	44399126	LC_{50} >2.3 mg/L(♂&♀)	4
81-4	Primary Eye Irritation-Rabbit	44399127	Slightly eye irritant	3
81-5	Primary Skin Irritation-Rabbit	44399128	Non-irritant	4
81-6	Dermal Sensitization-Rat	44399129	Skin sensitizer	NA

3.1.2 Subchronic and Chronic Toxicity.

Available toxicity studies are summarized in Table 3.

Systemic Toxicity
The primary target organ of clodinafop-propargyl is the liver for dogs, mice, and rats. The liver toxicity was evidenced by increased liver weight, elevated liver enzyme activities, and abnormal histopathological findings. An increased incidence of hepatoma and hepatocellular carcinoma was observed at the high dose (29.6 mg/kg/day) in a mouse carcinogenicity study.

For dogs only, skin lesions (e.g. pustules, erythema, and crusts) were observed in the subchronic and chronic dog feeding studies. It was noted that the skin lesions were observed at doses as low as 50 ppm (1.73 mg/kg/day) in the subchronic feeding study while skin lesions were observed at higher doses (500 ppm or 15.2 mg/kg/day) in the one-year feeding study.

Developmental/Reproductive Toxicity.
There was no evidence of reproductive toxicity; however, a fetotoxic effect was noted in rats. In the two-generation reproduction study, reduced fetal viability, decreased pup body weight, and dilatation of renal pelvis were observed at doses that produced maternal toxicity (decreased body weight gain, increased liver and kidney weights with histopathological changes). In the developmental toxicity study in rats, fetotoxic effects were observed at doses *lower* than those that produced maternal toxicity. Fetal anomalies consisted of an increased incidence of the

following: bilateral distension of the ureter and bilateral torsion of the ureter, hematoma to the head, absence of ossification in the sternebrae, incomplete ossification of the thoracic vertebral centra, absence of ossification in the caudal vertebral arches, unilateral 14th ribs, incomplete ossification of the metacarpals, and incomplete ossification of various cranial bones (parietal, interparietal, occipital, and squamosal). Also there was a significant but slight reduction (7%) in mean fetal body weights at the high-dose group compared to the control.

Carcinogenicity.
On September 29, 1999, the Cancer Assessment Review Committee (CARC) met to evaluate the carcinogenic potential of clodinafop-propargyl (CGA-184927). The studies evaluated included a 24-month chronic toxicity/carcinogenicity study in Tif: RAIf (SPF) albino rats and an 18-month carcinogenicity study in Tif:MAGf (SPF) albino mice as well as mechanistic studies submitted by the Registrant to support a non-linear mode of action for induction of prostate, ovarian, and liver tumors.

In the noted studies, clodinafop-propargyl was administered in the diet to rats (80/sex/group) at 0, 1, 10, 300 or 750 ppm (0, 0.031, 0.32, 10.18, or 26.28 mg/kg/day for males; and 0, 0.034, 0.36, 11.31, or 29.48 mg/kg/day for females, respectively) and to mice (60/sex/group) at 0, 1, 10, 100 or 250 ppm (0, 0.113, 1.10, 11.0 or 29.6 mg/kg/day for males and 0, 0.129, 1.25, 12.6 or 33.1 mg/kg/day for females, respectively).

Clodinafop-propargyl was carcinogenic to rats because: 1) In males there were significant increases in the pair-wise comparisons of the high-dose group (750 ppm or 26.28 mg/kg/day) with controls for prostate gland adenomas ($p<0.05$) and combined adenomas/carcinomas ($p<0.01$). There were also significant increasing trends for prostate adenomas and combined adenomas/carcinomas; 2) Females had a statistically significant ($p<0.05$) increased incidence at 750 ppm (29.5 mg/kg/day) by pair-wise comparison with the controls for ovarian tubular adenomas. There was also a statistically significant ($p<0.01$) increasing trend for these tumors. The dosing at the highest dose in males was considered to be adequate based on increased mortality, increased liver weights, and non-neoplastic changes in various organs. The CARC considered the prostate and ovarian tumors to be treatment-related.

Clodinafop-propargyl was carcinogenic to mice because: 1) Males had a statistically significant ($p<0.01$) increase in the pair-wise comparisons of the high dose group (250 ppm or 29.6 mg/kg/day) with the controls for hepatomas and combined hepatomas/carcinomas. The incidences of these tumors exceeded the range of historical controls. The increased incidence of carcinomas in high-dose males was considered by the CARC to be biologically significant. There were also statistically significant increasing trends for hepatomas ($p<0.01$), carcinomas ($p<0.05$), and combined hepatomas/carcinomas ($p<0.01$); 2) In females, the incidences of liver tumors were not significant by pair-wise comparison with controls and were within the historical control range. However, there were statistically significant increasing trends in hepatomas ($p<0.01$), and combined hepatomas/carcinomas ($p< 0.05$); 3) In females, there was a borderline increase in hemangiomas and angiosarcomas compared with controls. The combined incidence

of these tumors was outside the range of historical controls. These tumors are considered to be uncommon and therefore, the CARC concluded they could not be discounted.

The CARC determined that the mechanistic studies **do not** support the proposed mode of action for the occurrence of prostate and ovarian tumors in rats or liver and blood vessel tumors in mice.

In accordance with the EPA *Proposed EPA Weight-of-the-Evidence Categories*, August 1999, the CARC classified clodinafop-propargyl (CGA-184927) as **"likely to be carcinogenic to humans"** by the oral route based on the occurrence of prostate tumors in male rats, ovarian tumors in female rats, and liver tumors in both sexes of mice, as well as blood vessel tumors in female mice. For the quantification of human cancer risk, the CARC recommended a linear low-dose extrapolation approach based on the most potent of these tumor types. This approach is supported by possible genotoxic potential and the lack of confirmation of the mode of action of clodinafop-propargyl.

The most potent unit risk, $Q_1^*(mg/kg/day)^{-1}$, of those calculated for CGA 184927 (clodinafop-propargyl) is that for male mouse liver benign hepatoma and/or carcinoma combined tumor rates at 0.129 $(mg/kg/day)^{-1}$ in human equivalents. The dose levels used from the 78-week dietary study were 0, 1, 10, 100, and 250 ppm of clodinafop-propargyl. The corresponding tumor rates were 9/58, 13/57, 9/57, 14/57, and 38/57, respectively.

Mutagenicity.
The submitted genetic toxicology studies indicate that clodinafop-propargyl is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster V79 lung fibroblasts). There is also no evidence of clastogenicity *in vivo*. Similarly, clodinafop-propargyl did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes. However, the submitted studies do not satisfy the 1991 mutagenicity guideline requirements since the *in vitro* cytogenetic assay has been classified as unacceptable. It is recommended, therefore, that an *in vitro* cytogenetic assay be conducted to fulfill guideline requirements. This recommendation is strengthened by the evidence from the literature that propargyl alcohol, a possible metabolite of clodinafop-propargyl, induced chromosome aberration *in vitro* (Blakey, et al., 1994; see Attachment 3).

Blakey et al. (1994) indicated that propargyl alcohol induced chromosomal aberration in CHO cells *in vitro* with and without metabolic activation, while clodinafop-propargyl did not induce reverse mutation detectable with the *Salmonella*/mammalian microsome assay. The formation of propargyl alcohol from clodinafop-propargyl requires ester hydrolysis and under the conditions of the mutagenicity assays ester hydrolysis may not occur, thus giving the false impression that clodinafop-propargyl is non mutagenic.

Neurotoxicity.
There are no neurotoxicity studies available for clodinafop-propargyl. However, clinical signs indicative of neurotoxicity were observed in the dog, rat, and rabbit studies. In order to further

define the potential of neurotoxicity, the HIARC recommended acute and subchronic neurotoxicity studies to be conducted on this chemical. The FQPA Safety Factor Committee recommended that a developmental neurotoxicity study be conducted to evaluate hormonal responses associated with the developing fetal nervous system following pre- and postnatal exposure.

Metabolism.
In a metabolism study (MRID 44399159), two ^{14}C labeled variants of clodinofop-propargyl (one labeled on the 2 pyridil carbon and the other uniformly labeled on the phenyl ring, purity >98%) were administered to groups of five male Tif:RAI f (SPF) rats, approximately 7 weeks of age (weighing about 200 g at time of dosing) by gavage at concentrations of 25.2 mg/kg ([2-^{14}C]pyridil) and 24.6 mg/kg ([U-^{14}C]phenyl).

In the urine, the major metabolite was determined to be (R)-2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)-phenoxy]-propionic acid, reference material CGA-193469, accounting for 36.7% to 39.1% of the administered dose (AD). Metabolite fraction U3 hydrolysed to yield fraction U7 (i.e., CGA-193469), when treated with NaOH or HCl. Unchanged clodinofop-propargyl was not identified. In the feces, the major metabolite (fraction F*7) corresponded to the urinary metabolite U7 (CGA 193469), accounting for 15.7% to 16.9% of the AD. Metabolite fraction F*8 was determined to be unchanged clodinofop-propargyl, accounting for 0.4% to 1.7% of the AD. In the fat, all metabolites were reportedly acylglycerides, the majority of which were hybrid di- and triacylglycerides, (i.e., approximately 3.5% and 17.0% of the AD, respectively).

Endocrine Disruption.
There is evidence of potential endocrine disruption in rat studies with clodinafop-propargyl:

- The following special study observed the effects of clodinafop-propargyl on endocrine hormones *in vivo*.

  Trendelenburg, C. (1999). Effects on selected plasma concentrations and biochemical parameters in the liver upon subchronic administration to male adult rats. MRID no. 44767401.

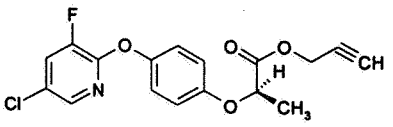
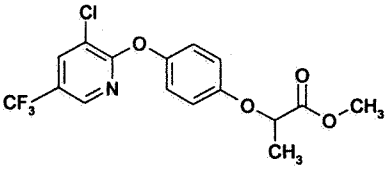
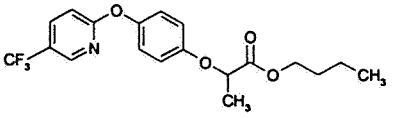
  Clodinafop-propargyl (94.3% a.i.) was administered to 10 male Tif:RAIf (SPF) rats/dose at dietary doses of 0 or 750 ppm (0 or 53.5 mg/kg/day) for 14 days. The treatment with clodinofop-propargyl significantly ($p < 0.05$) decreased the total liver microsomal testosterone oxidation rate to 34% of control. Hydroxylation rates at positions 2α and 16α decreased to 19% and 20% of control (significantly; $p < 0.05$), respectively, and the oxidation rate to androstenedione was decreased to 43% of control. The reduced hydroxylation rates at positions 2α and 16α and the conversion of testosterone to androstenedione indicated depletion of the male specific cytochrome P450 isoenzyme CYP2C11. Decrease in testosterone hydroxylation rates at positions 2 β, 6α, 6 β and 7α (63, 84, 70 and 50%, respectively) were indicative of partial depletion of cytochrome P450 isoenzymes of subfamilies CYP2A and CYP3A. The treatment resulted in

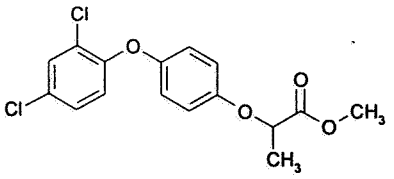
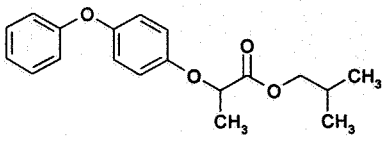
significant increases in hepatic aromatase activity ($p < 0.05$; 169%) and plasma estradiol concentration (not significant; 179% and 140% (CYP19A1) for 3 and 14 days, respectively) compared to control. The total and free plasma testosterone concentrations were not effected by treatment with clodinofop-propargyl. Plasma 5α-dihydrotestosterone level increased (not significantly; 198% of control) after 14 days of treatment.

- As indicated in the CARC document, clodinafop-propargyl has been classified as "likely to be carcinogenic to humans" by the oral route ***based on the occurrence of prostate tumors in male rats, ovarian tumors in female rats*** and liver tumors in both sexes of mice, as well as blood vessel tumors in female mice.

Structure Activity.
Two of the four structural analogs (i.e., haloxyfop-methyl and diclofop-methyl) were found to induce liver tumors in mice. The diphenyl ether like structure in the molecule may be responsible for the carcinogenic potential of these compounds. Fluazifop-butyl and diclofop-methyl are not mutagenic. The mutagenicity data on other compounds were not available.

Table 2. Structure-Activity Comparison

Compound	Structure	Carcinogenic Effect
Clodinafop-propargyl CAS 105511-96-4 PC 125203		- Prostate and ovarian tubular tumors in rats. - Liver tumors in mice -Blood vessell tumors in female mice
Haloxyfop-methyl CAS 69806-40-2 PC 125201		- Liver tumor (adenoma and carcinomas). - B6C3F1 mice. - Mutagenicity data not available.
Fluazifop-butyl CAS 69806-50-4 PC 122805		- No evidence of increased liver tumors; however, the dose levels may be inadequate. - Not mutagenic.

Diclofop-methyl (Hoelon) CAS 51338-27-3 PC 110902		- possible human carcinogen - Hepatocellular adenoma and/or carcinomas - NMRKf (SPF) mice. - Not mutagenic.
Clofop-isobutyl CAS 51337-71-4		- No data are available. - The chemical has been voluntarily canceled.

Mechanistic Studies

The Registrant proposed that clodinafop-propargyl (CGA-184927) acts as a peroxisome proliferator and is directly involved with the onset of liver carcinogenesis in the rodent. Peroxisome proliferation is a transcription-mediated process that involves activation by the peroxisome proliferator of a nuclear receptor in rodent liver called the peroxisome proliferator-activated receptor (PPARα), a member of the steroid hormone receptor superfamily. Upon activation by peroxisomal proliferators, PPARα forms a heterodimer with the retinoid-X-receptor. This dimer binds to peroxisome proliferator response elements (PPRE) in the promoter region of target genes known to be regulated by PPARα. PPARα induces mitogenesis and cell proliferation which can lead to the formation of hepatocellular tumors. Oxidative stress appears to play a significant role in this increased cell proliferation. It triggers the release of Tumor Necrosis Factor (TNFα) by Kupffer cells, which in turn acts as a potent mitogen in hepatocytes.

The effects caused by peroxisome proliferators in endocrine organs are likely to be a consequence of altered steroid hormone metabolism. The submitted special studies which describe the role of clodinafop-propargyl as a peroxisome proliferator and its role in induction of peroxisomal and microsomal enzymes are discussed in Attachment 2.

Mode of Action

On September 27, 1999, the Mechanism of Toxicity Assessment Review Committee (MTARC) met to evaluate the mechanistic studies submitted by the Registrant. The Registrant contended that clodinofop-propargyl acts as a rodent-specific peroxisome proliferator which manifests itself in the induction of peroxisomal and microsomal enzymes and alteration of steroid hormone metabolism resulting in tumor formation.

The MTARC determined that the submitted studies **do not** support the proposed mode of action of peroxisome proliferation as the mechanism of liver carcinogenicity for clodinafop-propargyl (CGA-184927) based on the following reasons: (1) the submitted data were based on rat studies; however, the liver tumors were observed in mice only which raises an uncertainty about the peroxisome proliferation mechanism of tumorigenesis in mice; (2) the structure activity

relationship data indicated that there may be other possible mechanisms which may contribute to the liver carcinogenesis.

