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

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

MEMORANDUM

Date: 01/08/2009

SUBJECT: **Cyhalofop-butyl: Human Health Risk Assessment for Proposed Uses on Wild Rice and A Proposed Amended Labeling for Clincher® SF Herbicide.**

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At the request of the Registration Division, the Health Effects Division (HED) has conducted a human health risk assessment for the active ingredient, cyhalofop-butyl, for the purposes of making a tolerance/registration eligibility decision for the existing use on rice, grain and the proposed use on wild rice, grain. In addition, requested changes in PPE and other label language are addressed.

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1.0 Executive Summary

Cyhalofop-butyl (R-(+)-n-butyl-2-(4-(4-cyano-2-fluorophenoxy)-phenoxy)propionate) is a diphenyl ether (aka oxyphenoxy acid ester) herbicide for which a food use on rice and wild rice has been proposed. Other members of this class of herbicides include fluazifop-butyl, fenoxaprop-ethyl, haloxyfop-methyl, diclofop-methyl, quizalofop-ethyl, fomesafen sodium, oxyfluorfen, acifluorfen sodium, nitrofen, and lactofen. All these esters form acid metabolites. Cyhalofop-butyl inhibits acetyl coenzyme A carboxylase, which catalyses an essential step in plant fatty acid biosynthesis.

Cyhalofop-butyl is formulated as Clincher® EC, an emulsifiable concentrate containing 29.6% cyhalofop-butyl as active ingredient (equivalent to 2.38 lbs ai/gal of product). Clincher® EC is a postemergence herbicide for the selective control of emerged grass weeds in drill-seeded and water-seeded rice. According to the proposed supplemental labeling, the maximum amount of active ingredient that can be applied is no more than 2 applications or 0.46 lbs. ai or 25 fluid ounces per acre during the growing season. Product may be applied up to 60 days before harvest. Applications of the herbicide may include a crop oil concentrate or nonionic surfactant as specified in the label at the rate of 0.25% (1 quart/100 gallons of spray solution). This product is applied aerially, and/or by groundboom equipment.

This memorandum presents the results of an assessment on the use of the herbicide cyhalofop-butyl on rice and wild rice in response to a tolerance petition submitted by Interregional Research Project Number 4 (IR-4). Clincher® EC (EPA Reg. No. 62719-356) was previously approved for use on rice with tolerances established on rice grain at 0.03 ppm and rice straw at 8.0 ppm. These tolerances were time-limited because of deficiencies in the toxicology database (i.e., inadequate dosing in carcinogenicity studies) and expired on 6/1/2007. IR-4 has requested that the rice field trial data be translated to wild rice, and that a tolerance be established for residues of cyhalofop-butyl plus its acid and diacid metabolites in rice, wild, grain, at 0.03 ppm. Wild rice straw is not a regulated commodity; therefore, a tolerance was not proposed for this commodity.

HED has re-evaluated the database for cyhalofop-butyl and found it to be adequate for purposes of evaluating the requested use expansion. However, due to revisions in 40 CFR Part 158, there is now a requirement for an immunotoxicity study (OPPTS Guideline 870-7800). Although the lack of this study now represents a data gap, HED does not believe that a database uncertainty factor is warranted at this time.

Cyhalofop-butyl has low or minimal acute toxicity via the oral (category IV), dermal (category IV) and inhalation routes of exposure (category IV). It is minimally irritating to the eye (category IV), non-irritating to the skin (category IV); and is not a dermal sensitizer.

Kidney effects were observed after subchronic and chronic dosing of the rat and mouse as well as in the rabbit developmental and rat reproduction studies. In the 90-day rat study, lipofuscin pigment deposition in proximal tubule kidney cells was noted in both sexes in addition to hepatocyte eosinophilic granules (males only); and in the 90-day mouse study (females only), there was an increase in absolute and relative kidney weights as well as swelling of the proximal

tubule cells. In the rabbit developmental study, 1/18 dams in the mid-dose group and 9/18 dams in the high-dose group died or were sacrificed *in extremis* after exhibiting hematuria (gross pathological examinations revealed cloudy or dark colored kidneys). Slight kidney tubular cell swelling was observed only in adult males in the rat reproductive toxicity study. In the 18-month mouse carcinogenicity study, kidney findings included tubular dilatation, chronic glomerulonephritis and hyaline casts in females (not males). In both sexes in the chronic/carcinogenicity rat study increased deposition of kidney changes (early and increased deposition of the pigments lipofuscin and hemosiderin in the renal proximal tubular cells) was observed. In addition, in females only, renal mineralization was observed.

In the 18-month mouse carcinogenicity study, hyperplasia of the stomach mucosal epithelium was reported in males only. Brown and/or atrophied thymuses as well as decreased thymus weight was observed in the 90-day dog study.

No reproduction and/or endocrine effects were noted in any of the studies. There were no maternal or fetal effects observed in either the rat or rabbit developmental studies up to the limit dose. There was no evidence of teratogenicity or indications of increased neonatal sensitivity in the developmental and reproduction toxicity studies.

There were no systemic or neurotoxicity effects noted at the limit dose in the gavage acute neurotoxicity study. In addition, in the 90-day feeding neurotoxicity study (males up to 75 mg/kg/day and females up to 250 mg/kg/day, limited by doses in other studies), there were no systemic or neurotoxicity findings.

In a previous 2002 risk assessment for cyhalofop-butyl, it was not possible to assess the carcinogenic potential of cyhalofop-butyl due to insufficient dosing in the rat and mouse carcinogenicity studies. In the absence of data, HED used the Q_1* value of 2.3×10^{-1} for the structural analog, diclofop-methyl for risk assessment purposes. Subsequently, two specific mechanistic studies [Peroxisome Proliferator Receptor-Alpha Reporter Assay (PPARά)] in the mouse were submitted to HED. Review of the data indicated that cyhalofop-butyl is not a liver toxicant/cancer for humans based on mechanistic information and that the doses in the original long-term studies were approaching a maximum tolerated dose (a repeat of the long-term studies would not provide useful information to the risk assessment and, therefore, would not be required). Accordingly, the quantification of cancer risk and the derivation of an RfD should not be based on liver effects since the PPARά rodent liver mode of action is not likely to occur in humans and because cyhalofop-butyl is a weak rodent liver PPARά agonist. There were no positive effects in the battery of mutagenic studies.

No observed toxic effects appeared to be associated with a single dose of cyhalofop-butyl in the submitted studies. Therefore, no appropriate endpoints were identified for establishing an acute reference dose for any population subgroup, including females age 13-49 years of age. For chronic dietary exposure, the carcinogenicity study in mice was used to calculate the chronic reference dose (cRfD) of 0.01 mg/kg/day. The NOAEL of 1.0 mg/kg/day was selected based upon the LOAEL of 10.3 mg/kg/day at which there were increased incidences of kidney tubular dilatation, hyaline casts and chronic glomerulonephritis in females. For the incidental oral short- and intermediate-exposure, the NOAEL of 4.3 mg/kg/day was based on the LOAEL of 14.1

mg/kg/day from a 90-day study in mice where there were enlarged kidneys in females with swelling of proximal tubular cells in 4/12 mice. No endpoints were selected for the short- or intermediate-term dermal exposure because no toxicity was noted at the limit dose in the 21-day dermal study. For short- and intermediate-term inhalation, the NOAEL of 4.3 mg/kg/day was chosen from the 90-day mouse study (incidental short- and intermediate-term noted above).

Based on hazard and exposure data, HED recommends the special FQPA Safety Factor be reduced to1x because there are low concerns, no evidence of increased susceptibility, no residual uncertainties with regard to pre- and/or postnatal toxicity, no evidence of neurotoxicity (a DNT study is not required), and high confidence that exposure estimates have not been underestimated.

Product chemistry data, residue chemistry data relevant to food use, and environmental fate data relevant to drinking water are adequate to assess human dietary exposure to cyhalofop-butyl and to its metabolites or degradates.

HED has conducted a new dietary exposure assessment. As per current policy, the new assessment incorporated exposure via residues in drinking water directly into the dietary exposure model. The resulting dietary cPAD risk estimates for the general U.S. population (4.5% cPAD) and the highest exposed population subgroups (all infants < 1 year old, 15% cPAD) are well below HED's level of concern (typically 100% of the PAD). The risk estimates are based on tolerance-level residues and an assumption of 100% crop treatment for the food uses, and "Tier 1" estimates for the drinking water contamination that may be associated with the crop use.

There are no residential uses proposed for cyhalofop-butyl; therefore, a residential exposure assessment is not required.

Based on the use patterns for cyhalofop-butyl and the information in the toxicological database, only the chronic exposure requires a quantitative aggregate assessment. The only source of exposure to cyhalofop-butyl that is appropriate for assessing aggregate risk is dietary (food and water) exposure. The chronic aggregate risk is based on tolerance-level residues and an assumption of 100% crop treatment for the food uses, and on "Tier 1" estimates for the drinking water contamination that may be associated with crop use. A determination of safety can be made for aggregate risk.

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to cyhalofop-butyl and any other substances. Also, cyhalofop-butyl does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that cyhalofop-butyl has a common mechanism of toxicity with other substances.

HED has completed occupational exposure assessments to evaluate the requested uses. Occupational risk estimates associated with application as well as post-application activities are

below HED's level of concern. The level of concern for margins of exposure of safety for occupational risk assessments is 100.

Furthermore, upon review of newly submitted Mode of Action studies on the liver, HED has determined that cyhalofop-butyl is not likely to be carcinogenic to humans. Therefore, the requirement for a closed system while mixing and loading for aerial application and the restriction of limiting aerial treatment to 800 acres on the current label, as a result of the previous cancer classification and Q* value, are no longer required.

ENVIRONMENTAL JUSTICE CONSIDERATIONS

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Whenever appropriate, nondietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been determined to require a review of their ethical conduct, and have received that review. The studies in PHED were considered appropriate (ethically conducted) for use in risk assessments.

CONCLUSIONS/RECOMMENDATIONS

Based on highly conservative, health-protective assumptions, there are no human health considerations that would preclude granting the requested uses of cyhalofop-butyl on rice and wild rice. The database for cyhalofop-butyl is complete except for the immunotoxicity study.

