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

OFFICE OF  
PREVENTION, PESTICIDES, AND  
TOXIC SUBSTANCES

**MEMORANDUM**

DATE: 25-SEP-2001

SUBJECT: PP# 9F06044. **BISPYRIBAC-SODIUM IN/ON RICE. Health Effects**  
**Division (HED) Risk Assessment.** PC Code: 078906. DP Barcode: D276557.  
Case#: 292209. Submission#: S582072.

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from proposed uses of bispyribac-sodium [sodium 2,6-bis[(4,6-dimethoxy-pyrimidin-2-yl)oxy]benzoate] in/on rice. This is the first food use request for bispyribac-sodium.

A summary of the findings and an assessment of human risk resulting from the proposed use of bispyribac-sodium is provided in this document. The risk assessment, the residue chemistry data review, and the dietary exposure risk assessment were provided by Jennifer R. Tyler (RAB1), the hazard characterization by Guruva Reddy (RAB1), the occupational/residential exposure assessment by Mark Dow (RAB1), and the drinking water assessment by Lucy Shanaman and R. David Jones of the Environmental Fate and Effects Division (EFED).

*Recommendation for Tolerances and Registration*

Provided a revised Section B with the modifications specified in Section 8.1 of this risk assessment is submitted and a successful Agency petition method validation (PMV) of the analytical method is reported, the residue chemistry and toxicological databases support the establishment of a conditional registration and permanent tolerances for residues of bispyribac-sodium *per se* in/on the following raw agricultural commodities (RACs):

Rice, grain .....	0.02 ppm
Rice, straw .....	0.02 ppm

**HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following data:**

- OPPTS 860.1300: Storage stability data for the benzene-labeled rice metabolism study.
- OPPTS 860.1480: Poultry feeding study.
- OPPTS 870.3465: 28-Day inhalation toxicity study. The HED Hazard Identification Assessment Review Committee (HIARC) recommended that protocol for the existing 90-day inhalation toxicity study should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.
- OPPTS 870.5300: *In vitro* mammalian cell gene mutation assay.

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## 1.0 EXECUTIVE SUMMARY

Bispyribac-sodium is a broad-spectrum, postemergence contact herbicide which controls grass and broadleaf weeds. The mode of action is the inhibition of the plant enzyme acetolactate synthetase (ALS). As this is the first petition for use of bispyribac-sodium in the United States, there are currently no tolerances, uses, or exemptions for this chemical. There are currently no registered or proposed residential uses of bispyribac-sodium.

Valent U.S.A. Corporation has submitted a registration application for use of bispyribac-sodium on rice, along with a petition to establish permanent tolerances on rice grain and straw. Concurrently, the petitioner is requesting Section 3 registration of Regiment™ Herbicide, a single end-use product containing 80% bispyribac-sodium as the active ingredient (a.i.). Regiment™ is a wettable powder (WP) formulation packaged in water-soluble bags.

### *Hazard Assessment*

The toxicological database for bispyribac-sodium is essentially complete with the exception of a 28-day inhalation toxicity study and an *in vitro* mammalian cell gene mutation assay. The acute toxicity battery of tests shows that bispyribac-sodium has a low acute toxicity profile (Categories III & IV) and is not a dermal sensitizer. The liver and bile duct were identified as the target organs in the subchronic and chronic toxicity studies in rats, mice, and dogs, and the reproduction toxicity study in rats. Males appear to be slightly more sensitive than females. Repeated dermal applications at the limit dose did not elicit systemic toxicity or dermal irritation. Bispyribac-sodium was negative for carcinogenicity in feeding studies in rats and mice and was classified as a “**not likely human carcinogen**” by the HIARC. Bispyribac-sodium was negative for developmental and offspring effects in both the developmental studies in rats and rabbits and the reproduction study in rats. The battery of mutagenicity studies on the parent and three major metabolites were all negative. Neurotoxicity data are not available nor required as the chemical is not a cholinesterase inhibitor and has shown no indications of central or peripheral nervous system effects in any other studies and does not appear to be structurally related to any other chemical that causes adverse nervous system effects. In the rat metabolism study, pretreatment, dose level, sex and position of radiolabel had little effect on the absorption, distribution, elimination and metabolism of bispyribac-sodium. Bispyribac-sodium was readily absorbed by male and female rats following intravenous or oral dosing. Most of the administered dose (>43%) was excreted in feces within 48 hours and elimination was essentially complete within 5 days.

### *Dose Response Assessment and FQPA Decision*

The HED HIARC met on July 26, 2001 to review the toxicological database for bispyribac-sodium with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to bispyribac-Sodium was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

The FQPA Safety Factor Committee (SFC) recommended that the FQPA safety factor to account for enhanced sensitivity of infants and children to be used in human health risk assessments (as required by FQPA of August 3, 1996) be reduced to 1x for the general U.S. Population and all population subgroups and scenarios in assessing the risk posed by this chemical. The acute and chronic population adjusted doses (aPAD and cPAD, respectively) are modifications of the acute and chronic RfDs to include the FQPA SF. The acute or chronic PAD is equal to the acute or chronic RfD divided by the FQPA SF. Consequently, the chronic RfD and cPAD values are equivalent (0.1 mg/kg/day). This decision was based on the following: 1) there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* or postnatal exposure; 2) a developmental neurotoxicity study (DNT) with bispyribac-sodium is not required; 3) the dietary food and drinking water exposure assessments will not underestimate the potential exposures for infants and children; and 4) there are currently no registered or proposed residential (non-occupational) uses of bispyribac-sodium.