The CARC concluded that peroxisome proliferation may be one of the mechanisms in inducing cytochrome p-450 enzymes that are involved in altering the steroid metabolism but the Registrant did not provide information to support their hypothesis. However, based on the pathological changes seen (hyperplasia and hypertrophy of hepatocytes), other mechanisms are plausible. Also, while the mutagenicity data indicate that clodinafop-propargyl is not mutagenic in bacteria or cultured mammalian cells, propargyl alcohol and propargyl aldehyde (a metabolite of propargyl alcohol) are known mutagens. The CARC recognizes that the peroxisome proliferators can act as liver tumor promoters and that there are quantitative differences in the degree of peroxisome proliferation between rodents, guinea pigs, marmosets, and humans. Although the mechanistic data in rats fulfill the criteria for peroxisome proliferation, the studies were conducted in rats while liver tumors were observed in mice only. The peroxisome proliferation study was not conducted in mice. The lack of liver tumors in rats raises uncertainty regarding the role of peroxisome proliferation in mouse liver tumorigenesis. No dose-related association of peroxisome proliferating activity with increase in liver tumors in mice was demonstrated. **The MTARC, therefore, concluded that these studies do not support the proposed mode of action for the occurrence of prostate and ovarian tumors in rats or liver and blood vessel tumors in mice.**

Table 3. Toxicity Summary Table for Clodinafop-propargyl (CGA 184927)		
Guideline No./ Study Type	**MRID No. (year)/ Doses/ Classification**	**Results**
870.3100/ 28-Day oral gavage	44399130 (1988) 0, 5, 40, 200 mg/kg/day Acceptable Study, Non-Guideline	NOAEL < 5 mg/kg LOAEL = 5 mg/kg for M and F based on liver toxicity (enzyme changes),
870.3100/ 13 week oral toxicity in rodent	44399132 (1988)/ 0, 2, 15, 120, 1000 ppm M: 0, 0.1, 0.9, 8.2, 70.0 mg/kg/day F: 0, 0.1, 0.9, 8.2, 71.1 mg/kg/day. Acceptable-Guideline	NOAEL = M: 0.9 mg/kg; F: 8.2 mg/kg/day LOAEL = M: 120 ppm (8.2 mg/kg/day); F: 1000 ppm (71.1 mg/kg/day) decreased body weight; based on increased liver weights and enzymes (AlPtase); decreased. thymus weight (atrophy). Reversed after 28 day recovery period.
870.3100/ 13 week oral toxicity in mice	44399138 (1989)/ 0, 2, 6, 50, 400 ppm M: 0,0.3, 0.9, 7.3, 53 mg/kg/day F: 0,0.3, 1.1, 8.6, 71.3 mg/kg/day Unacceptable-Guideline	NOAEL = M: 0.9mg/kg/day; F: 1.1mg/kg/day LOAEL = M: 7.3 mg/kg/day ; F: 8.6 mg/kg/day based on clinical chemistry; glucose, sodium, and chloride increases and hepatocellular hypertrophy in males and females.
870.3150 90-Day oral toxicity in dogs	44399139 (1989)/ 0, 10, 50 and 200 ppm for 90 days and 1/1000/500 ppm for days 1-54/55-66/67-90. M: 0,0.35, 1.7, 7.9, 0.04/34.7.16 mg/kg/day(♂) F: 0,0.4, 1.9, 7.2, 0.04/32.3/16.9 mg/kg/day Acceptable-Guideline	The NOAEL = M: 0.346 mg/kg/day, F: 1.89 mg/kg/day. The LOAEL = M: 1.73 mg/kg/day ; F: 7.16 mg/kg/day based on occurrence of skin lesions.
870.3200 28-Day dermal toxicity in rats.	44399141 (1987)/ 0, 50, 200 and 1000 mg/kg/day. Acceptable Guideline	Systemic NOAEL = 50 mg/kg/day Systemic LOAEL = 200 mg/kg based on dose-related increases in liver weights and clinical signs (piloerection and hunched posture) in male rats. Dermal NOAEL = 1000 mg/kg/day.

Guideline No./ Study Type	MRID No. (year)/ Doses/ Classification	Results
870.3700a Prenatal developmental in rats	44399145 (1989)/ 0, 5, 40, 160 mg/kg/day Acceptable Guideline	Maternal NOAEL = 160 mg/kg/day Maternal LOAEL > 160 mg/kg/day based on lack of effect. Developmental NOAEL = 5 mg/kg/day Developmental LOAEL = 40 mg/kg/day based on increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal).
870.3700b Prenatal developmental in rabbits	44399144 (1989)/ 0, 5, 25, 125, 175 mg/kg/day Acceptable Guideline	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL = 125 mg/kg/day based on mortality, clinical signs and body weight loss Developmental NOAEL = 125 mg/kg/day Developmental LOAEL >125 mg/kg/day
870.3800 Two Generation Reproduction	44399146 (1991)/ 0, 5, 50, 500 or 1000 ppm M: 0, 0.33, 3.21, 31.69, 64.24 mg/kg/day F: 0, 0.41, 3.77, 37.54, 73.60 mg/kg/day Acceptable Guideline	Parental/Systemic NOAEL= 3.2 mg/kg/day. Parental/Systemic LOAEL = 31.7 mg/kg/day based on decrease in body weight gain, reduced food consumption, increased liver and kidney weights and histopathological changes in the liver and renal tubules. Offspring NOAEL = 3.2 mg/kg/day Offspring LOAEL = 31.7 mg/kg/day based on reduced viability, decreased pup body weight and dilatation of renal pelvis. Reproductive NOAEL = 64.2 mg/kg/day. Reproductive LOAEL≥64.2 mg/kg/day
870.4100b Chronic toxicity nonrodent	44399128 (1990)/ 0, 10, 100 or 500 ppm M: 0, 0.3, 3.4, 15.2 mg/kg/day F: 0, 0.3, 3.4, 16.7 mg/kg/day Acceptable Guideline	NOAEL = M: 3.38mg/kg/day; F: 3.37 mg/kg/day LOAEL = M: 15.2 mg/kg/day ; F: 16.7 mg/kg/day based on occurrence of skin lesions, clinical signs, and reduced body weight gain and food consumption.
870.4200b Carcinogenicity mice	44399143 (1992)/ 0, 1, 10, 100, 250 ppm M: 0, 0.113, 1.10, 11.0 or 29.6 mg/kg bw/day F: 0, 0.129, 1.25, 12.6 and 33.1 mg/kg bw/day Acceptable Guideline	NOAEL = M: 1.10 mg/kg/day; F: 1.25 mg/kg/day LOAEL =M: 11.0 mg/kg/day; F: 12.6 mg/kg/day based on increase in liver enzyme activity and liver weights. Under the conditions of this study, clodinafop-propargyl induced hepatocellular tumors at 29.6 mg/kg. The chemical was tested at doses sufficient to measure its carcinogenic potential.

Guideline No./ Study Type	MRID No. (year)/ Doses/ Classification	Results
870.4300 Chronic/ Oncogenicity in the Rat.	44399147 (1992)/ 0, 1, 10, 300, 750 ppm M: 0,0.03, 0.3, 10.2, 26.3 mg/kg/day F: 0, 0.03, 0.4, 11.3, 10.2, 29.5 mg/kg/day Acceptable Guideline	NOAEL = M:0.03 mg/kg/day ; F: 0.03 mg/kg/day LOAEL = M: 0.3 mg/kg/day; F: 0.4 mg/kg/day based on hepatocytic hypertrophy, chronic progressive nephropathy, and tubular pigmentation. Under the conditions of this study, treatment with clodinafop-propargyl increased the incidence of prostate and ovarian tumors in rats at 750 ppm. For males, an increased incidence of prostate adenoma was seen in the high-dose group. The chemical was administered at a dose sufficient to test its carcinogenic potential.
870.5100 Gene Mutation Salmonella and Escherichia/liver microsome test.	44399153/ (1990) Acceptable Guideline	Neg. for mutagenicity.
870.5200 Gene Mutation Mutation test with Chinese Hamster cells V79	44399152/ (1987) Acceptable Guideline	Neg. for mutagenicity.
870.5315 Chromosome Studies; Human Lymphocytes in vitro.	44399154 (1988) Unacceptable Guideline	Owing to the conflicting results from the cytotoxicity assessment and the presence of rare complex chromosome aberrations both with and without S9 activation, the study is considered inconclusive.
870.5395 Micronucleus Test (Chinese Hamster)	44399151 (1987) Acceptable Guideline	No clear evidence that clodinafop-propargyl induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.
870.5550 DNA Repair Human Fibroblasts.	44399155 (1988) Unacceptable Guideline.	Compound precipitation was seen at doses ≥320 μg/mL: there was, however, no indication of a cytotoxic effect at any dose. The positive control induced the expected marked increases in UDS. There was, however, no evidence that CGA-184927 in the absence of S9 activation induced a genotoxic response in either trial.
870.5550 DNA Repair Rat Hepatocytes	44399156/ (1987) Acceptable Guideline	Compound precipitation was noted at levels ≥4000 μg/mL. Lethality was apparent in the preliminary cytotoxicity test at 94.8 μg/mL. The positive control induced the expected marked increases in UDS. There was, however, no evidence that clodinafop-propargyl induced a genotoxic response in either trial.
870.7485 Metabolism and pharmacokinetics,	44399159/(1989) Acceptable Guideline	The main metabolite was CGA 193469(76% in male urine). Additional 5% was in the form of taurine conjugate of CGA 193469. Similar distribution was found in feces.

Guideline.No./ Study Type	MRID No. (year)/ Doses/ Classification	Results
870.7485 Metabolism and pharmacokinetics,	44399160/ (1990) Acceptable Guideline	The major metabolite in urine and feces was determined to be CGA 193469, accounting for about 36% to 47% of the AD for males, and 80% to 85% of the AD for females. In addition, 11 minor metabolite fractions were isolated from urine and feces. Three were further identified as reference materials CGA 193468, CGA 214111 and unchanged clodinofop-propargyl.
Special Study: Determination Of Residues As CGA 193469 In Abdominal Fat After A 3-Month Oral Toxicity Study In Rat.	44399134 14 week treatment, 0, 2, 15, 120, 1000ppm	There was a dose-dependent increase in clodinofop-propargyl residues in fat samples from both sexes taken at the end of treatment (14 weeks) and after the 4-week recovery period (18 weeks). Concentrations of clodinofop-propargyl were higher in male rats at all dose levels tested. With the exception of low-dose group males, for all remaining groups, residues in the fat at 18 weeks had decreased by between 40% - 51.5% of the 14 week value.
Special Study Determination Of Residues As CGA 193469 In Abdominal Fat After 12 Months In Study.	44399135	1 ppm and 10 ppm, the concentration of CGA 184927 in the abdominal fat was higher in males when compared to females. At 300 and 750 ppm, the concentration of CGA 184927 in the abdominal fat was comparable between males and females. The results of this study also indicate that the clodinafop-propargyl residue in fat is reduced after 1 year of treatment compared to 3 month treatment.
Special Study: The Effect Of CGA 184927 On Selected Biochemical Parameters In The Rat Liver Following Subchronic Administration.	44399137	The effects of clodinafop-propargyl on selected liver enzymes in the rat were similar to the effects seen after subchronic treatment with known peroxisome proliferators (hypolipidemic compounds, phenoxyacetic acid derivatives). Hence, clodinafop-propargyl was considered to most likely be a peroxisome proliferator in the rat liver.
Special Study: Apparently clonal thyroid adenomas may contain heterogeneously growing and functioning cell subpopulations. New Frontiers in Thyroidology, p. 901-905, 1986	44399148/(1986)	The asynchronous growth rate of subsets of cells within the old adenomas as well as the intercellular heterogeneity of the endocytotic response to TSH suggests that clonal thyroid adenomas may acquire new qualities and can modify gene expression via much debated mechanism. The author concludes that the growth of benign thyroid tumors and progression does not require a change in genomic expression in any cell. The apparent heterogeneity of a tumor does not necessarily exclude its monoclonal origin.

Guideline No./ Study Type	MRID No. (year)/ Doses/ Classification	Results
Special Study: Assessment of hyperplastic and neoplastic lesions of the thyroid gland. TIPS, Vol. 8, p. 511-514.	44399149/(1987)	In cell cultures, TSH does not induce proliferation of human thyroid cells, but does stimulate the growth of cells obtained from rat and dog thyroids. Conventional procedures of evaluating carcinogenicity tests by simply counting tumors in rodents treated with high doses, and by mathematical extrapolation to the low doses to which humans are exposed, are not suitable for the proliferative reactions of the thyroid gland. In assessing the human risk, relevant conclusions can only be drawn if the physiological factors of growth control are known, and if the biological mechanisms by which chemicals initiate focal proliferation and support their progression to tumors are considered.
Special Study: Stott, W.T. Chemically induced proliferation of peroxisomes: Implications for risk assessment. Regulatory Toxicology and Pharmacology, Vol. 8, p. 125-159, 1988.	44399150 (1988)	The author concludes that a more appropriate MTD of a peroxisome proliferative agent in sensitive species would appear to be based upon evidence of the proliferation of peroxisomes and the induction of peroxisomal enzymes capable of producing an increased intracellular oxidative stress. Exceeding these dosages will only result in a predictable sequence of events leading, ultimately, to tumor formation due to physiological adaptation of the animal to the administered compound rather than from the direct effects of the compound itself.
Special Study Bieri, F. The Effect of CGA 193469, the Free Acid Derivative of CGA 184927, on Peroxisomal B-oxidation in Primary Cultures of Rat, Mouse, Marmoset and Guinea Pig Hepatocytes.	44399157 (1991).	This study characterized and compared the in vitro effects of clodinafop-propargyl on selected parameters (i.e., cytotoxicity and induction of peroxisomal beta-oxidation) in primary hepatocytes from various species. The monolayer cultures were treated with medium containing clodinafop-propargyl, CGA 193469 or propargyl alcohol at the appropriate concentrations (0.1 to 100 µg/mL), or solvent controls and incubated for three days. Hepatocytes were then examined for morphological alterations and cell viability. The lactate dehydrogenase (LDH) activity was measured as an indicator of cytotoxicity. In addition, protein content of hepatocytes were measured to determine the membrane damage. Peroxisomal beta-oxidation was measured in hepatocyte homogenates treated with [1-14]palmitoyl-CoA, a peroxisomal enzyme marker. Clodinafop-propargyl-induced cytotoxicity through propargyl alcohol.

Guideline No./ Study Type	MRID No. (year)/ Doses/ Classification	Results
Special Study Guyomard, C. (1992). Effects of CGA-193469, the acid derivative of CGA-184927, on the peroxisomal beta-oxidation in human hepatocytes.	44399158 (1992).	Under the conditions of this study, neither CGA 193469 nor bezafibric acid induced peroxisomal beta-oxidation in human hepatocytes, in vitro. However, in the absence of a known concurrent human positive control to validate the test system, (i.e., a substance known to elicit peroxisomal beta-oxidation in human hepatocytes,) this cannot be definitely concluded.
Special Study: Trendelenburg, C. Effects on selected plasma concentrations and biochemical parameters in the liver upon subchronic administration to male adult rats.	443767401/(1999). 0 and 750 ppm (0, 53.5 mg/kg/day for 14 days) males only Acceptable non-guideline.	Clodinafop-propargyl may act as a peroxisomal proliferating agent and alters monooxygenase activity in subfamilies of cytochrome P450 which are known to be involved in the synthesis or catabolism of steroid hormones.

3.2 Dose-Response Assessment

On April 29, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of clodinafop-propargyl (CGA 184927), established Reference Doses (RfDs), selected toxicological endpoints for acute and chronic dietary as well as occupational and residential exposure risk assessments.

A. Dietary Exposure:

Acute Dietary Exposure: An acute reference dose (RfD) was selected for the subpopulation of females 13-50 years old. This acute RfD of **0.05 mg/kg/day** is based on the no-observed-adverse-effect level (NOAEL) of 5 mg/kg/day selected from a developmental toxicity in rats (MRID no. 44399145) where an increased incidence of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal) were observed at 40 mg/kg/day (lowest-observed-adverse-effect-level; LOAEL). (The NOAEL of 5 mg/kg/day is divided by uncertainty factors (UF) for inter-species extrapolation (10x) and intra-species variability (10x).) Based on the conservative assumption that developmental toxicity could occur following a single exposure to a pregnant female, this endpoint is appropriate for acute risk assessment for females 13-50.

An acute RfD for the general population was also selected by the HIARC. The **acute RfD of 0.25 mg/kg/day** is based on a NOAEL of 25 mg/kg from a developmental toxicity study in rabbits (MRID no. 44399144) where maternal toxicity (increased mortality, clinical signs and body weight loss) was observed at 125 mg/kg/day. This study is suitable for general population because mortality, clinical signs, and maternal body weight loss occurred on the first measurement time point (day 2 after dosing). It is reasonable to assume that the effects could occur after a single dose.