HED recommends for establishing **permanent tolerances** for residues of cyhalofop-butyl, cyhalofop-acid and cyhalofop-diacid at **0.03 ppm** in/on **rice, grain,** and **rice, wild, grain**. Due to revisions in 40 CFR Part 158, there is now a requirement for an immunotoxicity study (OPPTS Guideline 870-7800). Although the lack of this study now represents a data gap, HED does not believe that a database uncertainty factor is warranted at this time. HED recommends that submission of an adequate immunotoxicity study be made a condition of registration for the uses on rice and wild rice.

2.0 Physical/Chemical Properties Characterization

The chemical structure and nomenclature of cyhalofop-butyl are provided in Table 1, below. The physicochemical properties of the technical grade of cyhalofop-butyl are presented in Table 2.0.

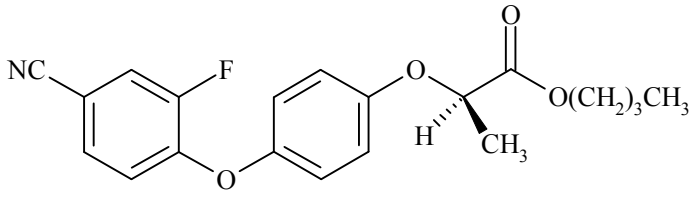
Table 2.0 Cyhalofop-butyl Nomenclature.	
Compound	
Common name	Cyhalofop-butyl
IUPAC name	2-(4-(4-cyano-2-fluorophenoxy)phenoxy)propanoic acid, butyl ester (R)
CAS name	R-(+)-n-butyl-2-(4-(4-cyano-2-fluorophenoxy)-phenoxy)propionate
CAS registry number	122008-85-9
End-use product (EPs) requested for registration	Clincher® CA Herbicide (29.6% Emulsifiable Concentrate)

TABLE 2 Physicochemical Properties of Cyhalofop-butyl.		
Parameter	Value	References
Melting point/range	45.5-49.5ºC	Memo, D277695, D. Davis, 4/10/2002
pH	9.0	
Relative Density (20ºC)	1.172 g/cm^3	
Water solubility (20ºC)	0.44 mg/L at pH 7	
Solvent solubility (g/L)	n-heptane 6.06 n-octanol 16.0 methoanol >250 acetone >250 ethyl acetate >250 acetonitrile >250	
Vapor pressure (25ºC)	5.3 x 10^{-8} kPa (4.0 x 10^{-7} mmHg)	
Octanol/water partition coefficient, Log(K_{OW}) (25ºC)	3.32	

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Studies available and considered (animal, human, general literature)

There are acceptable studies available for endpoint selection that include: 1) subchronic oral toxicity studies in rats, mice and dogs; 2) a chronic oral toxicity study in dogs, a chronic/carcinogenicity study in rats and a carcinogenicity study in mice; 3) developmental studies in rats and rabbits; 4) a reproduction study in rats; 5) acute as well as subchronic neurotoxicity studies in rats; and 6) a dermal toxicity study as well as a dermal penetration study in rats. There is also a complete mutagenicity battery and a metabolism studies in both the rat and dog.

3.1.1.2 Mode of action

Cyhalofop-butyl is a diphenyl ether (aka oxyphenoxy acid esters) herbicide for which there is a registered food use on rice. Other members of this class of herbicides include fluazifop-butyl, fenoxaprop-ethyl, haloxyfop-methyl, diclofop-methyl, quizalofop-ethyl, fomesafen sodium, oxyfluorfen, acifluorfen sodium, nitrofen and lactofen. All of these esters form acid metabolites. Cyhalofop-butyl inhibits acetyl coenzyme A carboxylase which catalyses an essential step in plant fatty acid biosynthesis.

3.1.1.3 Sufficiency of studies/data

Based on the proposed use pattern, the toxicology database for cyhalofop-butyl is adequate for risk assessment. A developmental neurotoxicity study is not required at this time. However, as part of the new 40 CFR158 requirments, an immunotoxicity study in rats and/or mice is required (see appendix II). In a 90-day feeding study in dogs, brown and/or atrophied thymuses and decreased thymus weights were reported. However, these effects were not observed in the 1-year dog study or in other species (rats, mice or rabbits) and were not seen in any tested species as a result of chronic exposure. The doses and endpoints selected for risk assessment (along with traditional uncertainty factors) are considered protective of potential immunotoxicity. Therefore, an additional 10x database uncertainty factor (UF_{DB}) is not warranted pending receipt of the required study.

3.1.2. Toxicological Effects

Cyhalofop-butyl has low or minimal acute toxicity via the oral (category IV), dermal (category IV) and inhalation routes of exposure (category IV). It is minimally irritating to the eye (category IV) and non-irritating to the skin (category IV); it is not a dermal sensitizer.

The target organs are the kidney in rats, mice and rabbits, the stomach in mice and the thymus in dogs. The mechanism of toxicity in test animals is not known. A common finding in many

studies is hepatocellular hypertrophy with a corresponding increase in liver weights. In the absence of adverse clinical chemistry and/or histopathologic findings, this was not considered to be of toxicological significance.

Kidney effects were observed after subchronic and chronic dosing as well as in the rabbit developmental and rat reproduction studies. In the 90-day rat study, lipofuscin pigment deposition in proximal tubule kidney cells was noted in both sexes in addition to hepatocyte eosinophilic granules (males only); and in the 90-day mouse study (females only), there was an increase in absolute and relative kidney weights as well as swelling of the proximal tubule cells. In the rabbit developmental study, 1/18 dams in the mid-dose group and 9/18 dams in the high-dose group died or were sacrificed *in extremis* after exhibiting hematuria (gross pathological examinations revealed cloudy or dark colored kidneys). Slight kidney tubular cell swelling was observed only in adult males in the reproductive toxicity study. In the 18-month mouse carcinogenicity study, kidney findings included tubular dilatation, chronic glomerulonephritis and hyaline casts in females (not males). In both sexes in the chronic/carcinogenicity rat study increased deposition of kidney changes (early and increased deposition of the pigments lipofuscin and hemosiderin in the renal proximal tubular cells) was observed. In addition, in females only, renal mineralization was observed.

In the 18-month mouse carcinogenicity study, hyperplasia of the stomach mucosal epithelium was reported in males only. Brown and/or atrophied thymuses as well as decreased thymus weight was observed in the 90-day dog study (no effects were observed in the chronic dog study at the doses tested).

No reproduction and/or endocrine effects were noted in any of the studies. There were no maternal or fetal effects observed in either the rat or rabbit developmental studies up to the limit dose. There was no evidence of teratogenicity or indications of increased neonatal sensitivity in the developmental and reproduction toxicity studies.

In a 21-day dermal toxicity study in rats, other than suggested liver adaptation, there were no systemic or dermal effects noted up to the limit dose. An acceptable/non-guideline dermal penetration study was performed (only one exposure duration instead of six).

There were no systemic or neurotoxicity effects noted at the limit dose in the gavage acute neurotoxicity study. In addition, in the 90-day feeding neurotoxicity study (males up to 75 mg/kg/day and females up to 250 mg/kg/day, limited by doses in other studies), there were no systemic or neurotoxicity findings.

HED previously determined that the doses administered in the 104-week chronic/carcinogenicity rat and 78-week carcinogenicity mouse studies were not adequate to characterize carcinogenicity in either study. In the absence of data, HED used the Q_1* value of 2.3×10^{-1} for the structural analog, diclofop-methyl for risk assessment purposes. For purposes of fulfilling this data gap requirement, the Registrant and HED agreed that, instead of repeating the two long-term rodent studies, specific mechanistic studies were to be conducted in the mouse. Upon review of the data, HED concluded that the results indicated that cyhalofop-butyl is not a liver toxicant or carcinogen for humans based on mechanistic information and that the doses in the original long-

term studies were approaching a maximum tolerated dose (a repeat of the long-term studies would not provide useful information to the risk assessment and, therefore, would not be required). Accordingly, the quantification of cancer risk and the derivation of an RfD should not be based on liver effects since the PPARά rodent liver mode of action is not likely to occur in humans and because cyhalofop-butyl is a weak rodent liver PPARά agonist (Evaluation of Mode of Action Data and Classification of Carcinogenicity of Cyhalofop-butyl, J. Kidwell, December 2007, TXR No. 0054798).

There were no positive effects in the following battery of mutagenic studies: bacterial reverse gene mutation (*Salmonella* strains and *E. coli),* mouse lymphoma, *In vitro* chromosomal aberration Chinese hamster lung (polyploidy induced when CHL [V79] cells treated for 48 hours in absence of S9, no clastogenic effect on DNA), *In vivo* micronucleus in mouse bone marrow cells and unscheduled DNA in rat hepatocytes.

3.1.3 Dose-response

For chronic dietary exposure, the carcinogenicity study in mice was used to calculate the chronic reference dose (cRfD) of 0.01 mg/kg/day. The NOAEL of 1.0 mg/kg/day was selected based upon the LOAEL of 10.3 mg/kg/day at which there were increased incidences of kidney tubular dilatation, hyaline casts and chronic glomerulonephritis in females. For the incidental short- and intermediate-term oral exposure assessment, the NOAEL of 4.3 mg/kg/day was based on the LOAEL of 14.1 mg/kg/day from a 90-day study in mice where there were enlarged kidneys in females with swelling of proximal tubular cells in 4/12 mice. No appropriate endpoints were identified for an acute reference dose for the general population or for females age 13-49 years of age. No observed toxic effects appeared to be associated with a single dose of cyhalofop-butyl in the submitted studies. No endpoints were selected for the short- or intermediate-term dermal exposure because no toxicity was noted at the limit dose in the 21-day dermal study. For short- and intermediate-term inhalation, the NOAEL of 4.3 mg/kg/day was chosen from the 90-day mouse study (see incidental short- and intermediate-term oral exposure noted above). The endpoint for the long-term dermal and inhalation exposure was the same as for the chronic RfD (NOAEL = 1.0 mg/kg/day, LOAEL =10.3 mg/kg/day).