Chronic Dietary: The HIARC selected a **chronic RfD of 0.0003 mg/kg/day** (NOAEL = 0.03 mg/kg/day; Uncertainty Factor = 100). This chronic RfD is based on a two year combined chronic/oncogenicity study in rats (MRID no. 44399147). In this study, the NOAEL of 0.03 mg/kg/day was based on observations of hepatocytic hypertrophy, chronic progressive nephropathy and tubular pigmentation at 0.3 mg/kg/day (LOAEL). The Uncertainty Factor accounts for both interspecies extrapolation (10X) and intraspecies variability (10X).

B. Occupational/Residential Exposure:

There are no proposed or registered residential uses; however, there is potential for residential exposure to spray drift resulting from aerial application. Based on the use pattern, there is potential for short-term exposures (private- one field) and intermediate-term exposure (commercial- several fields) during mixing, loading, application, and post-application activities. Long-term exposure is not expected to occur.

Short and Intermediate Term Dermal Endpoints: Short- and intermediate-term dermal endpoints of 50 mg/kg/day (NOAEL) were selected from a 28-day dermal toxicity study (MRID no. 44399141) where dose-related increases in liver weights and clinical signs (piloerection and hunched posture) in male rats were observed at 200 mg/kg/day (LOAEL). This study is selected because its duration and route of exposure are appropriate for short and intermediate term dermal exposure.

Short-Term Inhalation Risk Assessment: A short-term inhalation endpoint of 5 mg/kg/day (NOAEL) was selected from a developmental toxicity study in rats (MRID no. 44399145) where an increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal) were observed at 40 mg/kg/day (LOAEL). Only an acute inhalation toxicity study has been submitted to the Agency. There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database. Consequently, the oral values should be used for inhalation exposure risk assessment; the route-to-route extrapolation should be done as shown below.

Intermediate-Term Inhalation Risk Assessment: An intermediate-term inhalation endpoint of 0.9 mg/kg/day (NOAEL) was selected from a subchronic oral toxicity in rats (MRID no. 44399132) where increases in liver weights and enzyme activity were

observed in males at 8.2 mg/kg/day (LOAEL). Only an acute inhalation toxicity study has been submitted to the Agency. There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database. Consequently, the oral values should be used for inhalation exposure risk assessment; the route-to-route extrapolation should be done as follows:

> Convert the inhalation exposure component (i.e. μg a.i./day) using a 100% absorption rate (default value) and an application rate to an equivalent oral dose (mg/kg/day) and compare it to the oral value of 5 mg/kg/day and 0.9 mg/kg/day for short- and intermediate-term exposure scenarios, respectively, to calculate the MOEs.

Long-Term Dermal and Inhalation Risk Assessments: Based on the proposed use patterns, no long-term dermal or inhalation exposure is expected to occur. Therefore, no endpoints were selected.

C. Dermal Absorption:

No dermal absorption study was submitted. The HIARC estimated the % dermal absorption for CGA 184927 to be 2.5%. This dermal absorption rate was derived by taking the ratio of the LOAEL from the 28-day oral (gavage) toxicity study in rats (5 mg/kg/day) and the 28-dermal toxicity study in rats (200 mg/kg/day) based on the common endpoint of liver toxicity.

D. Application of Toxicology Endpoints for Aggregate Risk and Occupational Exposure Assessment:

For short term aggregate exposure risk assessment, oral and dermal exposures can not be combined due to differences in the toxicological endpoints via these routes. For intermediate-term aggregate exposure risk assessment, oral and dermal exposures can be combined since increased liver weights were observed via both of these routes. Oral and inhalation exposure can be combined since inhalation exposure is corrected to oral equivalent doses. Based on the current use pattern, long-term aggregate exposure risk assessment is not required. A MOE of 100 is required for occupational exposure risk assessment.

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

Table 4. Summary of Toxicology Endpoint Selections for Clodinafop-propargyl			
EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (For females 13+)	NOAEL=5 (UF=100)	Increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals, and various cranial bones.	Developmental toxicity study in rats
	Acute RfD (females 13+) = 0.05 mg/kg/day		
Acute Dietary (For general population)	NOAEL= 25 (UF=100)	Maternal toxicity (increased mortality, clinical signs and body weight loss)	Developmental toxicity study in rabbits
	Acute RfD (general population) = 0.25 mg/kg/day		
Chronic Dietary	NOAEL=0.03 (UF=100)	Hepatocytic hypertrophy, chronic progressive nephropathy, and tubular pigmentation	Chronic Toxicity -Rat
		Chronic RfD = 0.0003 mg/kg/day	
		Classified "Likely to be a human carcinogen" Q_1^***(mg/kg/day)$^{-1}$ = 0.129**	
Short-term (Dermal)	Dermal NOAEL=50 acceptable MOE ≥ 100	Increased liver weight and clinical signs (piloerection and hunched posture) in males	28-Day Dermal Toxicity- Rats
Intermediate-Term (Dermal)			
Long-term (Dermal)	Not Applicable	Based on the current use pattern, no long-term dermal exposure is expected to occur.	
Short-term (Inhalation)	Oral NOAEL= 5[a] acceptable MOE ≥ 100	See acute dietary	Developmental toxicity in rats
Intermediate-Term (Inhalation)	Oral NOAEL=0.9[a] acceptable MOE ≥ 100	Increased liver weight and enzyme activity in males	Subchronic oral toxicity study in rats
Long-term (Inhalation)	Not Applicable	Based on the current use pattern, no long-term inhalation exposure is expected to occur.	

[a] use route to route extrapolation

3.3 FQPA Considerations

The toxicology database for clodinafop-propargyl is incomplete. The HIARC has requested acute and subchronic neurotoxicity studies in order to further define the neurotoxic potential of this chemical due to the observation of clinical signs indicative of neurotoxicity in the dog, rat, and rabbit studies. At the April 29, 1999 meeting, the HIARC reserved its recommendation for a developmental neurotoxicity study for clodinafop-propargyl pending submissions and review of the acute and subchronic neurotoxicity studies.

On March 20, 2000, the FQPA Safety Factor Committee recommended that a developmental neurotoxicity study be conducted with clodinafop-propargyl based on the evidence of potential endocrine disruption in the special studies submitted by the Registrant including the Trendelenburg *in vivo* study (MRID no. 44767401). These mechanistic studies were not evaluated by the HIARC, but were included in the September 29, 1999 evaluation of clodinafop-propargyl by the CARC. **The FQPA SFC recommended that a developmental neurotoxicity study be conducted to evaluate hormonal responses associated with the developing fetal nervous system following pre- and postnatal exposure.**

The HIARC concluded that there is concern for the increased susceptibility of the young to exposure to clodinafop-propargyl based on the developmental toxicity study in rats where increased skeletal effects were observed at doses much lower (LOAEL of 40 mg/kg/day) than the maternal NOAEL (160 mg/kg/day). There was no evidence of increased susceptibility in the prenatal developmental toxicity study in rabbits since no treatment-related developmental toxicity was observed.

Although there was no evidence of reproductive toxicity, a fetotoxic effect was noted in the two-generation reproduction study in rats since reduced fetal viability, decreased pup body weight, and dilatation of renal pelvis were observed in the offspring at doses that produced relatively minimal parental toxicity (decreased body weight gain, increased liver and kidney weights with histopathological changes).

1. <u>FQPA Safety Factor Recommendation</u>

The Health Effects Division (HED) FQPA Safety Factor Committee met on March 6, 2000 and again on March 20, 2000 to evaluate the hazard and exposure data for clodinafop-propargyl and recommended that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) be retained at *up to* 10x in assessing the risk posed by this chemical.

2. <u>Rationale for Retaining the FQPA Safety Factor</u>

The FQPA SFC concluded that the FQPA safety factor be **retained at *up to* 10x** because:

- the toxicology database for clodinafop-propargyl is incomplete (acute, subchronic, and developmental neurotoxicity studies are required);
- there is quantitative evidence of increased susceptibility following *in utero* exposure to clodinafop-propargyl in the prenatal developmental study in rats;
- there is concern for qualitative increased susceptibility in the 2-generation reproduction study in rats; and
- a developmental neurotoxicity study has been required based on the evidence of potential endocrine disruption in the mechanism studies with clodinafop-propargyl.

3. Application of the Safety Factor - Population Subgroups / Risk Assessment Scenarios

When assessing **acute dietary exposure,** the safety factor is **retained at 10x** for the **females 13-50 years old population subgroup** since there are data gaps in the toxicology database for clodinafop-propargyl including a developmental neurotoxicity study and there is quantitative evidence of increased susceptibility following *in utero* exposure to clodinafop-propargyl in the prenatal developmental study in rats.

The safety factor can be **reduced to 3x** for the **infants and children population subgroups** when assessing acute dietary exposure since the increased susceptibility observed following *in utero* exposure is only of concern for females of childbearing age leaving only the uncertainty due to the data gap for the developmental neurotoxicity study.

The safety factor can be **reduced to 1x** for all other populations subgroups **not** included in females 13-50 years old and infants and children when assessing acute dietary exposure. The increased susceptibility observed following *in utero* exposure is only of concern for females of childbearing age. The data gap for developmental neurotoxicity is of concern for infants and children.

When assessing the **chronic dietary exposure,** the safety factor should be **retained at 10x** for **all population subgroups** since there is concern for qualitative increased susceptibility of the young demonstrated after repeated oral exposures in the 2-generation reproduction study and since there are data gaps in the toxicology database including a developmental neurotoxicity studies in rats.

Table 5. Determinations of the FQPA Safety Factor Committee

Exposure Scenario	FQPA Safety Factor To Be Applied	Calculation of PAD	Populations to Which PAD[1] Should be Applied
Acute dietary	10x	0.05 mg/kg/day / 10x = 0.005 mg/kg/day	Females 13-50 years old

Table 5. Determinations of the FQPA Safety Factor Committee			
	3x	0.25 mg/kg/day / 3x = 0.083 mg/kg/day	Infants and Children
	1x	0.25 mg/kg/day / 1x = 0.25 mg/kg/day	Other population groups
Chronic dietary	10x	0.0003 mg/kg/day / 10x = 0.00003 mg/kg/day	ALL population subgroups

[1] PAD = Population Adjusted Dose; RfD (acute or chronic) ÷ FQPA Safety Factor = Population Adjusted Dose

4.0 EXPOSURE ASSESSMENT

- Attachment 7: Proposed label for Discover™ Herbicide label, Novartis Corporation; EPA File Symbol 100-ONT

- Attachment 8: PP#7F04924. Clodinafop-propargyl on Wheat. Review of Analytical Methods and Residue Data. First Food Use Review (N. Dodd, 4/7/2000).

- Attachment 9: Acute and Chronic Dietary Exposure Analyses for Proposed Tolerances for Clodinafop-propargyl in/on Wheat Commodities. (M. Xue, 4/20/2000).

- Attachment 10: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Clodinafop-Propargyl on Wheat (K. O'Rourke, 4/4/2000).

- Attachment 11: Clodinafop-propargyl. Metabolism Assessment Review Committee (MARC) Decision Document for Meeting Held on 2/15/00. Chemical # 125203. DP Barcodes: D263288 and D263312. Case # 289249. Submission # S543995. (N. Dodd, 2/25/2000).

- Attachment 12: Tier I Estimated Environmental Concentrations of Clodinafop propargyl (Chemical: 125203). (J. Jordan, 11/1/1999).

- Attachment 13: Clodinafop Propargyl Drinking Water Assessment for Surface Water. (J. Lin and J. Jordan, 2/29/2000).

- Attachment 14: Chemical names and structures of clodinafop-propargyl and its metabolites identified in primary plant, animal, and rotational crop commodities:
  (14.1) Names and Structures of clodinafop-propargyl and its Metabolites
  (14.2) Figure 1. Proposed Wheat Metabolism Pathway of [^{14}C-Phenyl]CGA-178486/CGA-184927 and [2-^{14}C-Pyridyl]CGA-184927
  (14.3) Figure 2. Proposed Goat Metabolism Pathway of Clodinafop-propargyl
  (14.4) Figure 3. Proposed Hen Metabolism Pathway of Clodinafop-propargyl

4.1 Summary of Registered and Proposed Uses

Registered Uses. Clodinafop-propargyl has no currently registered uses.

Formulation.
Discover™ Herbicide (EPA File Symbol 100-ONT) is an emulsifiable concentrate which contains 22.3% clodinafop-propargyl active ingredient (ai) and 77.7% inerts. The formulation contains 2 lb ai/gal.

Proposed Use.
Discover™ Herbicide can be applied to all types of spring and winter wheat (including Durum) grown in Montana, Minnesota, North Dakota, and South Dakota. Discover™ Herbicide is applied postemergence to wheat from the 2-leaf stage to emergence of the 4th tiller. It is applied broadcast using ground equipment in at least 5 or 10 gal spray/A (use at least 10 gal spray/A under dry conditions and when treating Persian Darnel or Annual Ryegrass) or applied by aircraft in at least 3 or 5 gal spray/A (use at least 5 gal spray/A under dry conditions and when treating Persian Darnel or Annual Ryegrass). It should not be used to treat wheat underseeded to forages and should not be applied through any type of irrigation system. Grazing of livestock or feeding of forage from treated areas should not be done for a minimum of 7 days following application. Hay should not be fed for 30 days following application. Wheat (grain and straw) should not be harvested for 60 days following application. Only one application is proposed to be made per crop season.

The Section B/label should be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section B/label is made, the proposed use of clodinafop-propargyl on wheat will be adequately described. The proposed use directions will be adequate to allow an assessment of whether the residue data reflect the maximum residues likely to occur in food/feed.

4.2 Dietary Exposure

A very brief summary of information from the residue chemistry review (Attachment 8) is given below. Data gaps exist in the residue chemistry database (see Section 6.0 of this review). **Although the noted residue chemistry issues exist, this assessment is considered conservative and health protective. Except for the submission of revised Sections B and F and the availability of adequate EPA method validations, noted issues will not preclude the establishment of a time-limited registration.**
Metabolism in Plants. The fate of [^{14}C-phenyl]CGA-178486 [(R,S) 2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid, 2-propynyl ester] was studied in field grown spring wheat in St. Aubin, Switzerland after post-emergence foliar spray application of [^{14}C-phenyl] CGA-178486 at 2X. Grain was not extracted from the field study; extraction of grain in this study is not required since the total radioactive residue (TRR) in grain were <10 ppb. Leaves harvested at 41 days (ear emergence stage) and 61 days (milky stage) after treatment and straw

harvested at 82 days (mature stage) after treatment were extracted. The non-extractable radioactivity was 32.5% TRR in leaves (41-day PHI; ear emergence), 70.2% TRR in leaves (61-day PHI; milky stage), and 83.8% TRR in mature straw (82-day PHI). Metabolites were identified by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). The structures of the metabolites were confirmed by mass spectroscopy (MS). The structure of metabolite II_2 [(R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)] was also confirmed by ^{1}H-NMR. Residues identified in the extractable residues from leaves and straw were CGA-193468, CGA-144462, metabolite II_2 [(R,S) (2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)], and CGA-146445. No parent was found in leaves or straw. All identified metabolites were <10% TRR except CGA-146445 (10.3% TRR) in leaves (ear emergence; 41-days PHI).

Based on the structures identified, the following pathway of [^{14}C-phenyl] labeled CGA-178486/CGA-184927 in wheat is proposed: 1) hydrolysis of the parent ester molecule CGA-178486/CGA-184927 to form the acid CGA-144462/CGA-193469, and subsequent sugar conjugation of the acid; 2) hydroxylation of the 6-position of the pyridyl ring in CGA-144462/CGA-193469 to form metabolite II_2 and subsequent sugar conjugation; 3) cleavage of the ether bridge between the pyridinyl and phenyl rings in CGA-144462/CGA-193469, yielding CGA-146445/CGA-214111 and its corresponding sugar conjugate; and 4) cleavage of CGA-144462/CGA-193469 at the phenoxy-propanoic acid ether bridge to form CGA-193468.

The proposed wheat metabolism pathway is shown in Figure 1 (Attachment 14).

The nature of the residue in wheat is not adequately understood for the purposes of a <u>permanent</u> tolerance for the following reasons pertaining to the [^{14}C-phenyl] CGA-178486 (racemic mixture) study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 21.6% TRR, 8.8%TRR, and 2.3%TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (maturity), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified those residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted. It would be preferable to use a formulation containing only the "R" enantiomer in the future study.

c. The time from sampling to final analysis should be clarified for wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates

early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

The fate of [2-^{14}C-pyridyl] clodinafop-propargyl [(R) (2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid, 2-propynyl ester)] was studied in field grown spring wheat in St. Aubin, Switzerland after post-emergence foliar spray application of [2-^{14}C-pyridyl]clodinofop-propargyl at 2X. Leaves (49-day PHI; ear emergence), husks and leaves (68-day PHI; milky stage), and mature grain, husks, and straw (91-day PHI) were extracted. The non-extractable radioactivity in leaves was 41.5% TRR at ear emergence and 51.4% TRR at milky stage; the non-extractable radioactivity in grain, husks, and straw at maturity accounted for 76.9%, 71.0%, and 73.7% TRR, respectively. Metabolites were analyzed by thin layer chromatography (TLC), high performance liquid chromatography (HPLC), and mass spectroscopy (MS). The residues in leaves (49-day PHI), husks and leaves (68-day PHI), and mature grain, husks, and straw (91-day PHI) were analyzed for parent; no clodinafop-propargyl (<0.001 ppm) was detected. Only the residues in 49-day PHI leaves, 68-day PHI leaves, and 91-day PHI straw were further identified. The only metabolite which was identified was 2-hydroxy-3-fluoro-5-chloro-pyridine (IV_2); it accounted for 17.2% TRR in leaves (ear emergence; 49-day PHI), 10.8% TRR in leaves (milky stage; 68-day PHI), and 5.6% TRR in straw (91-day PHI). Only one other metabolite was isolated; this unknown accounted for <10% TRR in leaves and straw.

The identification of 2-hydroxy-3-fluoro-5-chloro-pyridine supports the proposed metabolic pathway as described under MRID no. 44399203: [2-^{14}C-pyridyl] labeled clodinafop-propargyl in wheat is metabolized by 1) hydrolysis of the parent ester molecule clodinafop-propargyl to form the acid CGA-193469, and subsequent sugar conjugation of the acid; 2) hydroxylation of the 6-position of the pyridyl ring in CGA-193469 to form metabolite II_2 and subsequent sugar conjugation; 3) cleavage of the ether bridge between the pyridinyl and phenyl rings in CGA-193469, yielding CGA-214111 and its corresponding sugar conjugate; and 4) cleavage of CGA-193469 at the phenoxy-propanoic acid ether bridge to form CGA-193468.

The nature of the residue in wheat is not adequately understood for the purposes of a <u>permanent</u> tolerance for the following reasons pertaining to the [2-^{14}C- pyridyl] clodinafop-propargyl study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 17.2% TRR, 10.8% TRR, and 5.6 %TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (mature), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified those residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted.

c. The time from sampling to final analysis should be clarified for the wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

The nature of the residue in wheat is adequately understood for the purposes of a registration with an expiration date. The residues of concern in wheat were determined by HED's Metabolism Assessment Review Committee (MARC) on 2/15/00 (D263288, N. Dodd, 2/25/00) to be clodinafop-propargyl and its acid metabolite CGA-193469. HED may revisit the MARC after additional wheat metabolism data have been submitted.

Metabolism in Rotational Crops. A confined rotational crop study for clodinafop-propargyl was submitted. Following one application of [2-^{14}C-pyridyl]clodinafop-propargyl to spring wheat at the rate of 125 g ai/ha (0.11 lb ai/A; approximately 2X), radioactivity levels in each of the rotational crops (lettuce, winter wheat, sugar beets, and corn) were ≤0.001 ppm at the rotational crop intervals tested (i.e., days between application of [2-^{14}C-pyridyl]clodinofop-propargyl and planting of the rotational crops: 98 days for lettuce, 159 days for winter wheat, 379 days for sugar beets, and 379 days for corn).

The submitted confined rotational crop data are adequate for a permanent tolerance provided that a) rotational crop restrictions are placed on the label of 98 days (or 3 months) for lettuce and other leafy vegetables, 159 days (or 5 months) for small grains (barley, oats, and rye), and one year (or 12 months) for all other crops for which uses are not established; and b) the dates of harvest and/or analysis of ½ mature lettuce are corrected.

If the petitioner wants shorter rotational crop restrictions, then a confined rotational crop study conducted at the soil aging intervals of 1, 4, and 12 months would be needed for three rotated crops (a small grain, a leafy vegetable, and a root crop) reflecting one application at the maximum label rate of 0.06 lb ai/A.

No field accumulation in rotational crop study was submitted. Pending results from the confined rotational crop study which may be conducted if the petitioner wants shorter rotational crop restrictions, this study may be required.

Metabolism in Animals.

Ruminants: One lactating goat was dosed with [^{14}C-phenyl] clodinafop-propargyl for ten consecutive days at a level of 5.9 ppm (18X). Total radioactive residues, expressed as clodinafop-propargyl equivalents, were ≤0.018 ppm in milk, ≤0.001 ppm in muscle, ≤0.004 ppm in fat, 0.011 ppm in liver, and 0.077 ppm in kidney.

Samples containing the following residue levels (expressed as clodinafop-propargyl equivalents) were extracted: 17 ppb in milk, ~1 ppb in meat, 3 ppb in fat, 11 ppb in liver, and 77 ppb in kidney. Extractable residues were 94% TRR in milk, 74% in fat, 67% in liver, and 64% in kidney. Due to a residue level below the LOQ (~1 ppb) in meat, no reliable values for percent extracted can be calculated. Clodinafop-propargyl was metabolized in the goat via hydrolysis to CGA-193469, which was further metabolized to form hybrid acylglycerides or CGA-193468. Most of the total radioactive residue in goat urine (96.3% - 97.0%) and feces (75.2% - 82.3%) was CGA-193469. Parent clodinafop-propargyl was not detected in urine or feces. In milk, the radioactivity (17 ppb clodinafop-propargyl equivalents) was 94% hybrid acylglycerides, which released CGA-193469 and two unidentified compounds upon saponification. In muscle containing 1 ppb clodinafop-propargyl equivalents, only CGA-193469 was detected (<1 ppb). In fat containing 3 ppb clodinafop-propargyl equivalents, CGA-193469 was found free (<1 ppb) and incorporated into hybrid acylglycerides (2 ppb). In liver containing 11 ppb clodinafop-propargyl equivalents, CGA-193469 (5 ppb) and traces of CGA-193468 and hybrid acylglycerides were found. In kidney containing 77 ppb clodinafop-propargyl equivalents, CGA-193469 (42 ppb), CGA-193468 (2 ppb) and hybrid acylglycerides (2 ppb) were found.

The proposed goat metabolism pathway is shown in Figure 2 (Attachment 14).

The nature of the residue in ruminants is not adequately understood for the purposes of a <u>permanent</u> tolerance for the following reason: The time from sampling to analysis should be clarified for milk and tissues. If the time between sampling and analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

For this use on wheat, the nature of the residue in ruminants is adequately understood for the purposes of a <u>time-limited registration</u>. The major residues in milk and tissues are hybrid acylglycerides (containing CGA-193469 as one component) and/or CGA-193469. The residues of concern in ruminants were determined by HED's Metabolism Assessment Review Committee (MARC) on 2/15/00 to be clodinafop-propargyl and its acid metabolite CGA-193469.

<u>Poultry</u>: Four laying hens were dosed with [^{14}C-phenyl] clodinafop-propargyl for 14 consecutive days at a level of 4.6 ppm (92X). Total radioactive residues, expressed as clodinafop-propargyl equivalents, were 2.626-3.901 ppm (av 3.164 ppm) in kidney, 0.110-0.192 ppm (av 0.138 ppm) in liver, 0.007-0.065 ppm (av 0.032 ppm) in peritoneal fat, 0.008-0.014 ppm (av 0.011 ppm) in skin (including fat), and 0.001- 0.002 ppm (av 0.001 ppm) in lean meat. Residues in eggs (white and yolk combined) ranged from 0.0000 ppm to 0.0342 ppm. The highest average daily residue level in eggs was 0.0224 ppm (n=4) on day 13. The average residue level in eggs over the 14-day study was 0.0147 ppm (n= 45). [The ppm for eggs represents a weighted sum of the residues

in egg whites and yolks; when the weight of the shell is excluded, eggs are 70% white and 30% yolk by weight.]

Samples containing the following residue levels (expressed as clodinafop-propargyl equivalents) were extracted: 2 ppb in egg white, 71 ppb in egg yolk, 1 ppb in lean meat, 11 ppb in skin and attached fat, 65 ppb in peritoneal fat, 138 ppb in liver, and 3164 ppb in kidney. Extractable residues were 95% TRR in egg white, 91% in egg yolk, 53% in lean meat, 95% in peritoneal fat, 67% in skin and attached fat, 50% in liver, and 65% in kidney. Clodinafop-propargyl was metabolized in hens via hydrolysis to CGA-193469. CGA-193469 was incorporated into hybrid acylglycerides or further metabolized to 2-[4-(6-hydroxy-5-chloro-3-fluoro-2-pyridinyloxy)-phenoxy]-propanoic acid (Metabolite 1E) or 2-(4-hydroxy-phenoxy)-propanoic acid (CGA-214111). In hen excreta, the major metabolite was Metabolite 1E, accounting for 51.3-54.5% of the TRR. Ten minor metabolites were resolved, of which three were identified: CGA 214111 (2.6-4.6%), CGA-193469 (6.1-8.6%), and clodinafop-propargyl (1.3%). The remaining metabolites in excreta were each ≤4% of the TRR. In egg white, 95% of the TRR (2 ppb) was CGA-193469. In egg yolk, 91% of the TRR (65 ppb) was hybrid acylglycerides which released CGA-193469 upon saponification. In lean meat containing 1 ppb clodinafop-propargyl equivalents, CGA-193469 (<1 ppb) and hybrid acylglycerides (<1 ppb) were found. In peritoneal fat, 88% of the TRR (57 ppb) was hybrid acylglycerides yielding CGA-193469 upon saponification. In skin and attached fat containing 11 ppb clodinafop-propargyl equivalents, the identified residues were Metabolite 1E (38% TRR; 4 ppb) and hybrid acylglycerides (29%TRR; 3 ppb), which released CGA-193469 upon saponification. In liver containing 138 ppb clodinafop-propargyl equivalents, the extractable residues were mainly very polar unidentified products remaining at the origin in the TLC radiochromatogram (46%TRR; 64 ppb). Metabolite 1E (3% TRR; 4 ppb) and traces of CGA-214111 were detected in liver. In kidneys containing 3164 ppb clodinafop-propargyl equivalents, about ⅔ of the residue was extractable (2057 ppb); TLC indicated traces of CGA-214111, Metabolite 1E (2%TRR; 62 ppb), and a highly polar fraction remaining at the origin of the TLC radiochromatogram (63% TRR; 1995 ppb). Significant amounts of CGA-214111 (50% TRR; ca 1582 ppb) were released from the non-extractables, the unidentified polar fraction remaining at the origin, and Metabolite 1E upon harsh extraction and drastic acidic or alkaline hydrolysis of a second kidney sample.

The proposed hen metabolism pathway is shown in Figure 3 (Attachment 1.4).

The nature of the residue in poultry is not adequately understood for the purpose of a <u>permanent</u> tolerance for the following reason: The time from sampling to final analysis should be clarified for eggs and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

For this use on wheat, the nature of the residue in poultry is adequately understood for the purpose of a time-limited registration. The major residues in eggs, lean meat, and fat were CGA-193469 and/or hybrid acylglycerides which released CGA-193469 on hydrolysis. Metabolite 1E (38% TRR) and hybrid acylglycerides (29% TRR) were found in skin and attached fat. Small amounts of Metabolite 1E and traces of CGA-214111 were found in liver and kidney. In liver, 50% of the radioactivity remained unextracted. In kidney, 35% of the TRR was unextracted before acid and base hydrolysis. Upon acid and base hydrolysis, 50% of the TRR was identified as products which yield CGA-214111, leaving 50% unidentified including 12% unextracted. Due to the low residues expected in poultry tissues at the 1X feeding level of 0.05 ppm, additional metabolism data (beyond that required in the above paragraph for a permanent tolerance) are not needed for this use on wheat. The residues of concern in poultry were determined by the MARC on 2/15/00 to be clodinafop-propargyl and its acid metabolite CGA-193469.

Enforcement Methods.

Wheat:

Analytical method REM 138.01 was used to determine clodinafop-propargyl in wheat in all of the residue/processing samples in the US and Canada and some of the storage stability samples. Clodinafop-propargyl is determined separately by high performance liquid chromatography (HPLC) with UV-detection. The limits of quantitation of the method for clodinafop-propargyl are 0.02 ppm for grain and 0.05 ppm for wheat forage and straw. A successful independent laboratory method validation was conducted for Method REM 138.01 on wheat grain, forage, hay, and straw. An EPA method validation of Method REM 138.01 has been requested (Attachment 8). The method validation was requested for clodinafop-propargyl on wheat grain, forage, and straw.

Analytical method REM 138.06 was used to determine CGA-193469 in wheat in some storage stability samples and in most of the residue studies in Canada. CGA-193469 is determined by high performance liquid chromatography (HPLC) with UV-detection. The limit of quantitation of the method for CGA-193469 is 0.05 ppm for wheat forage, grain, hay, and straw. A successful independent laboratory method validation was conducted for Method REM 138.06 on wheat grain, forage, and straw. An EPA method validation of Method REM 138.06 has been requested (Attachment 8). The method validation was requested for CGA-193469 on wheat grain, forage, and straw.

Analytical method REM 138.10 was used to determine CGA-193469 in wheat in all the residue/processing studies in the US and in some storage stability samples. CGA-193469 is determined by HPLC with UV-detection. The limits of quantitation for CGA-193469 are 0.02 ppm for wheat grain and 0.05 ppm for forage, hay, and straw. An EPA method validation of Method REM 138.10 has been requested (D254000, PP#7F04924, N. Dodd, 4/27/99). The method validation was requested for CGA-193469 on wheat grain, forage, and straw.

To establish a permanent tolerance, the following additional information is needed regarding the analytical methods used to obtain the storage stability and residue data: a) Radiovalidation data for Methods REM 138.01, 138.06, 138.10, and 138.12 are needed to demonstrate the efficiency of the methods in extracting and quantifying aged or bound residues in samples. (Radiovalidation data and recovery data at the limit of quantitation would be needed for Methods REM 138.02 and 138.05 if they were used to collect residue data which are acceptable. Methods REM 138.02 and 138.05 were used only to collect the Canadian residue data. HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies); b) Method REM 138.12 should be submitted.

Before EPA can determine whether adequate analytical methods are available for enforcement of permanent tolerances on wheat, the following additional information is needed for the proposed enforcement methods: a) For REM 138.01 and REM 138.06, either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of clodinafop-propargyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed. Provided that a specific confirmatory method is available, the Agency will not require that an interference study be conducted; b) Confirmatory methods are needed for Methods REM 138.01 and 138.06; c) The GC/MS confirmatory method in Method REM 138.10 includes derivatization with diazomethane. The petitioner should investigate whether another methylating agent could be substituted for diazomethane. If an alternative methylating agent is not available, EPA requires that justification for the use of diazomethane be provided. An alternative confirmatory method for REM 138.10 would be LC/MS. REM 138.10 could be rewritten to include LC/MS as the confirmatory method instead of GC/MS; d) Adequate EPA petition method validations are needed for the proposed enforcement methods. RAB3 has requested EPA petition method validations for REM 138.01, 138.06, and 138.10. These EPA petition method validations are underway. Adequate independent laboratory validations have been provided for methods REM 138.01 and 138.06.

Provided that the petition method validations which are being conducted by EPA are successful, adequate enforcement methods (MRID nos. 44399211, 44399213, and 44755302) are available to enforce registration with an expiration date on wheat.

Animals:

Analytical/enforcement methods for animal commodities are not needed for this use on wheat since secondary residues are not expected to occur in animal commodities and, therefore, tolerances on animal commodities are not needed.

Multiresidue Methods Testing. Multiresidue method testing data for clodinafop-propargyl and CGA-193469 in wheat grain have been submitted. Clodinafop-propargyl and CGA-193469 were tested through the FDA multiresidue methods according to the decision tree and protocols in the Pesticide Analytical Manual, Volume I (PAM I), Appendix II, Transmittal 96-1 (1/96).