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

In the rat metabolism study, absorption of the gavaged test article was 93-100%, and urinary excretion was the major route of elimination regardless of dose, label position or gender. Over 168 hours, 84-100% of the radioactivity was eliminated in urine, with 86-90% eliminated within 24 hours. Fecal excretion was <5%. There was no elimination via expired air. Over a 24-hour period, biliary elimination accounted for 1.7% and 20.1% of the administered dose in males and females, respectively, in the low-dose [ά-^{14}C]XRD-537 BE group, and 17.0% (males) and 11.6% (females) of the administered dose in the [β-^{14}C]XRD-537 BE low-dose group. The greatest radioactivity levels were found in liver, kidneys, plasma, whole blood, heart, lung, and stomach, with the highest tissue levels being found in the liver and kidney at 2 hours. Most tissue levels accounted <1% of the administered dose. Due to rapid excretion, levels in tissue/organ levels declined to near detection limits by 24 hours in all dose groups. There was a biphasic pattern for both labels with no substantial differences in pharmacokinetic indices (C_{msc}, t_{cmax}, $t_{1/2}$, AUC).

Time-to-maximum plasma concentration (t_{cmax} of 0.5 to 4 hrs) and elimination half-times ($t_{1/2}$ of 1.4 to 7.9 hrs) reflected the relatively rapid absorption. Females had somewhat shorter t_{cmax} and lower C_{max} values suggestive of saturated absorption processes. The acid metabolite (R-(+)-2-[4-(4-cyano-2-fluoro-phenoxy)phenoxy]propanoic acid) was the most prominent plasma fraction (~90-94% of the plasma activity for males and ~75-81% for females regardless of dose). No parent compound or other metabolites were detected. The acid metabolite was the most common product in urine and feces – 71-87% (urine) and 46-75% (feces) of the activity in those matrices.

In a dog metabolism study, no treatment related adverse effects were reported. Approximately 50% of a single gavage dose was absorbed over several hours. Blood and plasma radioactivity peaked after 1-2 hours. Clearance from plasma and blood was not especially rapid but nearly complete at 48 hours. Over 168 hours, excretion was 42.5-43.9% in the urine, and 48.6-50.6% in feces. Tissue distribution was not measured. The test article appears to be metabolized primarily by hydrolysis to R-(+)-2-[4-cyano-2-fluorophenoxy)phenoxy]propanoic acid which was found in both the urine and feces. Several other metabolites were also formed, each representing <5% of the administered dose. No parent compound was found in the urine, and only minimal amounts were detected in the feces. Level tested: Two male beagles were gavaged with ^{14}C XRD-537 BE and nonlabeled XRD-537 at a dose of 1 mg/kg.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The database is adequate to characterize potential pre- and/or post-natal risk for infants and children. Acceptable/guideline developmental toxicity studies in rats and rabbits and a reproduction study in rats were available for FQPA assessment.

3.3.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity observed in the submitted toxicology database which included acute and subchronic neurotoxicity studies.

3.3.3 Developmental Toxicity Studies

There were no treatment-related effects observed in dams or fetuses in the developmental toxicity study in rats up to the limit dose of 1000 mg/kg/day. In the rabbit developmental study (doses of 0, 40, 200 and 1000 mg/kg/day), 1/18 dams in the mid-dose group and 9/18 dams in the high-dose group either died or were sacrificed *in extremis* after exhibiting hematuria. Gross pathological examinations revealed the occurrence of cloudy or dark colored kidneys. No developmental toxicity was observed up to the limit dose of 1000 mg/kg/day.

3.3.4 Reproductive Toxicity Study

In the rat 2-generation reproduction study in rats (one litter/generation), there was slight kidney tubular cell swelling in males of both generations at the 86 mg/kg/day dose (HDT). There were no treatment-related effects seen in females or offspring up to 101 mg/kg/day.

3.3.5 Additional Information from Literature Sources

A literature search did not reveal information that would impact the risk assessment.

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

There is no concern for increased quantitative and/or qualitative susceptibility after *in utero* or postnatal exposure to cyhalofop-butyl in rat and rabbit developmental toxicity studies or in a reproduction study in rats.

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

The purposes of the Degree of Concern analysis are: (1) to determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment. If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by a FQPA safety factor and, if so, the size of the factor needed.

There is no evidence (quantitative or qualitative) of increased susceptibility and no residual uncertainties with regard to prenatal toxicity following *in utero* exposure to rats or rabbits (developmental studies) and pre and/or post-natal exposures to rats (reproduction study).

3.3.7 Recommendation for a Developmental Neurotoxicity Study

There was no evidence of neurotoxicity observed in adults following acute, subchronic or chronic exposure (including an acute and subchronic neurotoxicity studies) to cyhalofop-butyl or in offspring following prenatal or postnatal exposure. Additionally, there was no indication of increased susceptibility in either of the developmental studies or the reproduction study. Therefore, a DNT study is not required at this time.

3.4 FQPA Safety Factor for Infants and Children

After evaluating the toxicological and exposure data, the cyhalofop-butyl risk assessment team recommends that the FQPA SF be reduced to 1x based on the following:

The toxicological database for cyhalofop-butyl is complete for the intended uses (with the exception of an immunotoxicity study which is currently required by the latest 40 CFR Part 158).

- The toxicity data showed no increase in qualitative or quantitative susceptibility in fetuses and pups with *in utero* and post-natal exposure.

- The aggregate exposure assessment is based on HED-recommended tolerance-level residues and modeled drinking water estimates and will not underestimate exposure.

- Currently there are no registered or proposed residential uses of cyhalofop-butyl.

- There is no evidence of neurotoxicity in the reviewed database (including the acute and subchronic neurotoxicity studies).

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – Females age 13-49

No appropriate endpoint was identified for this population. There was no toxic effect attributable to a single dose in the cyhalofop-butyl toxicity database.

3.5.2 Acute Reference Dose (aRfD) – General Population

No appropriate endpoint was identified for this population. There was no toxic effect attributable to a single dose in the cyhalofop-butyl toxicity database.

Comments about Study/Endpoint/Uncertainty Factors:

3.5.3 Chronic Reference Dose (cRfD)

Study Selected: Carcinogenicity study – mice
MRID No.: 45000418
Dose and Endpoint for Risk Assessment: NOAEL = 1.0 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Chronic RfD} = \frac{1.0 \text{ mg/kg/day}}{100 \text{ (UF)}} = 0.01 \text{ mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors:
A carcinogenicity study in mice was used to select the dose and endpoint for establishing the cRfD of 0.01 mg/kg/day. The NOAEL of 1.0 mg/kg/day and LOAEL of 10.1 mg/kg/day were based on kidney effects including tubular dilatation, chronic glomerulonephritis and hyaline casts in females as well as hyperplasia of the stomach mucosal epithelium in males. The 2-year rat chronic/carcinogenicity feeding study with a NOAEL of 0.82/2.5 (M/F) mg/kg/day and a LOAEL of 3.4/25.0 (M/F) mg/kg/day, showed kidney effects as follows: early and increased deposition of the pigments lipofuscin and hemosiderin in the renal proximal tubular cells of both sexes, and renal mineralization in females. The rat study NOAELs were not chosen for endpoint dose for the following reasons: the NOAEL in the mouse study (1.0 mg/kg/day M/F) was similar to the male NOAEL in the rat study but was lower (2.5 mg/kg/day) than in the females; the finding of glomerulonephritis in the mouse study was considered to be a more toxic effect than the deposition of pigments in the rat study; and the dose-spacing was different in the two studies

(mice = 0.0, 0.3,1.0 and 10.0 mg/kg/day M/F; rats = 0.0, 0.1, 0.2, 0.8 and 3.4 mg/kg/day for males and 0.0, 0.2, 2.5 and 25.0 mg/kg/day for females.

Uncertainty factors (100x) include: 10x interspecies extrapolation, 10x intraspecies variability. The duration and route of the study are appropriate for chronic assessment; and, the NOAEL/LOAEL are protective of effects seen in other long-term studies (i.e., dogs, rats).

3.5.4 Dermal Absorption

Dermal absorption was ~ 25-34% for the spray formulation and ~ 11-16% for the EF-1218 formulation following a 24-hour dermal dosing. Within 48 hours, excretion was >85% in the urine and <1% in the feces, which is consistent with metabolism to water soluble metabolites and subsequent urinary excretion. [Only a 24-hour duration exposure instead of six exposure durations: acceptable/non-guideline.]

3.5.5 Dermal Exposure (Short- and Intermediate-Term)

Study Selected: 21-Day Dermal study - rat
MRID No.: 45000415
Dose and Endpoint for Risk Assessment: No endpoint selected

Comments about Study/Endpoint/Uncertainty Factors

In a 21-day dermal toxicity study conducted in rats (plus a recovery group) increased liver weights and clinical chemistry changes suggestive of liver adaptation were observed with reversibility occurring in the recovery group. The reversibility of the effects demonstrates these changes are biological markers of exposure, not toxicity. No systemic or dermal effects were observed at the limit dose of 1000 mg/kg/day. Therefore, no endpoint was selected for short- or intermediate-term dermal risk assessment.

3.5.6 Inhalation Exposure (Short- and Intermediate-Term)

Study Selected: 90-Day study – mice
MRID No.: 45000418
Dose and Endpoint for Risk Assessment: NOAEL = 4.3 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors:

No inhalation toxicity study was submitted. A 90-day feeding study in mice was used to select the dose and endpoint. The NOAEL of 4.3 mg/kg/day and LOAEL of 14.1 mg/kg/day were based on enlarged kidneys accompanied by swelling of the proximal tubule cells in 4/12 females. Uncertainty factors (100x) include: 10x interspecies extrapolation, 10x intraspecies variability. While route specific inhalation data are not available, this oral study has appropriate duration of exposure for this assessment. By default, HED is assuming 100% absorption (relative to oral absorption) when assessing inhalation exposure to cyhalofop-butyl.

3.5.7 Level of Concern for Margin of Exposure

Table 3.5.7. Summary of Levels of Concern for Risk Assessment			
Route	Short-Term (1-30 Days)	Intermediate-Term (1-6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	N/A	N/A	N/A
Inhalation	100	100	N/A
Residential Exposure			
There are no proposed or registered residential uses for cyhalofop-butyl.			