Clodinafop-propargyl was tested per Protocols C, D, and E. CGA-193469 was tested per Protocols B and C.

In Protocol C, clodinafop-propargyl yielded adequate detector responses to Section 302 DG5, DG13, and DG18 gas-liquid chromatography (GLC) systems. In Protocol D, clodinafop-propargyl was completely recovered through Florisil cleanup (Section 302 C1), and partially recovered through the complete method with Florisil cleanup (Section 302 E4/C1). No interferences were observed with Florisil cleanup. Significant interferences were observed in the method without Florisil cleanup. In Protocol E, clodinafop-propargyl was completely recovered through Florisil cleanup (Section 303 C1/C2), but only partially recovered through the complete method (Sections 303 E3/C1 and E3/C2). No significant interference was observed.

In Protocol B, CGA-193469 was partially recovered through gel permeation chromatography (GPC) (Section 402 C1a). The methyl ester of CGA-193469 was completely recovered through Florisil cleanup (Section 402 C1c); however, the methyl ester of CGA-193469 was only partially recovered through the complete method (Section 402 E4/C1). No interferences were observed. In Protocol C, CGA-193469 did not yield adequate detector responses to any of the Section 302 DG5, DG13, and DG18 gas-liquid chromatography (GLC) systems; however, the methyl ester of CGA-193469 yielded adequate responses to the GLC systems.

RAB3 (D255566, N. Dodd, 5/12/99) has forwarded the submitted multiresidue methods data to FDA for review to determine sufficiency. Multiresidue methods are not adequate for enforcement purposes; the parent and acid metabolite are only partially recovered through the appropriate multiresidue methods.

Freezer Storage Stability Data. Storage stability data were submitted for clodinafop-propargyl in wheat grain and straw. Clodinafop-propargyl declined 7%, 11%, 23% and 44% in wheat grain stored at -18°C for 85, 178, 372, and 728 days, respectively. Clodinafop-propargyl declined 28%, 36%, 37%, and 54% in wheat straw stored at -18°C for 85, 182, 380, and 731 days, respectively. The storage times for clodinafop-propargyl in grain and straw in the storage stability studies are adequate to cover maximum storage times for clodinafop-propargyl in grain and straw residue samples (62 days for grain and 70 days for straw in the US residue data and 580 days for grain and straw in the Canadian residue data). (Note: Since degradation was shown for clodinafop-propargyl in wheat grain and straw, storage stability data will be required for any future uses on all crops/substrates for which tolerances are requested.)

Storage stability data were also submitted for CGA-193469 in wheat grain and straw. CGA-193469 is stable in wheat straw stored at -18°C for at least 380 days. Pending receipt of the additional information requested below for MRID no. 44399210, HED tentatively concludes that CGA-193469 is stable in wheat grain stored at -20°C for at least 727 days. The storage times for CGA-193469 in grain and straw in the storage stability studies are adequate to cover maximum storage times for CGA-193469 in grain and straw residue samples (i.e., 95 days for grain and 141 days for straw in US residue data and 458 days for grain in the Canadian residue data) except for some straw residue samples in Canada (which were stored up to 458 days).

Adequate storage stability data have not been submitted. The following additional storage stability data are needed:

a. Additional data are needed for Study 300/91 (MRID no. 44399210). Raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples) should be submitted. Storage containers should be described. The method used to analyze the storage stability samples should be submitted or identified by number as a submitted method.

b. No storage stability data were submitted for forage. Storage stability data for forage are needed for the 105-day storage interval for clodinafop-propargyl and the 218-day storage interval for CGA-193469 in US residue samples. If the Canadian residue studies could be used (i.e., upgraded to acceptable), storage stability data for forage would be needed for the 434-day storage interval for clodinafop-propargyl and CGA-193469 in the Canadian residue samples; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. If Canadian studies could be used (i.e., upgraded to acceptable), storage stability data for CGA-193469 on straw for 458 days would be needed so that the tolerance could be adjusted for any storage degradation; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

d. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for clodinafop-propargyl; storage stability data are not needed for clodinafop-propargyl in processed commodities since they were analyzed within 30 days of their production. The storage time between processing and analysis for CGA-193469 was 51 days for aspirated grain, 45 and 125 days for germ, 45 days for bran, 42 days for middlings and shorts, and 37 days for low grade flour and patent flour. Storage stability data for CGA-193469 in aspirated grain fractions are not needed since this is an early season use and residues are not expected to occur in aspirated grain fractions. Storage stability data are not needed for bran, flour, middlings, and shorts since these matrices are similar to grain and can be covered by the storage stability data on grain. Storage stability data are needed for CGA-193469 in wheat germ for 45 and 125 days.

Magnitude of the Residue in Wheat. In the US, six field trials on spring wheat to determine residues of clodinafop-propargyl and CGA-193469 were conducted in the four states of ND (2), MN (1), MT (2), and SD(1) in crop year 1998. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500. A single foliar application of the clodinafop-propargyl 240 EC formulation (DISCOVER™) was applied with ground equipment at the rate of 28.33 g ai/A (0.06 lb ai/A; 1X). A 5X rate was also applied in one study (OW-HR-210-98/ND) 61 days before harvest. Score, an adjuvant, was used at a concentration of 1% (v/v). Samples were frozen after collection, shipped frozen, and stored frozen (-20°C) at the analytical laboratory. Analytical method REM 138.01, with modifications

for some substrates, was used to determine residues of clodinafop-propargyl by HPLC with ultraviolet detection. The limit of quantitation for clodinafop-propargyl (based on the lowest acceptable recovery level) was 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw. Recoveries of clodinafop-propargyl were 59-100% (average 87%, n=10) for forage, 82-110% (average 96%, n=7) for hay, and 71-105% (average 88%, n= 8) for straw at fortifications of 0.05 ppm. Recoveries of clodinafop-propargyl were 74-103% (average 86%, n=9) for grain at fortifications of 0.02 ppm. Analytical method REM 138.10, with modifications, was used to determine the metabolite CGA-193469 by HPLC with UV detection. The limit of quantitation for CGA-193469 (based on the lowest acceptable recovery level) was 0.05 ppm for forage, hay, straw, and grain. Recoveries of CGA-193469 were 56-100% (average 78%, n= 6) for forage, 74-127% (average 101%, n=3) for hay, 65-111% (average 88%, n= 8) for straw, and 68-127% (average 104%; n=7) for grain at fortifications of 0.05 ppm. Selected samples were analyzed for CGA-193469 by HPLC with mass spectrometric detection (LC/MS). Residues in the US studies at 1X were <0.05 ppm clodinafop-propargyl + <0.05 ppm CGA-193469 in wheat forage at a 7-day PHI (one study) and a 29-32 day PHI (6 studies); <0.05 ppm clodinafop-propargyl + <0.05 ppm CGA-193469 in wheat hay at a 30-day PHI; <0.05 ppm clodinafop-propargyl + ≤0.21 ppm CGA-193469 in wheat straw at an approximately 60-day PHI; and <0.02 ppm clodinafop-propargyl + <0.05 ppm CGA-193469 in grain at a 60-day PHI. Residues at 5X and a 61-day PHI were <0.02 ppm clodinafop-propargyl and <0.05 ppm CGA-193469 in wheat grain; and <0.05 ppm clodinafop-propargyl + <0.05 ppm CGA-193469 in wheat straw.

In Canada, fifteen field trials on spring wheat (hard red spring wheat and duram spring wheat) were conducted in Canada in 1989 (3), 1990 (3), 1991 (6), and 1992 (3). The locations of the 15 Canadian field trials relative to the overlapping US-Canadian zones defined in HED SOP 98.2 were reported. Four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14. An EC (emulsifiable concentrate) formulation of clodinafop-propargyl (CGA-184927) was applied at a rate of 80 g ai/ha (0.07 lb ai/A; 1.2X) in 100 liters spray solution/ha (10.7 gal/A). In each study, one postemergence foliar application was made to each of 3 or 4 plots. Assist (1%, vol/vol) was included in 8 of the studies. The application was made by bicycle sprayer in all of the studies except MRID no. 44399228 (small plot sprayer). Samples were stored frozen until shipment, shipped frozen, and then stored frozen (at -20°C) in the laboratory until analysis. The analytical methods were REM 138.01 for clodinafop-propargyl and REM 138.06 for CGA-193469 except in MRID's nos. 44399328, 44399329, and 44399330. In MRID's 44399328, 44399329, and 44399330, the methods were REM 138.01 for determination of clodinafop-propargyl in grain and straw, REM 138.02 for determination of CGA-193469 in grain, and REM 138.05 for determination of CGA-193469 in straw. The limits of quantitation for clodinafop-propargyl using REM 138.01 were 0.02 ppm in wheat grain and forage and 0.05 ppm in straw. The limits of quantitation for CGA-193469 using REM 138.06 were 0.01 or 0.05 ppm in wheat grain and 0.05 ppm in forage and straw. The limits of quantitation for CGA-193469 in wheat grain using REM 138.02 and in wheat straw using REM 138.06 were 0.05 ppm. Recoveries for clodinafop-propargyl using REM 138.01 were 74-103% (average 92%, n=4) in wheat grain and 69-87% (average 80%, n=3) in wheat forage at a fortification level of 0.04 ppm, and 80-111% (average 93%, n=4) in wheat straw at a fortification level of 0.1 ppm. Recoveries for CGA-193469 at a

fortification level of 0.1 ppm using REM 138.06 were 71-73% (average 72%, n=2) in wheat grain, 80-94% (average 86%, n=3) in wheat forage, and 70-104% (average 88%, n=3) in wheat straw. Recoveries for CGA-193469 at a fortification level of 0.1 ppm were 75% (n=1) for wheat grain using REM 138.02 and 107% (n=1) for wheat straw using REM 138.05. Residues in Canada were <0.02 ppm clodinafop-propargyl + <0.05 ppm CGA-193469 in wheat grain at PHI's ranging from 55-105 days, <0.05 ppm clodinafop-propargyl + ≤0.45 ppm CGA-193469 in straw at PHI's ranging from 55-105 days, and <0.02 ppm clodinafop-propargyl + <0.05 ppm CGA-193469 in forage at a 7-day PHI.

The proposed use indicates that forage could be fed/grazed at a 7-day PHI, hay could be fed at a 30-day PHI, and grain and straw could be harvested at a 60-day PHI. Based on the available residue data, residues of parent or CGA-193469 were less than the limit of quantitation (LOQ) in grain, forage, and hay in the US and in grain and forage in Canada at these PHI's; for straw, residues of the parent were <LOQ but maximum residues of 0.21 ppm CGA-193469 were found in the US (MT; 57-day PHI) and maximum residues of 0.45 ppm CGA-193469 were found in Canada (Manitoba/1991 trials; 60-day PHI). (For US data, the limits of quantitation for parent were 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw; the limit of quantitation for CGA-193469 was 0.05 ppm for grain, forage, hay, and straw. For Canadian data, the limits of quantitation for parent were 0.02 ppm for grain and forage, and 0.05 ppm for straw; the limits of quantitation for CGA-193469 were 0.01 or 0.05 ppm for grain, and 0.05 ppm for forage and straw.) However, the field trial residue data are not adequate to support a <u>permanent tolerance</u> for the following reasons:

a. Adequate geographic representation is not provided. (Wheat is not a minor crop, for which a regional registration would be accepted.) According to OPPTS 860.1500, a minimum of 20 field trials are needed to support a tolerance on wheat. The suggested distribution of wheat field trials is one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and 1 in Region 11. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies). Of the 15 Canadian field trials, four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14; however, the Canadian field trials have deficiencies which are not upgradeable (<u>see</u> below). Additional field trial residue studies are needed to support a permanent tolerance. For a 30-day PHI in forage, the additional studies would be one in Region 2, one in Region 4, three in Region 5, one in Region 6, one in Region 7, six in Region 8, and 1 in Region 11. (If a 7-day PHI in forage is desired, then the additional studies would be one in Region 2, one in Region 4, five in Region 5, one in Region 6, four in Region 7, six in Region 8, and one in Region 11.) Each study should include PHI's of 30 (or 7) days for forage, 30 days for hay, and 60 days for grain and straw. Spring (including hard red spring, duram, and white spring) and winter (including hard red winter, soft red winter, and white winter) varieties of wheat should be included in the studies. Each study should include DSV Adjuvant or similar adjuvant. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples should be included. Storage information including types of

storage containers and dates of extraction (as well as dates of storage and analysis) should be included.

b. Only spring wheat was used in the US and Canadian studies. Winter wheat should be included in the residue studies.

c. Forage was sampled at the proposed preharvest interval (PHI) of 7 days in only one US study and three Canadian studies.

d. Based on the available residue data, the petitioner should submit a revised Section F which proposes tolerances for the combined residues of clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid) at levels of 0.10 ppm for wheat grain, forage, and hay, and 0.50 ppm for wheat straw. These levels were obtained by adding the limits of quantitation and/or levels of residues for clodinafop-propargyl and CGA-193469. (Note that an "(R)" is needed in the chemical name of the parent to designate the "R" isomer.)

For the Canadian field trial residue studies, the following data should have been included. (HED is not recommending that the petitioner attempt to upgrade these studies to an acceptable level.)

a. Grain, forage, hay, and straw should be analyzed in each of the wheat field trial residue studies. (For an early season use, data on aspirated grain fractions are not needed.) Of the 15 Canadian studies, only grain and straw were analyzed in twelve studies and only forage was analyzed in three studies. Hay was not analyzed.

b. PHI's should reflect the proposed use. PHI's for grain and straw in the Canadian studies ranged from 55-105 days (with all but two studies with PHI's above 60 days) whereas the proposed PHI for grain and straw is 60 days.

c. Extraction dates were not provided for MRID nos. 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, and 44399231.

d. Storage containers were not described.

e. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples were not submitted.

Magnitude of the Residue in Wheat Processed Commodities. Wheat grain treated with a 240 EC formulation of clodinafop-propargyl (Discover™) at 1X and 5X was processed. Residues of clodinafop-propargyl and its metabolite CGA-193469 were <0.02 ppm in wheat grain and <0.05 ppm in the processed commodities (aspirated grain fractions, germ, bran, middlings, shorts, low

grade flour, and patent flour). Wheat germ from the 5X study containing a residue of 0.08 ppm CGA-193469 was reanalyzed by LC/MS at <0.05 ppm CGA-193469.

Pending submission of storage stability data on CGA-193469 in processed commodities (see storage stability section of this review), HED concludes that no concentration of clodinafop-propargyl or CGA-193469 occurred on processing.

Magnitude of the Residue in Meat, Milk, Poultry, and Eggs.

Ruminants: Based on the goat metabolism study and the maximum theoretical dietary burden, maximum radioactive residues (expressed as clodinafop-propargyl equivalents) in goat tissues and milk resulting from the proposed use on wheat would be 0.00095 ppm in milk, 0.00006 ppm in muscle, 0.00017 ppm in fat, 0.00431 ppm in kidney, and 0.00061 ppm in liver.

A ruminant feeding study is not needed and tolerances on milk and the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep are not needed because of the low residue levels found in milk, muscle, fat, liver, and kidney in the goat metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in milk and in the meat, fat, liver, and kidney of cattle, goats, hogs, horses, and sheep.

Poultry: Based on the poultry metabolism study and the maximum theoretical dietary burden, maximum radioactive residues (expressed as clodinafop-propargyl equivalents) in poultry tissues and eggs resulting from the proposed use on wheat would be 0.00004 ppm in muscle, 0.0014 ppm in fat, 0.0042 ppm in liver, and 0.00074 ppm in eggs.

Because of the low residue levels found in muscle, fat, liver, and eggs in the poultry metabolism study and the corresponding low radioactive residues calculated for the 1X feeding level, a poultry feeding study is not needed and tolerances on poultry tissues and eggs are not needed. This use falls under 40 CFR §180.6(a)(3) since no secondary residues are expected to occur in poultry commodities.

International Harmonization. Canada has recently reviewed a petition for clodinafop-propargyl on wheat. At this time, Canada has a default MRL of 0.1 mg/kg for clodinafop-propargyl on wheat. A Mexican limit exists for clodinafop-propargyl on wheat at 0.050 ppm. There are no Codex tolerances for clodinafop-propargyl on wheat. Therefore, no compatibility issues exist with Codex in regard to the proposed US tolerances discussed in this review.

4.2.1 Food Exposure

HED has conducted food only exposure assessments for clodinafop-propargyl (Attachment 9) using the Dietary Exposure Evaluation Model (DEEM™). This model incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For the acute food only risk assessment, the entire distribution of single day food consumption events is combined with a single residue level (deterministic analysis) to obtain a distribution of exposure in mg/kg/day. HED conducted a highly conservative Tier 1 acute food only exposure assessment for the combined residues of clodinafop-propargyl and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid) in/on wheat consisting of tolerance level residues (0.10 ppm) and assuming 100% crop treated.

For chronic food only risk assessments, DEEM™ calculates the three-day average of consumption for each sub-population combined with residues in commodities to determine average exposure in mg/kg/day. A Tier 3 chronic (non-cancer) food only exposure assessment was performed. The residue value used for the chronic food exposure assessment was 0.07 ppm in/on wheat. This value arises from the sum of the limit of quantitation (LOQ) of the clodinofop-propargyl (0.02 ppm) plus the LOQ of the metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid) in/on wheat grain (0.05 ppm). For this chronic DEEM run, HED is not rounding up to 0.10 ppm, as done for establishment of the tolerance. It is important to note that the residue value (0.07 ppm) is still *very* conservative and health protective. Additionally, 4% anticipated market share was utilized in the Tier 3 chronic (non-cancer) DEEM™ run. As residues were shown not to concentrate into wheat grain processed commodities, DEEM processing factors were turned off (i.e., set to 1) in all acute and chronic food only exposure assessments. The Biological and Economics Analysis Division (BEAD; A. Grube, 3/3/00) supplied HED with this anticipated market share value for the product, Discover™. The following is the logic used to estimate the 4% anticipated market share:

> Clodinafop propargyl is going to be competitive in the consumer market on acreage with the wheat pest, wild oats. Of the approximately 63 to 70 million acres of wheat grown in the U.S., about 6.5 million acres (i.e., approximately 10% of total) of wheat crop are treated to control wild oats. The Registrant expects to sell sufficient amount of Discover™ to treat [redacted] of the total wheat acreage). In other words, [redacted] would be [redacted] of the 6.5 million acres treated for wild oats. At present time, there are several competing products (2 other new herbicides and several older herbicides). [redacted]

A Tier 3 lifetime cancer risk from food only exposure assessment to the U.S. total population was performed using conservative residue levels of 0.07 ppm for wheat, assuming 4% crop treated, and application of the the Q_1* value of 0.129 $(mg/kg/day)^{-1}$ (Table 7).

COMMERCIAL/PROPRIETARY INFORMATION

4.2.1.1 Acute Assessment of Food Exposure

As shown in Table 4, there are three aPADs; 1) females 13-50 years old, 0.005 mg/kg/day, 2) infants and children, 0.083 mg/kg/day, 3) general population, 0.25 mg/kg/day. As shown below in Table 6, the acute food only risk estimate associated with clodinafop-propargyl use on wheat is below HED's level of concern (100% aPAD) for all population groups. Based on tolerance level residues and assuming 100% crop treated, the 95th percentile of food exposure is predicted to be up to **7.5%** of the aPAD for **nursing females ages 13-50 years**, the most highly exposed subgroup of females of childbearing age. For a Tier 1 analysis, HED considers exposure at the 95th percentile of exposure. A complete listing of acute food only exposure estimates for the 95th, 99th, and 99.9th percentile of food exposure is included as Attachment 9.

The aPAD for infants and children is calculated to be 0.083 mg/kg/day. Based on the food only exposure assessment and at the 95th percentile of exposure, the highest exposed subgroup of infants and children is **children 1-6** years old which is utilizes up to **1.0% of the aPAD.**

The aPAD for the general population and subgroups not included above is calculated to be 0.25 mg/kg/day. Based on the food only exposure assessment and at the 95th percentile of exposure, the **total U.S. population** in addition to all **male only** subgroups utilize up to **< 1.0% of the aPAD**. It is also worthwhile to mention that even at the 99.9th percentile of exposure, the acute risk to total U.S. population and all subgroups not included in females 13-50 years old and infants and children is predicted to be ≤ 1.0% of the aPAD.

Table 6. Acute Dietary Exposure Estimates

Population Subgroup [a]	95th Percentile	
	Exposure (mg/kg/day)	% aPAD
US Population	0.00041	<1.0%
Children 1-6 yrs	0.00076	1.0%
Females (13+/nursing)	0.00037	7.5%
Males (13-50)	0.00039	<1.0%

[a] Population subgroups shown include females of childbearing age for acute exposure; the U.S. general population and the maximally exposed subpopulation of adults, infants and children, and women of child-bearing age for chronic exposure.

4.2.1.2 Chronic Assessment for Food Exposure

The chronic (non-cancer) food risk estimate associated with clodinafop-propargyl use in/on wheat is below HED's level of concern (100% of cPAD). As shown in Table 4, the cPAD for applicable to all subgroups of the U.S. populations is 0.00003 mg/kg/day. The Tier 3 analysis was performed using residues of 0.07 ppm for wheat and assuming 4% crop treated. It is important to note that the residue value (0.07 ppm) is *very* conservative and health protective. The most highly exposed subgroup, **children 1-6 years old** utilizes up to **32% of the cPAD.**

The **total U.S. population** utilizes up to **14% of the cPAD**. A complete listing of chronic exposure estimates for all DEEM™ population subgroups is included as Attachment 9.

Table 7. Chronic Dietary Tier 3 Exposure Estimates		
Population Subgroup	**Exposure, mg/kg/day**	**% cPAD**
U.S. Population (total)	0.000004	14%
Children 1-6 yrs	0.000009	32%
Children 7-12 yrs	0.000007	22%
Females 13-50 yrs (nursing)	0.000004	14%
Males 13-19	0.000005	16%

4.2.1.3 Cancer Assessment for Food Exposure

The Tier 3 DEEM™ analysis using conservative residue values of 0.07 ppm for wheat and assuming 4% crop treated estimates that chronic exposure to the U.S. population will be 0.000004 mg/kg/day. Applying the Q_1* value of 0.129 $(mg/kg/day)^{-1}$ results in a lifetime cancer risk from food only exposure to clodinafop-propargyl of $\mathbf{5.3\times10^{-7}}$. This is below HED's level of concern of $\mathbf{1.0\times10^{-6}}$.

4.2.2 Water

Because clodinafop-propargyl is a new chemical, the Agency currently lacks sufficient water-related exposure data from monitoring to complete a *quantitative* drinking water exposure analysis and risk assessment for clodinafop-propargyl. Therefore, the Agency is presently relying on computer-generated estimated environmental concentrations (EECs). PRZM/EXAMS with the index reservoir and percent crop area approach has been used to generate EECs for *surface* water based on estimates of both clodinafop-propargyl and the major degradate, CGA-196469 {(R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)phenoxy]-propanoic acid)}. SCI-GROW is an empirical model based upon actual monitoring data collected for a number of pesticides which serve as benchmarks. SCI-GROW has been used to predict EECs in *ground* water for both clodinafop-propargyl and CGA-196469. These models take into account the use patterns and the environmental profile of clodinafop-propargyl, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of chemicals from the source water. The primary use of these models by the Agency at this stage is to provide a coarse screen for assessing whether a pesticide is likely to be present in drinking water at concentrations which would exceed human health levels of concern. Ground and surface water exposure estimates for use of Discover™ on wheat were provided by the

Environmental Fate and Effects Division (EFED; Memos from J. Jordan, 10/4/1999 and 2/29/00, Attachments 12 and 13) with the use rate of 0.0625 lbs ai/A.

4.2.2.1 Environmental Fate Properties

Clodinafop-propargyl that reaches the soil following application to the foliage is metabolized *rapidly* (t-1/2 = 2-3 hours to 1.5 days) to the major degradate CGA-193469. The parent's rapid degradation should greatly limit its leaching potential even in low organic matter soils where it may exhibit some mobility. CGA-193469 reaches its maximum concentration (67.5 - 95.2 % of applied) in 1 - 2 days following application of the herbicide; over-all aerobic soil metabolism half-lives range from 28.1 to 70.6 days, and average 47.7 (plus or minus 19.1 days). Aerobic soil metabolism study results indicate that substantial quantities of the CGA-193469 degradate formed during the first day will be available for runoff and leaching for one to several weeks post application.

Adsorption/desorption studies indicate that CGA-193469 appears to be mobile in soils low to moderate in organic matter. Results of soil column leaching also indicate that CGA-193469 would be mobile in relatively low organic matter soils found in the major wheat growing areas of the U.S. Despite substantial mobility in low organic soils, the leaching potential of CGA-193469 may be modified to some extent by its moderate persistence in surface soil under aerobic conditions. However, as CGA-193469 moves from the aerobic surface to lower depths, it may become substantially more persistent due to decreased aerobic microbial activity and/or redox potential. Consequently, under some conditions, *CGA-193469 may have substantial potential to leach to ground water.*

EFED calculated an anaerobic aquatic metabolism t-1/2 for CGA-193469 of 513 days for the water/sediment system, which indicates that any *CGA-193469 reaching the anaerobic portions of deep water columns or anaerobic/sediment will be extremely persistent.*

4.2.2.2 Ground Water Modeling

The SCI-GROW (Screening Concentration in Ground Water) screening model (version 1.0, dated 11/12/1997) developed in EFED is a regression model based upon actual groundwater monitoring data collected for the registration of a number of pesticides. The current version of SCI-GROW appears to provide realistic estimates of pesticide concentrations in shallow, highly vulnerable ground water sites (i.e., sites with sandy soils and depth to ground water of 10 to 20 feet).

For screening purposes, EFED has used the screening model SCI-GROW to generate generally conservative estimates of clodinafop-propargyl and CGA-193469 in ground water based on a single aerial application of 0.0625 lb ai/acre of Discover™. The estimated ground water EECs

for **clodinafop-propargyl** and **CGA-193469** in ground water are **5.0 x 10^{-6} μg/L and 0.044 μg/L,** respectively.

4.2.2.3 Surface Water Modeling

The PRZM/EXAMS model was used to simulate the pesticide runoff, erosion, and drift following the application of pesticide on the treated field and to provide the exposure estimates in the receiving aquatic environment. PRZM/EXAMS is a field-scale model which treats watersheds as large fields. It assumes that the entire area of the watershed is planted with the crop of interest (i.e., 100% crop coverage). This assumption may not hold for area larger than a few hectares, such as watershed containing drinking water reservoirs. Therefore, pesticide concentrations for drinking water purpose (peak and/or long-term average) were estimated with PRZM/EXAMS and model results from PRZM/EXAMS were adjusted by a factor that represents the maximum percent crop area found for the crop or crops being evaluated.

The index reservoir represents potential drinking water exposure from a specific area (Illinois) with specific cropping patterns, weather, soils, and other factors. Use of an index reservoir for areas with different climates, crops, pesticide used, sources of water (e.g., rivers instead of reservoirs, etc), and hydrogeology creates uncertainties. If a community derives its drinking water from a large river, then the estimated exposure would likely be lower than the actual exposure. Conversely, a community that derives its drinking water from smaller bodies of water with minimal outflow would likely get higher drinking water exposure that estimated using the index reservoir. Areas with a more humid climate that use a similar reservoir and cropping patterns would likely get more pesticides in their drinking water than predicted levels. A single steady flow has been used to represent the flow through. Discharge from the reservoir also removes chemical from it so this assumption will underestimate removal from the reservoir during wet periods and overestimate the concentration in the pond depending upon the annual precipitation pattern at the site. The index reservoir scenario uses the characteristic of a single soil to represent the soil in the basin. In fact, soils can vary substantially across even small areas, and thus, this variation is not reflected in these simulations. The index reservoir scenario does not consider tile drainage. Areas that are prone to substantial runoff are often tile drained. This may underestimate exposure, particularly on a chronic basis. EXAMS is unable to easily model spring and fall turnover which results in complete mixing of the chemical through the water column at these times. Because of this inability, Shipman City Lake has been simulated without stratification. There is data to suggest that Shipman City Lake does indeed stratify in the deepest parts of the lake at least in some years. This may result in both over and underestimation of the concentration in drinking water depending upon the time of the year and the depth of the drinking water intake.

The estimated surface water EECs used for acute dietary exposure (1 in 10 year peak concentration) for **clodinafop-propargyl** and **CGA-193469** in surface water are **0.23 μg/L and 0.0017 μg/L,** respectively. The estimated surface water EECs used for chronic dietary exposure

(1 in 10 year average annual mean) for **clodinafop-propargyl** and **CGA-193469** in surface water are **1.10 μg/L and 0.11 μg/L,** respectively.

Table 8. EEC's for Clodinafop-propargyl and 2 Metabolites in Surface Water		
Chemical Species	**Acute EECs (μg/L)**	**Chronic EECs (μg/L)**
Clodinafop-propargyl	Ground Water 5.0×10^{-6}	Ground Water 5.0×10^{-6}
	Surface Water 0.23	Surface Water 0.0017
CGA-193496	Ground Water 0.044	Ground Water 0.044
	Surface Water 1.1	Surface Water 0.11

4.2.2.4 Calculation of DWLOCs

A drinking water level of comparison (DWLOC) is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative EECs provided by computer modeling (SCI-GROW and PRZM/EXAMS).

HED back-calculates DWLOCs by a two-step process: 1) exposure [food + (if applicable) residential] is subtracted from PAD to obtain the maximum acceptable exposure allowed in drinking water; 2) DWLOCs are then calculated using the calculated value from above and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When DWLOCs are greater than or equal to EECs, HED considers the aggregate risk [from food + water + (if applicable) residential exposures] to be acceptable. At the present time, clodinafop-propargyl is only to be used on wheat; no residential uses are established or proposed.

For acute dietary exposure scenarios, the DWLOC values are all in excess of the modeled EEC values reported by EFED. DWLOCs calculated for acute dietary exposure range from **1.4×10^2** to **8.7×10^3 μg/L** for the most sensitive population, **females 13-50 years old**, and the **total U.S. population**, respectively.

For chronic (non-cancer) dietary exposure scenarios, the DWLOC values are all greater than the modeled EEC values reported by EFED. Of the EECs provided by EFED for ground and surface water estimates of clodinafop-propargyl and CGA-193469, the surface water EEC for chronic exposure to CGA-193469 has the largest value **(0.11 μg/L).** DWLOCs calculated for chronic

dietary exposure range from **0.21** to **0.91** **μg/L** for the most highly exposure population, **children 1-6 years old,** and the **total U.S. population**, respectively.

For estimation of lifetime cancer risk through dietary exposure, the DWLOC values are greater than or equal to the modeled EEC values reported by EFED. As stated above, the largest EEC value is for the surface water chronic exposure to CGA-193469 **(0.11 μg/L).** The Tier 3 DEEM™ analysis using residues of 0.07 ppm for wheat and assuming 4% crop treated estimates that chronic exposure to the U.S. population will be 0.000004 mg/kg/day. It is important to note that the residue value (0.07 ppm) is *very* conservative and health protective. Applying the Q_1* value of 0.129 $(mg/kg/day)^{-1}$ results in a food only risk of $\mathbf{5.3\times10^{-7}}$. Following an aggregate dietary (food + water) assessment for lifetime cancer risk, the resulting DWLOC is **0.13 μg/L.** This cancer DWLOC is *slightly greater than* the EEC for chronic exposure to CGA-193469 in surface water.