3.5.8 Classification of Carcinogenic Potential

HED previously determined that the 104-week chronic/carcinogenicity study in rats as well as the 78-week carcinogenicity study in mice did not include doses of the chemical high enough to adequately characterize carcinogenicity. The Registrant and HED agreed that, instead of repeating the two long-term rodent studies, specific mechanistic studies were to be conducted in the mouse. Two studies were performed and HED agreed that the results indicated that cyhalofop-butyl is not a liver toxicant or carcinogen for humans based on mechanistic information and that the doses in the long-term studies were approaching a maximum tolerated dose (a repeat of the long-term studies would not provide useful information to the risk assessment and, therefore, would not be required). Accordingly, the quantification of cancer risk and the derivation of an RfD should not be based on liver effects since the PPARά rodent liver mode of action is not likely to occur in humans and because cyhalofop-butyl is a weak rodent liver PPARά agonist (Evaluation of Mode of Action Data and Classification of Carcinogenicity of Cyhalofop-butyl, J. Kidwell, December 2007, TXR No. 0054798).

Therefore, the classification is: “Not Likely to be Carcinogenic to Humans.”

3.5.9 Summary of Toxicological Doses and Endpoints for Cyhalofop-butyl for Use in Human Risk Assessments

Table 3.5.9a Toxicological Doses and Endpoints for Cyhalofop-butyl for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General Population, including Infants and Children)	N/A	N/A	N/A	**No appropriate endpoint identified.**
Acute Dietary (Females 13-49 years of age)	N/A	N/A	N/A	**No appropriate endpoint identified.**
Chronic Dietary (All Populations)	NOAEL = 1.0 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.01 mg/kg/day cPAD = 0.01 mg/kg/day	**Carcinogenicity – mice** LOAEL = 10.0 mg/kg/day, based on effects on the kidney including tubular dilatation, chronic glomerulonephritis and hyaline casts in females as well as hyperplasia of the stomach mucosal epithelium in males.
Cancer (oral, dermal, inhalation)	Because of the mechanistic studies submitted by the Registrant and a review by HED, it has been determined that the cancer classification be:"Not Likely to be Carcinogenic to Humans."			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = Food Quality Protection Act Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. N/A = not applicable.

Table 3.5.9b Summary of Toxicological Doses and Endpoints for Cyhalofop-butyl for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal (1-30 days) and Intermediate-term (1-6 months)	N/A	N/A	N/A	**21-Day Dermal - rats** No systemic or dermal effects at the LIMIT dose (1000 mg/kg/day)
Inhalation Short-(1-30 days) and Intermediate-term (1-6 months)	NOAEL = 4.3 mg/kg/day IAF=100%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Occupational LOC for MOE = 100	**90-Day Oral - mice** LOAEL = 14.1 mg/kg/day (M/F), based on enlarged kidneys in females with swelling of proximal tubular cells in 4/12 mice.
Cancer (oral, dermal, inhalation)	Because of the mechanistic studies submitted by the Registrant and a review by HED, it has been determined that the cancer classification be: "Not Likely to be Carcinogenic to Humans."			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable. IAF=inhalation absorption factor, FQPA SF = Food Quality Protection Act Safety Factor.

3.6 Endocrine Disruption

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

There was the no indication in the available data that the endocrine system may have been affected by cyhalofop-butyl.

4.0 Dietary Exposure Risk Characterization

Cyhalofop-butyl is formulated as Clincher® EC, an emulsifiable concentrate containing 29.6% cyhalofop-butyl as active ingredient (equivalent to 2.38 lbs ai/gal of product). Clincher® EC is a postemergence herbicide for the selective control of emerged grass weeds in drill-seeded and water-seeded rice. According to the proposed supplemental labeling, the maximum amount of active ingredient that can be applied is 0.46 lbs. (25 fluid ounces of product) per acre during the growing season. The product may be applied twice with the last application being up to 60 days before harvest. Applications of the herbicide may include a crop oil concentrate or nonionic surfactant as specified in the label at the rate of 0.25% (1 quart/100 gallons of spray solution). The use directions for wild rice are outlined in Table 4.0.

Table 4.0. Summary of Directions for Use of Cyhalofop-butyl on Wild Rice.						
Method of Application	Formulation	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Rice and Wild Rice						
Broadcast foliar Ground or aerial	29.6% Emulsifiable Concentrate EPA Reg # 59639-357	0.24-0.28 (2.38 lb ai/gallon)	2	0.46	60	Applications are to be made with crop oil concentrate at a rate of 2.5% v/v. A spray volume of 10-15 gallons per acre should be used. Sequential applications must be made at least 10 days apart. Do not apply through any type of irrigation system. Do not allow discharge of paddy water from treated areas for a minimum of 7 days after the most recent application. 12-hour resticted entry interval (REI)

4.1 Pesticide Metabolism and Environmental Degradation

4.1.1 Metabolism in Primary Crops

Residue Chemistry Memo D267558, 11/13/01, M. Nelson, (PP# 0F6089)
HED MARC Decision Memo Y. Donovan, DP# 277192, 11/13/2001

The nature of cyhalofop-butyl residues in rice is adequately understood based upon acceptable ^{14}C metabolism studies conducted on rice. Much of the administrated material was incorporated into natural plant components (starch, lignin,etc.). The principal residues in rice are the parent compound and the diacid metabolite. The acid metabolite occurred to a lesser degree. HED assumes that the metabolism in wild rice is the same as that in rice.

4.1.2 Metabolism in Livestock

Residue Chemistry Memo D267558, 11/13/01, M. Nelson, (PP# 0F6089)

The proposed use on wild rice does not result in an increase in residues that are expected to occur in animal commodities. As a result, there is still no reasonable expectation of finite cyhalofop-butyl residues of concern in egg, milk and edible livestock tissues [Category 3, 40 CFR §180.6(a)]. Therefore, the requirements for tolerances, analytical methods, and data depicting magnitude of the residue in eggs, milk and edible livestock tissues are not required. The

Category 3 situation may not remain applicable if additional livestock feed items are proposed for tolerances in the future.

4.1.3 Analytical Methodology

Residue Chemistry Memo D267558, 11/13/01, M. Nelson, (PP# 0F6089)

GC/MS Method GRM 99.06 is the enforcement method for determining cyhalofop-butyl residues of concern in/on rice commodities. Method GRM 99.06 quantitates residues of cyhalofop-butyl and cyhalofop-acid as the acid equivalent, and residues of cyhalofop-diacid and cyhalofop-amide as the diacid equivalent. The validated method LOQ for cyhalofop-acid and cyhalofop-diacid is 0.01 ppm each in all rice matrices, except in straw, where the LOQ for cyhalofop-diacid is 0.05 ppm.

Method GRM 99.06 has had a successful laboratory validation (ILV). It has also undergone a successful petition method validation by ACB/BEAD (Memo, D272679, E. Kolbe, 3/18/2002). A copy of the method can be obtained from ACB/BEAD. Method GRM 99.06 was also the residue analytical method used in the analysis of rice commodities collected from the field trial, processing, and storage stability studies. The concurrent method recoveries indicate that the method is adequate for data collection.

4.1.4 Multiresidue Methods

Residue Chemistry Memo D278385, 8/15/03, M. Nelson, (PP# 1F06313)

Complete recovery of cyhalofop-butyl was achieved through Protocol D (without Florisil cleanup and using NPD detection), and through Protocol E. The acid and diacid metabolites do not appear to be recovered by any of the FDA MRMs.

4.1.5 Environmental Degradation

(Drinking Water Assessment for the Proposed Section 3 Registration of Cyhalofop-butyl for New Uses on Wild Rice Grown in California; K. White; October 2008)

Review of the environmental fate data of cyhalofop-butyl indicate that the parent is degraded to cyhalofop-acid, cyhalofop-amide, cyhalofop-diacid, 3-fluoro-4-(4-hydroxyphenoxy)benzoic acid (FHPBA), and 3-fluoro-4-(4-hydroxyphenoxy)benzonitrile (DP).

Hydrolysis and photolysis are much slower (half-lives ranged from 25 days to stable at pH 5 and 7) compared to biological degradation at neutral to acidic pH. Abiotic hydrolysis is more rapid at pH 9 (half-life = 2 days).

The major degradates of Cyhalofop-butyl (acid, amide, diacid) are generally water-soluble and acidic. The pKa of Cyhalofop-acid is 3.80, which makes it an anion at pH 7, and its solubility is 251 mg/L. Reliable sorption data on cyhalofop-butyl is not available. Sorption of cyhalofop-acid in the aquatic environment was not well predicted by organic carbon and K_d values ranged from 0.46 – 6.2 L/kg. The K_d values for cyhalofop-amide ranged from 0.3 – 0.47 L/kg and the K_d for cyhalofop-diacid ranged from 5.7 – 10.4 L/kg. Not enough data was available to evaluate the relationship of sorption to percent OC for the diacid and amide.

These properties indicate that the degradates will have little tendency to volatilize, or to sorb to soil. The degradates will be quite mobile due to the low Koc values. Cyhalofop-butyl residues will likely degrade in the water column, and be substantially mineralized to carbon dioxide. Residues in paddy water from California and Arkansas field studies dissipated to below detectable levels after 28 days.

Cyhalofop-butyl and cyhalofop-acid may exist as an R or S enantiomer. The active ingredient registered is in the R form; however, conversion to the S enantiomer may occur in the natural environment.

4.1.6 Comparative Metabolic Profile

Metabolism and environmental fate studies indicate that cyhalofop-butyl is generally biologically available. The parent compound along with the acid, diacid, and amide metabolites were the primary residues in rice and environmental fate studies. In rats and dogs, the most common metabolite was the acid metabolite and very little of the administered material remained in the form of the parent compound. Most of the absorbed material was eliminated fairly rapidly in the rat (24 hours) and dog (48 hours) studies. The available data indicate that cyhalofop-butyl undergoes significant metabolism in plants, animals, and the environment, and that the acid metabolite can be found in a variety of systems.