As indicated in Section 4.2.2, conversion from the parent compound to the primary degradate, CGA-193469 occurs at a high rate (i.e., up to 90% of parent hydrolyzes to CGA-193496 within hours to days). The MARC concluded that parent (clodinafop-propargyl) and its acid metabolite (CGA-193469) are the residues of concern which need to be included in the tolerance expression and used for dietary risk assessment for wheat and water. Because the models used to obtain the EECs for clodinafop-propargyl and CGA-193469 are highly conservative screening models not designed specifically for estimating concentrations in drinking water and because of the conversative nature of the food exposure assessment (anticipated residues at LOQ for parent + metabolite), HED believes this aggregate cancer dietary assessment **will not underestimate** exposure and that chronic dietary exposure from clodinafop-propargyl residues in food and drinking water **will not exceed HED's level of concern for lifetime cancer risk**

Table 9. Drinking Water Levels of Comparison for Aggregated Exposures for Clodinafop-propargyl					
Scenario/Population Subgroup[a]	**Population-Adjusted Dose, mg/kg/day**	**Exposure, mg/kg/day**	**% of PAD for food only exposure**	**Maximum Water Exposure, mg/kg/day**	**DWLOC, µg/L[b]**
Acute				GW Clodinafop EEC = 5×10^{-6} GW CGA-193496 EEC = 0.044 SW Clodinafop EEC = 0.23 SW CGA-193496 EEC = 1.10	
U.S. Population (total)	0.25	0.00041	<1.0%	0.25	8.7×10^{3}
Children 1-6 yrs	0.083	0.00076	1.0%	0.083	8.3×10^{2}
Females 13+ nursing	0.005	0.00037	7.5%	0.0046	1.4×10^{2}
Males 13-19	0.25	0.00039	<1.0%	0.25	8.7×10^{3}
Chronic				GW Clodinafop EEC = 5×10^{-6} GW CGA-193496 EEC = 0.044 SW Clodinafop EEC = 0.0017 SW CGA-193496 EEC = 0.11	
U.S. Population (total)	0.00003	0.000004	14%	0.000026	0.91
Children 1-6 yrs	0.00003	0.000009	32%	0.000021	0.21
Females 13+ nursing	0.00003	0.000004	14%	0.000026	0.78
Males 13-19	0.00003	0.000005	16%	0.000025	0.88
Scenario/Population Subgroup[a]	**Acceptable Cancer Risk**	**Exposure, mg/kg/day**	**Calculated Cancer Risk**	**Maximum Water Exposure, mg/kg/day**	**DWLOC, µg/L[b]**
Cancer				GW Clodinafop EEC = 5×10^{-6} GW CGA-193496 EEC = 0.044 SW Clodinafop EEC = 0.0017 SW CGA-193496 EEC = 0.11	
U.S. Population (total)	1×10^{-6}	0.000004	5.3×10^{-7}	0.0000037	0.13

[a] Population subgroups shown include the U.S. general population and the maximally exposed subpopulation of adults, infants and children, and women of child-bearing age for each exposure scenario.

[b] DWLOC = Maximum Water Exposure (mg/kg/day) × 1000 µg/mg × body weight (70 kg general population/males 13+, 60 kg females 13+, 10 kg infants and children) ÷ Water Consumption (2 L/day adults, 1 L/day infants and children).

4.3 Occupational Exposure

An occupational and residential risk assessment for clodinafop-propargyl has been prepared as a separate document (Memo, May 4, 2000, K. O'Rourke, D264699). This assessment is included as Attachment 10. The Executive Summary from that assessment is as follows:

Occupational exposure is expected from the use of clodinafop-propargyl. The dermal toxicity endpoint (NOAEL = 50 mg/kg/day) was chosen for both short-and intermediate-term occupational exposure, based on the results of a 28-day dermal toxicity study in rats. The effects seen were increased liver weight and clinical signs (piloerection and hunched posture) in males. There were no inhalation toxicity studies available for risk assessment. For short-term inhalation toxicity, the inhalation exposure is converted to an oral-equivalent dose (100% absorption) and compared to the oral endpoint (NOAEL = 5 mg/kg/day) from a developmental study in rats. This endpoint is applicable to females 13+ years old, and therefore uses a 60-kg body weight in the calculations. For intermediate-term inhalation toxicity, the inhalation exposure is converted to an oral-equivalent dose and compared to the oral endpoint (NOAEL = 0.9 mg/kg/day) from a subchronic oral toxicity study in rats. These calculations result in Margins of Exposure (MOEs) which are compared to the target MOE of 100 to determine any risk concerns. Please note that for intermediate-term exposures, similar effects (increased liver weight) were observed in the studies selected for the intermediate-term dermal and inhalation endpoints; therefore, the intermediate-term dermal and inhalation MOEs were combined into a Total MOE for comparison to the target MOE of 100.

To quantify cancer risk, the Q_1* of 0.129 mg/kg/day^{-1} (calculated based on male mouse liver benign hepatoma and/or carcinoma combined tumor rates) is multiplied by the estimated doses from occupational exposure. Dermal doses are first adjusted for dermal absorption (i.e., 2.5%) because the Q_1* is based on an oral study, while inhalation doses are assumed to be 100% absorbed. Cancer risks for handlers and reentry workers that exceed 10^{-4} are indicative of concern, and require measures such as additional PPE or engineering controls to mitigate exposure, with the goal of achieving a risk level of 10^{-6} or less.

There are no residential uses registered for clodinafop-propargyl.

Chemical-specific handler exposure data were submitted in support of this Section 3 registration. Two of these submissions (MRID#s 443992-33 and -34) were surrogate exposure assessments for aerial applicators and groundboom mixer/loaders, based on an analysis of Pesticide Handlers Exposure Database (PHED) data sets. However, HED performed its own analysis of these scenarios using the PHED Surrogate Table for unit exposure values.

Data from the submission on Field Operator Exposure for mixing/loading and applying using groundboom sprayer (MRID# 443992-35) were used in this assessment; the approach taken is in harmony with the Canadian risk assessment for Horizon™.

Handlers of clodinafop-propargyl (Discover™) were assessed for exposure during open mixing/loading to support aerial and groundboom application, using PHED unit exposure values. Aerial and groundboom operators, as well as flaggers for aerial application, were assessed separately, using PHED unit exposure values for closed cockpit, open-cab tractor, and baseline clothing, respectively. Also, handlers who mix, load and apply by groundboom were assessed together, using unit exposure values obtained from a registrant-sponsored study. The MOEs, under all the above circumstances, range from **5.2×10^2 to 5.9×10^5 for handlers. These MOEs are greater than the target (100) and do not exceed HED's level of concern.** The cancer risks range from **2.3×10^{-7} to 2.1×10^{-6}**, which also do not exceed HED's level of concern.

The proposed label for Discover™ has a 12-hour restricted entry interval (REI). The technical material has a Toxicity Category IV for Acute Inhalation and Primary Skin Irritation; all other acute effects are Category III. Per the Worker Protection Standard (WPS), a 12-hour restricted entry interval (REI) is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours is in compliance with the WPS.

Postapplication risk assessment uses the same dermal toxicity endpoints and Q_1* as for handlers above. No inhalation exposure scenarios were identified for postapplication activities because once sprays and dusts settle, inhalation exposure is not expected; therefore, this postapplication route of exposure was not assessed. Postapplication risks were assessed for workers entering wheat fields to scout and irrigate. Wheat is assumed to be mechanically harvested. The Agency acknowledges that there is some potential for exposure during harvesting because individuals engaged in fully mechanized activities have short-term excursions from the protected area for various reasons (e.g., unclogging machinery or equipment inspection for breakage). In these cases, the WPS § 170.112(c) Exception for short-term activities applies. Because the application being made relatively early in the growth cycle (i.e., 1 to 6 leaf stage on main stem), dislodgeable residues are expected to be significantly reduced by the time of harvest, due to degradation, growth of the plant, and absorption by the plant material. The MOE resulting from postapplication exposure is 3,100 as early as the day of application. **This MOE is greater than the target (100) and does not exceed HED's level of concern.** The cancer risk on the day of application is **9.9×10^{-7}**, which also does not exceed HED's level of concern.

4.4 Non-Occupational/Residential Exposure

There are no existing or proposed residential uses for this product. However, 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 the groundboom application. 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.

4.5 Cumulative Exposure

Clodinafop-propargyl belongs to the oxyphenoxy acid ester class of herbicides; this class of herbicides also includes the active ingredients fluazifop-butyl, fenoxaprop-ethyl, diclofop-methyl, quizalofop-ethyl, and haloxyfop-methyl. HED does not currently have data available to determine with certainty whether clodinafop-propargyl has a common mechanism of toxicity with any other substances. For the purposes of this human health risk assessment, HED has not assumed that clodinafop-propargyl has a common mechanism of toxicity with other pesticides.

4.6 Endocrine Disruption

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of clodinafop-propargyl and its end-use products for endocrine effects may be required.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

5.1 Acute Aggregate Dietary Risk (Food + Water)

Acute (non-cancer) aggregate risk from food + drinking water exposures to clodinafop-propargyl was described in detail in Section 4.2.1 (Food exposure) and 4.2.2 (Water exposure) of this document. Below is a summary of this risk analysis.

As shown in Table 4, there are three aPADs; 1) females 13-50, 0.005 mg/kg/day, 2) infants and children, 0.0.083 mg/kg/day, 3) general population, 0.25 mg/kg/day. As shown below in Table 9, the acute food only risk estimate associated with clodinafop-propargyl use on wheat is below HED's level of concern (100% aPAD) for all population groups. Based on tolerance level residues and assuming 100% crop treated, the 95th percentile of exposure is predicted to be up to **7.5%** of the aPAD for **nursing females ages 13-50**, the most highly exposed subgroup of females of childbearing age. The aPAD for infants and children is calculated to be 0.083 mg/kg/day. Based on the food only exposure assessment, at the 95th percentile of exposure the highest exposed subgroup of infants and children is **children 1-6** years old which utilizes up to **1.0% of the aPAD.**

The aPAD for the general population and subgroups not included in females 13-50 years old and infants and children is calculated to be 0.25 mg/kg/day. Based on the food only exposure assessment at the 95th percentile of exposure, the **total U.S. population** in addition to all **male only** subgroups are exposed to **< 1.0% of the aPAD**.

The EECs (Table 9) provided by EFED for assessing acute aggregate dietary risk are **5.0×10^{-6} μg/L and 0.044 μg/L** (in ground water, based on SCI-GROW for clodinafop-propargyl and CGA-193469, respectively) and **0.23 μg/L and 1.10 μg/L** (in surface water, peak value based on PRZM/EXAMS for clodinafop-propargyl and CGA-193469, respectively). The back-calculated DWLOCs (Table 9) for assessing acute aggregate dietary risk **range from 1.4×10^2 μg/L to 8.7×10^3 μg/L** for women of childbearing age (13-50 years old) and the general U.S. population.

The acute EECs generated by SCI-GROW and GENEEC are less than the Agency's level of comparison (the DWLOC value for each population subgroup) for clodinafop-propargyl residues in drinking water as a contribution to acute aggregate exposure.

HED thus concludes with reasonable certainty:

- combined residues of clodinafop-propargyl and its acid metabolite, CGA-193469, in drinking water will not contribute significantly to the aggregate acute human health risk

- the acute aggregate exposure from combined residues of clodinafop-propargyl and its acid metabolite, CGA-193469, in food and drinking water **will not exceed the Agency's level of concern** (100% of the acute PAD) for acute dietary aggregate exposure by *any* population subgroup.

EPA generally has no concern for exposures below 100% of the acute PAD, because it is a level at or below which aggregate dietary exposure over a single day or single dose will not pose appreciable risks to the health and safety of *any* population subgroup. This risk assessment is considered high confidence, conservative, and very protective of human health.

5.2 Chronic (Non-Cancer) Aggregate Dietary Risk (Food + Water)

Chronic (non-cancer) aggregate risk from food + drinking water exposures to clodinafop-propargyl was described in detail in Section 4.2.1 (Food exposure) and 4.2.2 (Water exposure) of this document. Below is a summary of this risk analysis.

The chronic (non-cancer) food risk estimate associated with clodinafop-propargyl use in/on wheat is below HED's level of concern (100% of cPAD). As shown in Table 4, the cPAD for applicable to all subgroups of U.S. populations is 0.00003 mg/kg/day. The Tier 3 analysis was performed using conservative residue values of 0.07 ppm for wheat and assuming 4% crop treated. The most highly exposed subgroup, **children 1-6 years old** utilizes up to **32% of the cPAD.** The **total U.S. population** utilizes up to **14% of the cPAD**.

The EECs (Table 9) provided by EFED for assessing chronic aggregate dietary risk are **5.0 x 10^{-6} μg/L and 0.044 μg/L** (in ground water, based on SCI-GROW for clodinafop-propargyl and CGA-193469, respectively) and **0.0017 μg/L and 0.11 μg/L** (in surface water, based on the annual mean PRZM/EXAMS for clodinafop-propargyl and CGA-193469, respectively). The back-calculated DWLOCs (Table 9) for assessing chronic aggregate dietary risk **range from 0.21 μg/L** for the most highly exposed population subgroup (children 1-6 years old) to **0.91 μg/L** for the U.S. Population (48 states - all seasons).

HED thus concludes with reasonable certainty:

- combined residues of clodinafop-propargyl and CGA-193469 in drinking water will not contribute significantly to the aggregate chronic human health risk

- the chronic aggregate exposure from combined residues of clodinafop-propargyl and its acid metabolite, CGA-193469, in food and drinking water **will not exceed the Agency's level of concern** (100% of the chronic PAD) for chronic dietary aggregate exposure by *any* population subgroup.

EPA generally has no concern for exposures below 100% of the chronic PAD, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of *any* population subgroup. This risk assessment is considered high confidence, conservative, and very protective of human health.

5.3 Cancer Aggregate Dietary Risk (Food + Water)

In the estimation of lifetime cancer risk for dietary exposure scenarios, the DWLOCs are greater than or only *slightly greater than* the modeled EEC values reported by EFED. As stated above, the largest EEC value is for the surface water chronic exposure to CGA-193469 **(0.11 μg/L).** The Tier 3 DEEM™ analysis using residues of 0.07 ppm for wheat and assuming 4% crop treated estimates that chronic exposure to the U.S. population will be 0.000004 mg/kg/day. It is important to note that the residue value (0.07 ppm) is *very* conservative and health protective. Applying the Q_1* value of 0.129 $(mg/kg/day)^{-1}$ results in a food only risk for cancer of **5.3×10^{-7}**. Following an aggregate dietary (food + water) assessment for lifetime cancer risk, the resulting DWLOC is **0.13 μg/L**. This cancer DWLOC is *slightly greater than* the EEC for chronic exposure to CGA-193469 in surface water. Because the models used to obtain the EECs for clodinafop-propargyl and CGA-193469 are highly conservative screening models not designed specifically for estimating concentrations in drinking water and because of the conversative nature of the food exposure assessment (anticipated residues at LOQ for parent + metabolite), HED believes this aggregate cancer dietary assessment will not underestimate exposure and that chronic dietary exposure from clodinafop-propargyl residues in food and drinking water **will not exceed HED's level of concern for lifetime cancer risk**

HED thus concludes:

- chronic dietary exposure from clodinafop-propargyl residues in food and drinking water **will not exceed HED's level of concern for lifetime cancer risk.**

5.4 Short- and Intermediate-Term Aggregate Dietary and Non-Dietary Risks (Food + Water + Residential)

These aggregate risk assessments take into account chronic dietary exposure from food and water (considered to be a background exposure level) plus (short- and/or intermediate-term, as applicable) indoor and outdoor residential exposures.

The HIARC selected doses and toxicological endpoints (Table 3) for assessments of short- and intermediate-term dermal and inhalation risk. However, since there are no residential uses for clodinafop-propargyl (either established or pending) at this time, these risk assessments are not currently required.

There are no existing or proposed residential uses for this product. However, 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 the groundboom application. 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.