4.1.7 Toxicity Profile of Major Metabolites and Degradates

The metabolism, or degradation of cyhalofop-butyl, has been studied in the rat, dog, plants, and in the environment. The available environmental fate data indicates that the route of metabolism (hydrolysis) in drinking water was similar to that observed in plant and animals. No additional metabolites of any significance were observed. The diacid was the major residue in crop field trials, but was not observed as a rat metabolite. Based on structure-activity relationship (SAR) considerations, HED concluded that this metabolite is likely to be of comparable toxicity to the parent. Separate toxicology studies on the diacid were not required.

4.1.8 Pesticide Metabolites and Degradates of Concern

Table 4.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Cyhalofop-butyl, Cyhalofop-acid, Cyhalofop-amide, Cyhalofop-diacid	Cyhalofop-butyl, Cyhalofop-acid, and Cyhalofop-diacid
	Rotational Crop	N/A	N/A
Livestock	Ruminant	N/A	N/A
	Poultry	N/A	N/A

Table 4.1.8 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression		
Matrix	Residues included in Risk Assessment	Residues included in Tolerance Expression
Drinking Water	Cyhalofop-butyl, Cyhalofop-acid, Cyhalofop-amide, Cyhalofop-diacid	N/A

4.1.9 Drinking Water Residue Profile

(Drinking Water Assessment for the Proposed Section 3 Registration of Cyhalofop-butyl for New Uses on Wild Rice Grown in California; K. White; October 2008)

An updated drinking water assessment was conducted for the proposed uses on the wild rice (K. White; D; 10/17/2008). To account for exposure to potential residues in water under the most conservative scenario, the value of 21 ppb was used in the chronic dietary exposure assessment. Water-borne residues were incorporated in the DEEM-FCID assessment into the food categories "water, direct, all sources" and "water, indirect, all sources."

SCI-GROW was used to derive the Expected Environmental Concentrations **(**EEC) for ground water. The input parameters used in the SCI-GROW model resulted in an estimated groundwater concentration of 0.16 ug/L (parts-per-billion).

Since the last drinking water assessment was completed in 2001, a standard model was developed to estimate surface water concentrations from use of pesticides on rice, the Tier I Rice Model. The model was modified to account for possible aerobic aquatic degradation and aquatic dissipation over time and used to estimate surface water concentrations in water released from the rice paddy (tail water). Peak surface water EECs for the tail water ranged from 12 – 279 µg/L for total residues. The annual average concentrations ranged from 0.13 – 21 µg/L.

Modeling results are presented in Table 4.1.9.

Table 4.1.9. Summary of Estimated Surface Water and Groundwater Concentrations for Cyhalofop-butyl , cyhalofop-acid and cyhalofop-diacid			
	Surface Tail Water Conc., ppb [a]	Surface Tail Water Conc., ppb [b]	Groundwater Conc., ppb [c]
Acute or Peak	279	12	0.152
Chronic (non-cancer)	21	0.13	0.152

[a] From the Tier 1 Rice Model with Aerobic Aquatic Degradation only Considered

[b] From the Tier 1 Rice Model with Aquatic Dissipation Considered

[c] From the SCI-GROW model (Version 2.3) assuming a maximum seasonal use rate of 0.23 lb ai/A.

Monitoring Data

Cyhalofop-butyl and its degradates were not detected in surface water and drinking water monitoring studies conducted in California where rice is grown.

Surface Water Monitoring Study

Dow AgroSciences submitted a study entitled, "Surface water monitoring of cyhalofop-butyl in a California rice growing region in 2001," MRID 45573201. Surface water monitoring was conducted weekly on Thursdays from May 24 to August 9, 2001. Application began on May 4, about three weeks before the monitoring began. Samples were collected from the Cross Canal where it enters the Feather River at State Highway 99. Dow states that this sampling site integrates drainage from the five-county area where application of cyhalofop-butyl was allowed under the Section 18 registration (155,000 acres in Hydrologic Catalog Unit number 180201109). According to California Pesticide Use Reports, 788 lbs of cyhalofop-butyl was applied to 2,688 acres of rice in the monitored watershed (Sacramento River) in 2001.

It is difficult to interpret the results of the study. While it is encouraging that no parent or metabolites were detected at 0.5 ppb, the chronic drinking water level of comparison was lower, estimated to be 0.015 ppb in 2002 (HED Aggregate Assessment, 4/10/2002). Additionally, 1) we do not know when paddy water was released in relation to when surface water samples were collected, 2) the one week sampling interval was a long period and could easily miss residues in water, and 3) the environmental chemistry method did not have an independent laboratory validation as required. Control samples were collected from an area where cyhalofop-butyl was not used and fortified with cyhalofop-butyl in the lab. The data tables in the study report are difficult to read but recoveries appear to range from 8-96%, with stored samples yielding lower recoveries. This indicates that a large percentage of residues in the water samples may have been lost due to the analytical method or during storage. The analytical method report indicates a much higher recovery rate with average recoveries ranging from 88 – 107% for the different compounds. Finally, monitoring should begin closer in time to the start of chemical application, rather than the 20-day lag in the study.

Drinking Water Monitoring Study

A drinking water monitoring study was also submitted (MRID 47380601) and is still being reviewed by the Agency. According to the report, approximately 4,250 kg of cyhalofop-butyl was applied in California (Sutter, Yuba, Placer, Glenn, Colusa, Sacramento, and Butte counties) between May 5, 2002 and July 21, 2002 under a Section 18 Specific Exemption. Water samples were collected on a semi-weekly basis from the drinking water facility intakes of Sacramento and West Sacramento facilities from April 30 to July 18, 2002. Cyhalofop-butyl, cyhalofop-acid, cyhalofop-amide, and cyhalofop-diacid residues were not found at the limit of quantitation (0.1 µg/L) in any drinking water samples. Cyhalofop-butyl was detected in one sample near the limit of detection of 0.04 µg/L at the West Sacramento facility.

While it is encouraging that no parent or metabolites were detected at 0.1 ppb, it is difficult to interpret the results of the study because the environmental chemistry method did not have an independent laboratory validation as required. Control samples included matrix spikes (deionized water spiked with cyhalofop-butyl) with recoveries of cyhalofop-butyl ranging from 78-102%. Assuming the method was a valid method and significant loss did not occur with storage and transport, this study indicates that when approximately 4,250 kg of cyhalofop-butyl is applied in the Sacramento Valley area on rice, drinking water exposure to Sacramento

residents getting water from the two facilities monitored will be less than 0.1 µg/L. It does not provide any information about drinking water intakes upstream of the Sacramento and West Sacramento areas or for when applications exceed 4,250 kg in a season.

OPP has no information on the effect of drinking water treatment on cyhalofop-butyl and its degradates. The softening of drinking water will generally result in an increase in pH and could result in hydrolysis of the butyl ester to the acid.

4.1.10 Food Residue Profile

4.1.10.1 Crop Field Trials

(M. Nelson, D267558, 11/13/2001)

Rice grain field trial residues ranged from below the combined LOQ of 0.01 ppm to a maximum of 0.0253 ppm. Of the 42 field trial samples analyzed, 35 of them had residue levels that were below the combined LOQ (0.01 ppm).

The results of storage stability testing for cyhalofop-butyl, cyhalofop-acid, and cyhalofop-diacid can be found in the residue chemistry summary document prepared for rice. The storage stability data are adequate to support the submitted field trial and metabolism studies for cyhalofop-butyl.

4.1.10.2 Confined and Field Accumulation in Rotational Crops

(M. Nelson, D267558, 11/13/2001)

The same cultural practices are followed for rice and wild rice. For this reason, the rotational crops would be the same for the two commodities. The confined rotational crop study using spring wheat, leaf lettuce, and radishes was deemed adequate for the purposes of characterizing the nature of the cyhalofop-butyl residues in rotational crops. HED concluded that the proposed 3-month plantback interval for crops other than rice was adequate. HED further concluded that field rotational crop studies were not required. The proposed label for wild rice specifies a plantback interval of 3 months for crops other than rice. HED's conclusions concerning the rotational crop studies and the plantback interval apply to the current petition for wild rice.

4.1.10.3 Meat, Milk, Poultry, and Eggs

For the purpose of this petition only, the data requirements for magnitude of cyhalofop-butyl residues of concern in eggs, milk, and edible tissues of animals are waived based on low levels of radioactive residues observed from the animal metabolism studies. In the event that tolerances are proposed on additional livestock feed items in the future, the Agency will recalculate the maximum dietary burdens and reassess the need for animal feeding studies and tolerances.

4.1.10.4 Processed Food and Feed

Residues of cyhalofop (cyhalofop-butyl and cyhalofop-acid, determined as the acid equivalent) and cyhalofop-diacid were each less than the method LOQ (<0.010 ppm) in/on rice grain treated with Clincher™ (2.38 lb/gal EC formulation) at 1.40 lb ai/A (5x the maximum proposed single

application rate and 3x the maximum proposed seasonal rate). Following processing of treated rice grain according to simulated commercial practices, residues did not concentrate in bran and polished rice; residues concentrated marginally (1.1-1.2x) in hulls. Based on the results of the current processing study, tolerances for cyhalofop-butyl residues of concern in the processed commodities of rice are not required.

4.1.11 International Residue Limits

No international harmonization issues are associated with this petition, as there are no established or proposed Canadian, Mexican or Codex MRLs for residues of cyhalofop-butyl on the proposed crops rice and wild rice.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Acute Dietary Exposure/Risk

No toxicological endpoint attributable to a single dose of cyhalofop-butyl was identified by the Cyhalofop-butyl Risk Assessment Team; therefore, an acute dietary risk is not a concern.

4.2.2 Chronic Dietary Exposure/Risk

(Chronic Dietary (Food and Drinking Water) Exposure Analysis for the Section 3 Registration Action, D. Dotson, D358391, 01/07/09)

A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analysis was performed to support the Section 3 requests for existing use on rice and the proposed use on wild rice.

A chronic dietary (food and drinking water) exposure and risk assessment was conducted for cyhalofop-butyl using tolerance-level residues, a conservative estimate of residues in drinking water, and 100% crop treated assumptions. Cyhalofop-butyl exposure from the existing use on rice and the proposed use on wild rice results in an estimated risk equivalent to 4.5% of the chronic population adjusted dose (cPAD) for the U.S. population. The most highly exposed population subgroup is all infants (<1 year old), whose estimated risk is 15% of the cPAD.

Table 4.2.2. Summary of Dietary Exposure and Risk for Cyhalofop-butyl (Food and Drinking Water)

Population Subgroup	Acute Dietary		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	N/A		0.000451	4.5	N/A	

Table 4.2.2. Summary of Dietary Exposure and Risk for Cyhalofop-butyl (Food and Drinking Water)						
Population Subgroup	Acute Dietary		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
All Infants (< 1 year old)			0.001473	**15**		
Children 1-2 years old			0.000675	6.7		
Children 3-5 years old			0.000630	6.3		
Children 6-12 years old			0.000435	4.4		
Youth 13-19 years old			0.000328	3.3		
Adults 20-49 years old			0.000422	4.2		
Adults 50+ years old			0.000440	4.4		
Females 13-49 years old			0.000419	4.2		

4.2.3 Cancer Dietary Exposure and Risk

Cyhalofop-butyl is classified as a "Not likely to be Carcinogenic to Humans." Therefore there is no cancer concern for this compound.

5.0 Residential Exposure/Risk Pathway

There are no cyhalofop-butyl containing products registered for use in residential areas and no new use is being proposed at this time. Therefore, a residential exposure assessment is not applicable.

5.1 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents living in close proximity to spraying operations. This situation is particularly the case with aerial application. However, to a lesser extent, spray drift resulting from the ground application of cyhalofop-butyl could also be a potential source of exposure. The Agency has been working with the Spray Drift Task Force (a membership of U.S. pesticide registrants), EPA Regional Offices, 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 database submitted by the Spray Drift Task Force, and is developing a policy on how to apply appropriately 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 risks associated with pesticide application.

6.0 Aggregate Risk Assessments

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

As noted previously, acute risk is not a concern for cyhalofop-butyl. There are also no residential uses; therefore, the chronic aggregate exposure and risk are equivalent to dietary (food and water) exposure and risk, and these are below HED's level of concern. Since there are no residential uses, short- and intermediate-term aggregate risks do not exist. In addition, cancer risks are not a concern due to cyhalofop-buyl being classified as not likely to be carcinogenic to humans.

7.0 Cumulative Risk

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for cyhalofop-butyl and any other substances, and cyhalofop-butyl does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA assumed that cyhalofop-butyl does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposure

(Cyhalofop-Butyl: Occupational Exposure and Risk Assessment for Proposed Use on Wild Rice and Proposed Amended Labeling for Clincher ® SF Herbicide; M. Collantes; D354880; December 2008)

The herbicide, cyhalofop-butyl is a diphenyl ether (aka oxyphenoxy acid esters) herbicide for which a food use on rice has been proposed. Clincher® EC is a postemergence herbicide for the selective control of emerged grass weeds in drill-seeded and water-seeded rice. Cyhalofop-butyl is formulated as Clincher® EC, an emulsifiable concentrate containing 29.6% cyhalofop-butyl as active ingredient (equivalent to 2.38 lbs ai/gal of product).
The proposed use pattern calls for 1-2 postemergence foliar applications of Clincher® EC at 0.24-0.28 lb ai/A per application with a minimum 10-day retreatment interval, and a maximum seasonal rate of 0.46 lb ai/A. Application can be made when rice plants are at the 1-2 leaf growth stage and up to 60 days prior to harvest. This product is applied aerially, and by

groundboom equipment. Based on the number of seasonal applications indicated on these product labels, exposures are expected to be short- and intermediate-term in duration.

8.1 Handler Exposure

Occupational exposure and risk resulting in MOEs greater than or equal to 100 are not of concern to HED. All handler scenarios resulted in MOEs greater than the level of concern (MOEs ≥ 100) at baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks, no respirator), while aerial applicator risks were assessed for enclosed cockpits (engineering controls). No endpoints were selected for the short- or intermediate-term dermal exposure because no toxicity was noted at the limit dose in the 21-day dermal study. Summaries of the short- and intermediate-term inhalation MOEs are provided in **Table 8.1**.

Table 8.1: Short- and Intermediate-term Handler Exposure and Risk for Cyhalofop-butyl

Exposure Scenario (Scenario #)	Mitigation Level	Inhalation Unit Exposure (mg/lb ai)	Crop	Application Rate (lb ai/acre)	Amount Treated (acres/day)	Inhalation Dose [a] (mg/kg/day)	Total MOE[b]
Mixer/loader							
Clincher® EC Groundboom	Baseline	0.0012	Wild rice	0.28	80	0.00038	11,000
			Rice		200	0.00096	4,500
Clincher® EC Aerial			Wild Rice		350	0.0017	2,600
			Rice		1200	0.0058	750
Applicator							
Clincher® EC Groundboom	Baseline	0.00074	Wild Rice	0.28	80	0.00024	18,000
			Rice		200	0.00059	7,300
Clincher® EC Aerial	Engineer Controls	0.000068	Wild Rice		350	0.000095	45,000
			Rice		1200	0.00033	13,000
Flagger							
Clincher® EC	Baseline	0.00035	Rice	0.28	350	0.00049	8,800

a. Short- and Intermediate-term Inhalation Dose (mg/kg/day) = [Rate (lb ai/A) x IAF (100%) x UE (mg /lb ai) x Acres Treated A/day)] / BW (70 kg)

b. Inhalation MOE = NOAEL (4.3 mg/kg/day)/ Total Dose (mg/kg/day)

8.2 Postapplication

Postapplication inhalation exposure potential is anticipated to be negligible as all agricultural activities are conducted outdoors and the vapor pressure for cyhalofop-butyl is 4.0×10^{-7} mmHg. No major postapplication activities that result in significant exposure to cyhalofop-butyl are expected prior to harvesting. Harvesting will likely be done with mechanized equipment. In addition, as no short- or intermediate-term dermal endpoints of concern were selected for cyhalofop-butyl, a quantitative risk assessment for postapplication activities was not required.

8.3 Label Amendment

Based on newly submitted Mode of Action studies on the liver, HED has determined that cyhalofop-butyl is not likely to be carcinogenic to humans. Therefore, the requirement for a closed system while mixing and loading for aerial application and the restriction of limiting aerial treatment to 800 acres on the current label, as a result of the previous cancer classification and Q* value, are no longer required.

8.4 Restricted Reentry Interval

The Toxicity Category for the technical is IV for oral, dermal, and inhalation toxicity, as well as for eye and skin irritation. Cyhalofop-butyl is not a dermal sensitizer. Under the Worker Protection Standard for Agricultural Pesticides, active ingredients classified as acute toxicity categories IV are assigned a 12-hour REI. Based on the acute toxicity of cyhalofop-butyl, the 12 hour restricted-entry interval appearing on the proposed label is in compliance with the Worker Protection Standard (WPS).

9.0 Data Needs and Label Requirements

9.1 Toxicology

As part of the revised 40 CFR Part 158, an immunotoxicity study (OPPTS 870.7800) is required for registration of a pesticide.

9.2 Residue Chemistry None

9.3 Occupational and Residential Exposure None.

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food uses for cyhalofop-butyl are in the table below. Use of the new guideline numbers does not imply that the new guideline protocols were used.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	Yes	Yes
870.1200 Acute Dermal Toxicity	Yes	Yes
870.1300 Acute Inhalation Toxicity	Yes	Yes
870.2400 Primary Eye Irritation	Yes	Yes
870.2500 Primary Dermal Irritation	Yes	Yes
870.2600 Dermal Sensitization	Yes	Yes
870.3100 Oral Subchronic (rodent)	Yes	Yes
870.3150 Oral Subchronic (nonrodent)	Yes	Yes
870.3200 21-Day Dermal	Yes	Yes
870.3250 90-Day Dermal	No	No
870.3465 90-Day Inhalation	No	No
870.3700a Developmental Toxicity (rodent)	Yes	Yes
870.3700b Developmental Toxicity (nonrodent)	Yes	Yes
870.3800 Reproduction	Yes	Yes
870.4100a Chronic Toxicity (rodent)	Yes	Yes
870.4100b Chronic Toxicity (nonrodent)	Yes	Yes
870.4200a Oncogenicity (rat)	Yes	Yes
870.4200b Oncogenicity (mouse)	Yes	Yes
870.4300 Chronic/Oncogenicity	Yes	Yes
870.5100 Mutagenicity—Gene Mutation - bacterial	Yes	Yes
870.5300 Mutagenicity—Gene Mutation - mammalian	Yes	Yes
870.5385 Mutagenicity—Mammalian Bone Marrow Chromosome Aberration Aberrations	Yes	Yes
870.5550 Mutagenicity—Unscheduled DNA Synthesis	No	No
870.6200a Acute Neurotoxicity Screening Battery (rat)	Yes	Yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	Yes	Yes
870.6300 Developmental Neurotoxicity	No	No
870.7485 General Metabolism	Yes	Yes
870.7600 Dermal Penetration	No	No
870.7800 Immunotoxicity	Yes	No
Special Studies for Ocular Effects		
Acute Oral (rat)	No	No
Subchronic Oral (rat)	No	No
Six-month Oral (dog)	No	No

A.2 Toxicity Profile Tables for Cyhalofop-butyl.