5.5 Long-Term Aggregate Dietary and Non-Dietary Risks (Food + Water + Residential)

Based on the proposed use patterns, no long-term dermal or inhalation exposure is expected to occur. Therefore, no endpoints were selected by the HIARC. **Thus, long-term aggregate risk assessments are not required.**

6.0 DEFICIENCIES/DATA NEEDS

Toxicology

- Acute Neurotoxicity Study in Rats (81-8; OPPTS 870.6200)

Subchronic Neurotoxicity Study in Rats (82-7; OPPTS 870.6200)
In vitro cytogenetic assay (84-2; OPPTS 870.5375)
Developmental Neurotoxicity Study in Rats (83-6, OPPTS 870.6300)

Product Chemistry

- **None.**

Residue Chemistry

The data gaps in the residue chemistry database are listed below. The data gaps are discussed in detail in Attachment 8. **Although the noted residue chemistry issues exist, this assessment is considered conservative and health protective. Except for the submission of revised Sections B and F and the availability of adequate EPA method validations, noted issues will not preclude the establishment of a time-limited registration.**

OPPTS GLN 860.1200: PROPOSED USES

1. The Section B/label should be revised to change the feeding/grazing restriction on forage to 30 days since limited residue data are available at a 7-day PHI. Provided the above revision to the Section B/label is made, the proposed use of clodinafop-propargyl on wheat will be adequately described. The proposed use directions will be adequate to allow an assessment of whether the residue data reflect the maximum residues likely to occur in food/feed.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN PLANTS

2. The nature of the residue in wheat is not adequately understood for the purposes of a permanent tolerance for the following reasons pertaining to the [^{14}C-phenyl] CGA-178486 (racemic mixture) study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 21.6% TRR, 8.8% TRR, and 2.3% TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (maturity), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified those residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted. It would be preferable to use a formulation containing only the "R" enantiomer in the future study.

c. The time from sampling to final analysis should be clarified for the wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final

analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

3. The nature of the residue in wheat is not adequately understood for the purposes of a permanent tolerance for the following reasons pertaining to the [2-^{14}C- pyridyl] clodinafop-propargyl study:

a. Due to large amounts of the radioactivity being nonextractable with acetonitrile:water (8:2) and by Soxhlet extraction with methanol, only 17.2% TRR, 10.8% TRR, and 5.6 %TRR were identified in leaves (ear emergence), leaves (milky stage), and straw (mature), respectively. The petitioner should have attempted to extract more of the radioactivity using acid, base, and enzymes and then characterized/identified those residues.

b. Residues in grain were not identified in the field study. The identity of residues in grain resulting from application to the plant in a manner simulating expected field use are needed. The study should be conducted at a higher rate than the 2X study which was submitted.

c. The time from sampling to final analysis should be clarified for the wheat samples. If the time between sampling and final analysis of the field samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses should show that the basic profile of radiolabeled residues has not changed during that time.

4. The nature of the residue in wheat is adequately understood for the purposes of a registration with an expiration date. The residues of concern in wheat were determined by MARC to be clodinafop-propargyl and its acid metabolite CGA-193469. HED may revisit the MARC after additional wheat metabolism data have been submitted.

OPPTS GLN 860.1300: NATURE OF THE RESIDUE IN LIVESTOCK

Ruminants

5. The nature of the residue in ruminants is not adequately understood for the purposes of a permanent tolerance for the following reason: The time from sampling to final analysis should be clarified for milk and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

Poultry

6. The nature of the residue in poultry is not adequately understood for the purpose of a permanent tolerance for the following reason: The time from sampling to final analysis should be clarified for eggs and tissues. If the time between sampling and final analysis of the samples exceeded 6 months, evidence should be provided that the identity of residues did not change during the period between collection and final analysis. Such evidence would be analyses of representative substrates early in the study and at its completion. To be acceptable, such analyses would show that the basic profile of radiolabeled residues has not changed during that time.

OPPTS GLN 860.1340: RESIDUE ANALYTICAL METHODS

Plants

7. To establish a permanent tolerance, the following additional information is needed regarding the analytical methods used to obtain the storage stability and residue data: a) Radiovalidation data for Methods REM 138.01, 138.06, 138.10, and 138.12 are needed to demonstrate the efficiency of the methods in extracting and quantifying aged or bound residues in samples. (Radiovalidation data and recovery data at the limit of quantitation would be needed for Methods REM 138.02 and 138.05 if they were used to collect residue data which are acceptable. Methods REM 138.02 and 138.05 were used only to collect the Canadian residue data. HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies); b) Method REM 138.12 should be submitted.

8. Before EPA can determine whether adequate analytical methods are available for enforcement of permanent tolerances on wheat, the following additional information is needed for the proposed enforcement methods: a) For REM 138.01 and REM 138.06, either an interference study must be submitted which determines whether other pesticides registered on wheat will interfere with the analysis of clodinafop-propargyl residues by the enforcement method or a specific confirmatory method such as mass spectroscopy is needed as discussed in OPPTS GLN 860.1340. Provided that a specific confirmatory method is available, the Agency will not require that an interference study be conducted; b) Confirmatory methods are needed for Methods REM 138.01 and 138.06; c) The GC/MS confirmatory method in Method REM 138.10 includes derivatization with diazomethane. The petitioner should investigate whether another methylating agent could be substituted for diazomethane. If an alternative methylating agent is not available, EPA requires that justification for the use of diazomethane be provided. An alternative confirmatory method for REM 138.10 would be LC/MS. REM 138.10 could be rewritten to include LC/MS as the confirmatory method instead of GC/MS; d) Adequate EPA petition method validations are needed for the proposed enforcement methods. RAB3 has requested EPA petition method validations for REM 138.01, 138.06, and 138.10. These EPA petition method validations are underway. Adequate independent laboratory validations have been provided for methods REM 138.01 and 138.06.

9. Provided that the petition method validations which are being conducted by EPA are successful, adequate enforcement methods (MRID nos. 44399211, 44399213, and 44755302) are available to enforce registration with an expiration date on wheat.

OPPTS GLN 860.1380: STORAGE STABILITY DATA

10. Adequate storage stability data have not been submitted. The following additional storage stability data are needed:

a. Additional data are needed for Study 300/91 (MRID no. 44399210). Raw data, including residues (ppm) found and representative chromatograms (for standards, controls, freshly fortified samples, and stored samples) should be submitted. Storage containers should be described. The method used to analyze the storage stability samples should be submitted or identified by number as a submitted method.

b. No storage stability data were submitted for forage. Storage stability data for forage are needed for the 105-day storage interval for clodinafop-propargyl and the 218-day storage interval for CGA-193469 in US residue samples. If the Canadian residue studies could be used (i.e., upgraded to acceptable), storage stability data for forage would be needed for the 434-day storage interval for clodinafop-propargyl and CGA-193469 in the Canadian residue samples; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

c. If Canadian studies could be used (i.e., upgraded to acceptable), storage stability data for CGA-193469 on straw for 458 days would be needed so that the tolerance could be adjusted for any storage degradation; however, HED is not recommending that the petitioner attempt to upgrade the Canadian residue studies to an acceptable level.

d. No storage stability data were submitted for wheat processed commodities. The storage time between processing and analysis was ≤25 days for clodinafop-propargyl; storage stability data are not needed for clodinafop-propargyl in processed commodities since they were analyzed within 30 days of their production (OPPTS 860.1520). The storage time between processing and analysis for CGA-193469 was 51 days for aspirated grain, 45 and 125 days for germ, 45 days for bran, 42 days for middlings and shorts, and 37 days for low grade flour and patent flour. Storage stability data for CGA-193469 in aspirated grain fractions are not needed since this is an early season use and residues are not expected to occur in aspirated grain fractions. Storage stability data are not needed for bran, flour, middlings, and shorts since these matrices are similar to grain and can be covered by the storage stability data on grain. Storage stability data are needed for CGA-193469 in wheat germ for 45 and 125 days.

OPPTS GLN 860.1500: MAGNITUDE OF THE RESIDUE IN PLANTS

11. The proposed use indicates that forage could be fed/grazed at a 7-day PHI, hay could be fed at a 30-day PHI, and grain and straw could be harvested at a 60-day PHI. Based on the available residue data, residues of parent or CGA-193469 were less than the limit of quantitation (LOQ) in grain, forage, and hay in the US and in grain and forage in Canada at these PHI's; for straw, residues of the parent were <LOQ but maximum residues of 0.21 ppm CGA-193469 were found in

the US (MT; 57-day PHI) and maximum residues of 0.45 ppm CGA-193469 were found in Canada (Manitoba/1991 trials; 60-day PHI). (For US data, the limits of quantitation for parent were 0.02 ppm for grain and 0.05 ppm for forage, hay, and straw; the limit of quantitation for CGA-193469 was 0.05 ppm for grain, forage, hay, and straw. For Canadian data, the limits of quantitation for parent were 0.02 ppm for grain and forage, and 0.05 ppm for straw; the limits of quantitation for CGA-193469 were 0.01 or 0.05 ppm for grain, and 0.05 ppm for forage and straw.) However, the field trial residue data are not adequate to support a permanent tolerance for the following reasons:

a. Adequate geographic representation is not provided. (Wheat is not a minor crop, for which a regional registration would be accepted.) According to OPPTS 860.1500, a minimum of 20 field trials are needed to support a tolerance on wheat. The suggested distribution of wheat field trials is one in Region 2, one in Region 4, five in Region 5, one in Region 6, five in Region 7, six in Region 8, and 1 in Region 11. The US field trials were conducted in Region 5 (2 studies) and Region 7 (four studies), as defined in OPPTS 860.1500. Of the 15 Canadian field trials, four studies were conducted in extended Zone 5, seven studies were conducted in extended Zone 7, and four studies were conducted in extended Zone 14; however, the Canadian field trials have deficiencies which are not upgradeable (see Conclusion 12 below). Additional field trial residue studies are needed to support a permanent tolerance. For a 30-day PHI in forage, the additional studies would be one in Region 2, one in Region 4, three in Region 5, one in Region 6, one in Region 7, six in Region 8, and 1 in Region 11. (If a 7-day PHI in forage is desired, then the additional studies would be one in Region 2, one in Region 4, five in Region 5, one in Region 6, four in Region 7, six in Region 8, and one in Region 11.) Each study should include PHI's of 30 (or 7) days for forage, 30 days for hay, and 60 days for grain and straw. Spring (including hard red spring, duram, and white spring) and winter (including hard red winter, soft red winter, and white winter) varieties of wheat should be included in the studies. Each study should include DSV Adjuvant or similar adjuvant. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples should be included. Storage information including types of storage containers and dates of extraction (as well as dates of storage and analysis) should be included.

b. Only spring wheat was used in the US and Canadian studies. Winter wheat should be included in the residue studies.

c. Forage was sampled at the proposed preharvest interval (PHI) of 7 days in only one US study and three Canadian studies.

d. Based on the available residue data, the petitioner should submit a revised Section F which proposes tolerances for the combined residues of clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) and its metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid) at levels of 0.10 ppm for wheat grain, forage, and hay, and 0.50 ppm for wheat straw. These levels were obtained by adding the limits of quantitation and/or levels of residues for clodinafop-propargyl and CGA-193469. (Note that an "(R)" is needed in the chemical name of the parent to designate the "R" isomer.)

12. For the Canadian field trial residue studies, the following data should have been included. (HED is not recommending that the petitioner attempt to upgrade these studies to an acceptable level.)

a. Grain, forage, hay, and straw should be analyzed in each of the wheat field trial residue studies. (For an early season use, data on aspirated grain fractions are not needed.) Of the 15 Canadian studies, only grain and straw were analyzed in twelve studies and only forage was analyzed in three studies. Hay was not analyzed.

b. PHI's should reflect the proposed use. PHI's for grain and straw in the Canadian studies ranged from 55-105 days (with all but two studies with PHI's above 60 days) whereas the proposed PHI for grain and straw is 60 days.

c. Extraction dates were not provided for MRID nos. 44399217, 44399218, 44399219, 44399220, 44399221, 44399222, 44399223, 44399224, 44399225, 44399226, 44399227, and 44399231.

d. Storage containers were not described.

e. Raw data and representative chromatograms of standards, controls, fortified samples, and treated samples were not submitted.

OPPTS GLN 860.1520: MAGNITUDE OF THE RESIDUE IN PROCESSED FOOD/FEED

13. Pending submission of storage stability data on CGA-193469 in processed commodities (see storage stability section of this review), HED concludes that no concentration of clodinafop-propargyl or CGA-193469 occurred on processing.

OPPTS GLN 860.1850: CONFINED ACCUMULATION IN ROTATIONAL CROPS

14. The submitted confined rotational crop data are adequate for a permanent tolerance provided that a) rotational crop restrictions are placed on the label of 98 days (or 3 months) for lettuce and other leafy vegetables, 159 days (or 5 months) for small grains (except wheat), and one year (or 12 months) for all other crops; and b) the dates of harvest and/or analysis of ½ mature lettuce are corrected.

15. If the petitioner wants shorter rotational crop restrictions, then a confined rotational crop study conducted at the soil aging intervals of 1, 4, and 12 months would be needed for three rotated crops (a small grain, a leafy vegetable, and a root crop) reflecting one application at the maximum label rate of 0.06 lb clodinafop-propargyl ai/A.

OPPTS GLN 860.1900: FIELD ACCUMULATION IN ROTATIONAL CROPS

16. No field accumulation in rotational crop study was submitted. Pending results from the confined rotational crop study which may be conducted if the petitioner wants shorter rotational crop restrictions, this study may be required.

HED cannot recommend for the proposed permanent tolerances for clodinafop-propargyl on wheat for reasons given in the conclusions above.

Provided the petitioner submits a revised Section B/label and a revised Section F and EPA's method validation is satisfactory (see Conclusions 1, 9, and 11d above), there will be no residue chemistry data requirements that would preclude the establishment of a time-limited registration for the combined residues of clodinafop-propargyl (propanoic acid, (R)2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-, 2-propynyl ester) and its acid metabolite (R)(2-[4-(5-chloro-3-fluoro-2-pyridinyloxy) phenoxy]-propanoic acid) in/on wheat grain, forage, and hay at 0.10 ppm and wheat straw at 0.50 ppm while the remaining concerns are addressed.

7.0 ATTACHMENTS

Attachment 1: Clodinafop-propargyl - Report of the Hazard Identification Assessment Review Committee (6/2/99, Y. Yang).

Attachment 2: PP#7F04924 CLODINAFOP PROPARGYL (PC Code: 125203) Toxicology Disciplinary Chapter for Registration Support Document (S. Gross, 4/21/00).

Attachment 3: Cancer Assessment Document: Evaluation of the carcinogenic potential of clodinafop-propargyl (CGA184927). (11/7/99, Y. Yang)

Attachment 4: REVISED CGA 184927 (Clodinafop-Propargyl) Quantitative Risk Assessment (Q_1^*) Based On Tif:RAIf(SPF) Albino Rat and Tif:MAGf(SPF) Albino Mouse Chronic Dietary Studies With $^3/_4$'s Interspecies Scaling Factor. (3/2/00, L. Brunsman).

Attachment 5: Clodinafop-propargyl (CGA 184927): Assessment of Mode of Action on Liver Carcinogenicity. (9/21/99, Y. Yang)

Attachment 6: CLODINAFOP-PROPARGYL: Report of the FQPA Safety Factor Committee. (4/4/00, B. Tarplee)

Attachment 7: Proposed label for Discover™ Herbicide label, Novartis Corporation; EPA File Symbol 100-ONT

Attachment 8: PP#7F04924. clodinafop-propargyl on Wheat. Review of Analytical Methods and Residue Data. First Food Use Review (N. Dodd, 4/7/2000).

Attachment 9: Acute and Chronic Dietary Exposure Analyses for Proposed Tolerances for Clodinafop-propargyl in/on Wheat Commodities. (M. Xue, 4/20/2000).

Attachment 10: Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Clodinafop-Propargyl on Wheat (K. O'Rourke, 4/4/2000).

Attachment 11: Clodinafop-propargyl. Metabolism Assessment Review Committee (MARC) Decision Document for Meeting Held on 2/15/00. Chemical # 125203. DP Barcodes: D263288 and D263312. Case # 289249. Submission # S543995. (N. Dodd, 2/25/2000).

Attachment 12: Tier I Estimated Environmental Concentrations of Clodinafop propargyl (Chemical: 125203). (J. Jordan, 11/1/1999).

Attachment 13: Clodinafop Propargyl Drinking Water Assessment for Surface Water. (J. Lin and J. Jordan, 2/29/2000).

Attachment 14: Chemical names and structures of clodinafop-propargyl and its metabolites identified in primary plant, animal, and rotational crop commodities:
(14.1) Names and Structures of Clodinafop-propargyl and its Metabolites
(14.2) Figure 1. Proposed Wheat Metabolism Pathway of [^{14}C-Phenyl]CGA-178486/CGA-184927 and [2-^{14}C-Pyridyl]CGA-184927
(14.3) Figure 2. Proposed Goat Metabolism Pathway of Clodinafop-propargyl
(14.4) Figure 3. Proposed Hen Metabolism Pathway of Clodinafop-propargyl

8.0 DISTRIBUTION

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