Table A.2.1 Acute Toxicity Profile - Test Substance				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute Oral - Rat	45000237	LD50 >5000 mg/kg (limit test)	**Toxicity Category IV**
870.1100	Acute Oral - Mice	45000238	LD50 >5000 mg/kg (limit test)	**Toxicity Category IV**
870.1200	Acute Dermal - Rat	45000240	LD50 >2000 mg/kg (limit test)	**Toxicity Category III**
870.1200	Acute Dermal - Rat	45381901 45000241	LD50 >5000 mg/kg (2.5 x the limit dose)	**Toxicity Category IV**
870.1300	Acute Inhalation - Rat	45000401	LC50 >5.63 mg/L (2.8 x the limit concentration)	**Toxicity Category IV**
870.2400	Primary Eye Irritation - Rabbit	45000403	Minimally irritating	**Toxicity Category IV**
870.2500	Primary Skin Irritation - Rabbit	45000405	Essentially nonirritating	**Toxicity Category IV**
870.2600	Dermal Sensitization - Guinea Pig	45000407	Not a dermal sensitizer	**N/A**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	Subchronic (4 and 13 Week) Feeding - Rat	45000413 (1991) Acceptable/Guideline Main - 0, 3 (males), 10 (females), 25 (males), Satellite - 0, 25, 400 (males), 800 (females), or 1600 mg/kg/day in the feed for 4 weeks.	**NOAEL (male) ≥400 mg/kg/day (HDT)** **NOAEL (female) 400 mg/kg/day** **LOAEL (female) = 800 mg/kg/day (HDT) based on perineal soiling and reduced body weights and body weight gain.** The only short-term effect was perineal staining. Onset was late except in 60% of the 800 mg/kg/day females which had involvement as early as day 16. The only functional observation battery (FOB) finding was perineal soiling at the high-dose in 1/10 males and 6/10 females. In addition to the 13 week study, which included a FOB, a 4 week satellite was used to determine organ weight and microscopic changes in potential target tissues.
870.3100	Subchronic Feeding - Rat	45014705 (1993) Acceptable/Guideline Levels tested: 0, 30, 300, 1000, or 3000 ppm in the feed (0, 1.719, 17.43, 60.5, or 189.5 mg/ kg/day in males; 0, 1.958, 19.64, 65.3, or 199.6 mg/kg/day in females) in Fischer strain.	**NOAEL = 60.5 / 65.3 mg/kg/day, M/F** **LOAEL = 189.5 / 199.6 mg/kg/day, M/F (HDT) based on kidney toxicity (lipofuscin pigment deposition in proximal tubule cells) in both sexes, and possible liver toxicity (hepatocyte eosinophilic granules) in males.** No short-term effects were observed which could be used for a short-term endpoint.
870.3100	Subchronic Feeding - Mice	45000412 (1991) Acceptable/Guideline Levels tested (main): 0, 1 (males), 3, 10, 30, or 100 (females) mg/kg/day in the feed. Levels tested (pilot): 0, 10 (males), 30, 100, or 350 (females) mg/kg/day in the	**NOAEL (male) ≥30 mg/kg/day (HDT)** **NOAEL (female) ≥100 mg/kg/day (HDT)**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		feed.	
870.3100	Subchronic Feeding - Mice	45014706 (1993) Acceptable/Guideline Levels tested: 0, 3, 30, 100, or 300 ppm in the diet (0, 0.4, 3.6, 12.4, or 37.5 mg/kg/day in males; 0, 0.4, 4.3, 14.1, or 41.4 mg/kg/day in females)	**NOAEL (male) ≥37.5 mg/kg/day (HDT)** **NOAEL (female) = 4.3 mg/kg/day** **LOAEL (female) = 14.1 mg/kg/day based on enlarged kidneys (20% absolute and relative) accompanied by swelling of the proximal tubule cells (4/12 mice).** Kidney weights and pathology were normal in males. Compared to controls, absolute and (relative) kidney weight increases in females were 1, 14, 20, and 23% (-1, 12, 20, and 18%); and proximal tubular cell swelling incidences were 0/12, 0/12, 0/12, 4/12, and 6/12 at doses of 0, 3, 30, 100, and 300 ppm, respectively.
870.3150	Subchronic Feeding - Dog	45014707 (main) 45000410 (pilot, palatab.) (1994 Acceptable/Guideline Levels tested: 0, 100, 500, or 2500 ppm (0, 2.91, 14.7, or 75.2 mg/kg/day in males; 0, 3.17, 15.6, or 79.4 mg/kg/day in females)	**NOAEL = 14.7 / 15.6 mg/kg/day, M/F** **LOAEL = 75.2 / 79.4 mg/kg/day, M/F (HDT) based on brown and/or atrophied thymuses, and decreased thymus weight.** MRID 45000410 was a combination 4-week pilot toxicity and a 2 week palatability study. Doses in the palatability study were 250, 500, or 1000 mg/kg/day. At 1000 mg/kg/day, food consumption was dramatically reduced, suggesting decreased palatability of the treated diet.
870.3200	21-Day Dermal - Rat	45000415 (1999) Acceptable/Guideline Levels tested: 0, 10, 100, 1000 mg/kg/day in aqueous 0.5% methylcellulose, 6 hours/day, 5 days/week for 4 weeks. A recovery group was held for a 2 week period.	**Systemic NOAEL ≥1000 mg/kg/day (limit dose)** **Dermal NOAEL ≥1000 mg/kg/day (limit dose)** Increased liver weights and clinical chemistry changes suggestive of liver adaptation were observed during the dosing interval. The reversibility of the clinical chemistry and liver weight effects in the recovery group demonstrates these changes are biological markers of exposure, not toxicity.
870.3700	Gavage Developmental	45014709 (1992)	**Maternal NOAEL =1000 mg/kg/day (limit dose)**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	Toxicity - Rat	Acceptable/Guideline Levels tested: 0, 25, 250, or 1000 mg/kg/day by gavage on gestation days 6-15.	**Developmental NOAEL ≥1000 mg/kg/day (limit dose)**
870.3700	Gavage Developmental Toxicity - Rabbit	45014710 (1994) Acceptable/Guideline Levels tested: 0, 40, 200, or 1000 mg/kg/day by gavage on gestation days 6-18	**Maternal NOAEL = 40 mg/kg/day** **Maternal LOAEL = 200 mg/kg/day based on maternal death (1/18 dams at 200 and 9/18 at 1000 mg/kg/day exhibited hematuria and died or were sacrificed *in extremis* with gross pathology showing cloudy or dark colored kidneys)** **Developmental NOAEL ≥1000 mg/kg/day (limit dose)** .
870.3800	Feeding Reproductive Toxicity - Rat	45000419 (1994) Acceptable/Guideline Levels tested: Dietary levels of 0, 10, 100, or 1000 ppm (F0 males - 0, 0.495-1.049, 4.88-10.68, or 50.0-102.9 mg/kg/day; F1 males - 0, 0.499-1.361, 4.85-13.75, or 51.1-138.7 mg/kg/day; F0 females - 0, 0.695-1.113, 6.75-11.13, or 69.2-113.1 mg/kg/day; F1 females - 0, 0.750-1.430, 7.42-13.96, or 74.8-147.7 mg/kg/day) in Crj:CD (SD) strain.	**Systemic NOAEL (males) = 100 ppm (4.85-13.75 mg/kg/day)** **Systemic LOAEL (males) = 1000 ppm (50.0-138.7 mg/kg/day) based on kidney lesions (slight tubular cell swelling) in F0 and F1 male rats.** **Systemic NOAEL (females) ≥1000 ppm (69.2-147.7 mg/kg/day, HDT)** **Reproductive NOAEL ≥1000 ppm (50.1-138.7 mg/kg/day for males; 69.2-147.7 mg/kg/day for females)** **Offspring NOAEL ≥1000 ppm (50-147.7 mg/kg/day)** No short-term effects were observed which could be used for a short-term endpoint. Acceptable/Guideline
870.4100	Chronic Feeding	45014708	**NOAEL ≥46.7 / 45.9 mg/kg/day; M/F**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	Toxicity - Dog	(1994) Acceptable/Guideline Levels tested: 0, 50, 300, or 1800 ppm in the feed (males- 0, 1.22, 7.59, and 46.7 mg/kg/day; females - 0, 1.29, 7.63, and 45.9 mg/kg/day.	**(HDT)** No short-term effects were observed which could be used for a short-term endpoint.
870.4200	Carcinogenicity Feeding - Mouse (18 months)	45000418 (1994) Unacceptable/Guideline Levels tested: 0, 3, 10, or 100 ppm (0, 0.31, 1.0, and 10.06 mg/kg/day in males; 0, 0.29, 1.0, or 10.28 mg/kg/day in females) in CD-1 strain. Satellite groups were sacrificed at 26 and 52 weeks	**NOAEL = 1.0 mg/kg/day** **LOAEL = 10.06 / 10.28 mg/kg/day, M/F (HDT) based on effects on the kidney including tubular dilatation, chronic glomerulonephritis, and hyaline casts in females, and hyperplasia of the stomach mucosal epithelium in males.** There was no evidence of carcinogenic potential under the conditions of this study. Dosing was too low to elicit frank toxicity and inadequate to assess carcinogenic potential. The high dose of approximately 10 mg/kg/day was based on the endpoint of liver hypertrophy which is an adaptive response. No short-term effects were observed which could be used for a short-term endpoint. .
870.4300	Chronic Feeding Toxicity/Carcinogenicity-Rat	45000417 (1994) Acceptable/Guideline (chronic toxicity) Unacceptable/Guideline (carcinogenicity Levels tested: 0, 3, 6, 24, or 100 ppm (0, 0.1020, 0.2047, 0.823, or 3.44 mg/kg/day) in males; 0, 6, 60, or 600 ppm (0, 0.2451, 2.475, or 24.97 mg/kg/day) in females for 104	**NOAEL = 0.823 mg/kg/day in males and 2.475 mg/kg/day in females** **LOAEL = 3.44 mg/kg/day (HDT in males), 24.97 mg/kg/day (HDT in females) based on the early and increased deposition of the pigments lipofuscin and hemosiderin in the renal proximal tubular cells of both sexes, and renal mineralization in female rats.** There were no treatment-related increases in tumor incidence, compared to controls. **Dosing was too low to elicit frank toxicity and inadequate to assess carcinogenic potential.** No short-term effects were observed which could be used for a short-term endpoint.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		weeks in Fischer strain. Satellite groups were sacrificed at 13, 26, 52, and 78 weeks.	
870.5100	Bacterial Reverse Gene Mutation Test (Ames Assay)	45000421 (1991) Acceptable/Guideline	Negative in Salmonella TA strains and E. coli WP2 uvrA.
870.5300	Gene Mutation in Mouse Lymphoma L5178Y TK Cells	45014711 (1996) Acceptable/Guideline	Negative
870.5375	In Vitro Chromosomal Aberration in Chinese Hamster Lung	45000423 (1991) Acceptable/Guideline	Polyploidy was induced when CHL (V79) cells were treated for 48 hours in the absence of S9, but there was no clastogenic effect on DNA.
870.5395	In Vivo Mammalian Cytogenetics - Micronucleus Assay in Mouse Bone Marrow Cells	45000422 (1991) Acceptable/Guideline	Negative
870.5550	Unscheduled DNA Synthesis in Rat Hepatocytes	45000420 (1991) Acceptable/Guideline	Negative
870.6200	Gavage Acute Neurotoxicity - Rats	45000409 (1998) Acceptable/Guideline Doses: 0, 200, 600 or 2000 by gavage	**NOAEL ≥2000 mg/kg (limit dose) based on the absence of clinical signs, a lack of effects on FOB parameters and motor activity, and the absence of neuropathologic lesions.**

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200	Feeding Subchronic Neurotoxicity - Rats	45000509 (1999) Acceptable/Guideline Levels tested: 0, 2, 20, or 75 (males) / 250 (females) mg/kg/day for 13 weeks.	**NOAEL ≥75/ ≥250 mg/kg/day M/F (HDT) based on the absence of clinical signs, lack of effects on FOB parameters and motor activity, and absence of neuropathologic lesions.** NOTE: The doses tested were based on mild systemic effects (perineal soiling, reduced body weights, and lipofuscin pigment deposition in proximal tubule cells) at similar doses in two subchronic feeding studies in rats, and were too low to elicit toxicity in this study.
870.xxxx [special study]	Pharmacology - Mice and Rabbits - Special Study	45000424 (1992) Acceptable/Non-Guideline Levels tested in mice: 0, 4.88, 19.5, 78.1, 313, 1250, or 5000 mg/kg as a single I.P. dose. Levels tested in rabbits: 0, 313, 1250, 2500 or 5000 mg/kg as single gavage dose	**Mice:** A single I.P. dose of 1250 or 5000 mg/kg was lethal to all male and female mice within 24 hours. Death occurred as early as three hours at 5000 mg/kg and was preceded by behavioral and motor function abnormalities (e.g., alterations in alertness, visual placing, spontaneous activity, motor incoordination, decreased muscle tone, and compromised autonomic reflexes), some of which appeared as early as 30 minutes postdosing. Male and female mice responded similarly. **NOAEL = 78.1 mg/kg** **LOAEL = 313 mg/kg (based on minimal effects including decreased spontaneous activity, minor alterations in muscle tone, and minor changes in autonomic functions such as slight hyperthermia, and slightly decreased respiratory rate).** **LD ≥1250 mg/kg** **Rabbits:** One of three rabbits gavaged at 5000 mg/kg showed decreased spontaneous activity, prostration, decreased muscle tone, compromised autonomic reflexes, and decreased respiratory and heart rate at one day after dosing, and died on Day 4. There were no clinically significant findings in the remaining rabbits of the 5000 mg/kg dose group or any lower dose groups, and no significant effects on EKGs or blood pressure

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			in any dosed rabbits. **NOAEL = 2500 mg/kg** **LOAEL = 5000 mg/kg (based on the response of one of three test subjects including decreased spontaneous activity, prostration, decreased muscle tone, compromised autonomic reflexes, decreased respiratory and heart rate at one day after dosing, and death on day 4).**
870.7485	Absorption, Metabolism, and Excretion - Dog	45000425 (1995 Acceptable/Non-Guideline (Two dogs were used instead of four; and tissue distribution was not measured.) Level tested: Two male beagles were gavaged with [∝-14C]XRD-537 BE and nonlabeled XRD-537 at a dose of 1 mg/kg.	No treatment-related adverse effects were reported. Approximately 50% of a single gavage dose was absorbed over several hours. Blood and plasma radioactivity peaked after 1-2 hours. Clearance from plasma and blood was not especially rapid but nearly complete at 48 hours. Over 168 hours, excretion was 42.5-43.9% in the urine, and 48.6-50.6% in the feces. Tissue distribution was not measured. The test article appears to be metabolized primarily by hydrolysis to R-(+)-2-[4-cyano-2-fluorophenoxy)phenoxy]propanoic acid which was found in both the urine and feces. Several other metabolites were also formed, each representing <5% of the administered dose. No parent compound was found in the urine, and only minimal amounts were detected in the feces.
870.7485	Metabolism and Pharmacokinetics - Rat	45000427 (main) 45000426 (prelim.) 45000528 (stability, homog.) (1995) Acceptable/Guideline	Absorption of gavaged test article was 93-100%, and urinary excretion was the major route of elimination regardless of dose, label position, or gender. Over 168-hours, 84-100% of the radioactivity was eliminated in urine, with 86-90% eliminated within 24 hours. Fecal excretion was <5%. There was no elimination via expired air. Over a 24-hour period, biliary elimination accounted for 1.7 % and 20.1% of the administered dose in males and females, respectively, in the low-dose [α-14C]XRD-537 BE group, and 17.0% (males) and 11.6% (females) of the administered dose in the [β-14C]XRD-537 BE low-dose group.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			The greatest radioactivity levels were found in liver, kidneys, plasma, whole blood, heart, lung, and stomach, with the highest tissue levels being found in the liver and kidney at 2 hours. Most tissue levels accounted for <1% of the administered dose. Due to rapid excretion, tissue/organ levels declined to near detection limits by 24 hours in all dose groups. There was a biphasic pattern for both labels with no substantial differences in pharmacokinetic indices (Cmax, tcmax, t1/2, AUC). Time-to-maximum plasma concentration (tcmax of 0.5 to 4 hrs) and elimination half-times (t1/2 of 1.4 to 7.9 hrs) reflected the relatively rapid absorption. Females had somewhat shorter tcmax and lower Cmax values suggestive of saturated absorption processes. The acid metabolite (R-(+)-2-[4-(4-cyano-2-fluoro-phenoxy)phenoxy]propanoic acid) was the most prominent plasma fraction (~90-94% of the plasma activity for males and ~75-81% for females regardless of dose). No parent compound or other metabolites were detected. The acid metabolite was the most common product in urine and feces–71-87% (urine) and 46-75% (feces) of the activity in those matrices. Levels tested (main study): single low dose (1 mg/kg), single high dose (50 mg/kg), and a 14-day repeated low dose (1 mg/kg/day) using non-labeled XRD-537 BE, and [α-14C] XRD-537 BE or [β-14C] XRD-537 BE by gavage.
870.7600	Dermal Penetration - Rat	45000505 (1998) Acceptable/Non-Guideline (Only one exposure duration (24 hours) was used instead of six. Levels tested: Four	Dermal absorption was ~25-34% for the spray formulation and ~11-16% for the EF-1218 formulation following a 24 hour dermal dosing. Within 48 hours, excretion was >85% in the urine and <1% in the feces, which is consistent with metabolism to water soluble metabolites and subsequent urinary excretion.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		Fischer 344 rats were dermally dosed for 24 hours with 14C-labeled DE-537 n-butyl ester and nonlabeled DE-537 n-butyl ester in two formulations–200 mg/mL test article in EF1218 (Clincher EDC with which DE-537 n-butyl ester is normally formulated) and a spray solution–at 0.005, 1.0, or 1.8 mg/cm^2.	
870.xxxx [special study]	Hepatocellular Proliferation in Rats	45000414 (1991) Acceptable/Non-Guideline	In a subchronic oral toxicity study in rats (MRID 45000413), satellite rats dosed for 4 weeks had hepatocellular hypertrophy and focal necrosis at all dose levels. Although multiple necrotic foci accompanied by inflammatory cells were graded very slight, and were not considered dose-related, this study was performed to explore these findings. An initial dramatic increase in DNA synthesis during the first week of treatment was followed by hepatocellular hypertrophy at subsequent observations. This was the reason for enlarged livers observed in XRD-537nBu-treated rats. Levels tested: 0, 3.0, 25, 100, or 400 mg/kg/day in the diet with sacrifices at 1, 2, 4, and 13 weeks. One week prior to sacrifice, 10 µL BrdU/hour was administered via an ALZET osmotic pump implanted subcutaneously. BrdU is a DNA stain used to quantify hepatocellular proliferation.
870.xxxx [special study]	28-Day Mechanistic Study for Evaluation of Peroxisome Proliferation	46471101 (2004) Acceptable/Non-Guideline	Increased liver weight and hepatocellular hypertrophy at ≥5 mg/kg/day (M&F); ecrosis at ≥50 (M) & 150 (F) mg/kg/day. Increased peroxisomal acyl-CoA oxidase

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	(Mouse)	Doses: 0, 0.5, 5, 50 &150 mg/kg/day	activity ≥5 mg/kg/day (M) and ≥50 mg/kg/day (F). Increases are reversible. Peroxisome volume density in hepatocytes increased ≥0.5 mg/kg/day (M) and ≥5 mg/kg/day (F). Increases are reversible.
870.xxxx [special study]	Evaluation of Activity in a Peroxisome Proliferator Receptor-Alpha Reporter Assay (Mouse)	46471102 (2004) Acceptable/Non-Guideline Doses: 10^{-7}, 10^{-6}, 10^{-5}, $2x10^{-5}$, $5x10^{-5}$, 10^{-4}, $2x10^{-4}$ & $5x10^{-4}$ M; also: positive control activator (WY14643); PPAR-γ specific activator (Ciglitazone); non-activator (TPA)	Cyhalofop-butyl binds to the PPAR-ά receptor and activates a downstream reporter gene. Considered a weak PPAR-ά agonist.
870.xxxx [special study]	Discussion of Mechanistic data in the mouse.	46471103 (2005) Acceptable/Non-Guideline	Discussion of mechanistic data in the mouse in support of a waiver for repeating chronic studies.

A.3 – Rationale for Toxicology Data Requirements.

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
The immunotoxicity study is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

A.4 – Recommended Tolerances for Cyhalofop-butyl.

Appendix IV. Recommended Tolerance Summary for Cyhalofop-Butyl.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Rice, grain	0.03	0.03	Adequate data are available on the representative crop of rice and wild rice.
Rice, wild, grain	0.03		