No appropriate endpoint was available to quantitate risk to the general U.S. population or to females 13-50 years old from a single-dose administration of bispyribac-sodium; therefore, there is no acute RfD or aPAD. The short-term incidental oral and inhalation endpoints were selected from a rabbit developmental study in combination with a range finding study. The no-observed-adverse-effect-level (NOAEL) of 100 mg/kg/day was based on lethargy, diarrhea, and decreased body weight gain observed at the lowest-observed-adverse-effect-level (LOAEL) of 300 mg/kg/day in the range-finding study. In addition, no developmental toxicity was seen. The intermediate-term incidental oral and inhalation endpoints were selected from a subchronic oral toxicity dog study. The NOAEL for this study was 100 mg/kg/day and was based on increased salivation and slight proliferation of the intrahepatic bile duct in both sexes observed at 600 mg/kg/day. The HIARC did not identify hazards for dermal risk assessment for any durations since no systemic toxicity was observed at the limit dose (1000 mg/kg) via dermal route in a 21-day rat dermal toxicity study. The chronic dietary and long-term inhalation endpoints were selected from the chronic dog study. The NOAEL of 10 mg/kg/day was based on dose-related increase in hyperplasia of the intrahepatic bile ducts in both sexes and granulation of the liver in females observed at the LOAEL of 100 mg/kg/day. The chronic RfD is 0.1 mg/kg/day and the cPAD is 0.1 mg/kg/day. In accordance with the Draft Carcinogenicity Risk Assessment Guideline (July 1999) the HIARC classified bispyribac-sodium as a "not likely human carcinogen" based on the lack of evidence of carcinogenicity in rats and mice. Therefore, a cancer risk assessment is not required. Because an oral study was selected for all durations of inhalation exposure, a 100% inhalation absorption factor was used in the route-to-route extrapolation.

### *Occupational Exposure Estimates*

Based on the proposed use patterns, short-term inhalation exposures are expected for commercial and private (farmers treating their own crops) mixer/loaders and applicators. HED believes that the most highly exposed pesticide handler activities are likely to be a mixer/loader supporting aerial application operations and an applicator using ground boom apparatus. Private (i.e., grower) applicators may perform both functions, that is, mix, load and apply the material. HED Science Advisory Council for Exposure draft Policy (29 March 2000) "Combining Mixer/Loader/Applicator Data" directs that although the same individual may perform both

tasks, they shall be assessed separately. Since no chemical-specific data are available to assess potential exposure to workers, the exposure and risk assessment presented in this document are based on the Pesticide Handler Exposure Database Version 1.1 (PHED, Surrogate Exposure Guide, August 1998). The proposed label directs pesticide handlers to wear long-sleeved shirt, long pants, waterproof gloves, and shoes and socks. HED's level of concern for occupational exposures to bispyribac-sodium is a Margin of Exposures (MOEs) below 100. The MOEs for pesticide handlers are greater than  $5.2 \times 10^5$ , and, therefore, do not exceed HED's level of concern.

### *Dietary Exposure Estimates*

A chronic dietary exposure analysis was conducted using the Dietary Exposure Evaluation Model (DEEM™, ver 7.73), which utilizes consumption data from the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). Acute and cancer dietary exposure analyses were not conducted since no acute doses or endpoints were selected for the general U.S. population (including infants and children) or the females 13-50 years old population subgroup and bispyribac-sodium was classified as not a carcinogen, respectively. All bispyribac-sodium residues were <LOD (<0.005 ppm) in the rice grain crop field trials and there was no concentration of residues in the processing study. There is no reasonable expectation of finding finite bispyribac-sodium residues of concern in milk, meat, fat, or meat byproducts of ruminants as a result of the proposed uses on rice [Category 180.6(a)(3)]. No poultry feeding study was submitted. However, based on the results of the poultry feeding study and the calculated poultry maximum theoretical dietary burden (MTDB), dietary exposure to bispyribac-sodium residues in poultry commodities is expected to be minimal. The need for poultry tolerances will be determined upon submission of an adequate poultry feeding study. A Tier 1 chronic dietary exposure analysis for bispyribac-sodium was performed for the general U.S. population and all population subgroups, using proposed tolerance level residues and 100% crop treated (CT) information for all rice commodities. For chronic dietary risk estimates, HED's level of concern is >100% cPAD. The chronic exposure estimates for the general U.S. population and all population subgroups accounted for <1% of the cPAD, and, therefore, do not exceed HED's level of concern.

### *Drinking Water*

Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of bispyribac-sodium levels in surface and ground water were made using models. The estimated environmental concentration (EEC) for groundwater [using SCI-GROW (Screening Concentration in Ground Water) model] was 0.0072 ppb. Because OPP currently has no official model for estimating EECs in surface water due to rice culture, a screening calculation method was developed; therefore, the EECs are provisional only. Estimates were made for each of the three major rice growing regions in the United States: the Gulf Coast of Louisiana and Texas, the Mississippi Valley including parts of northern Louisiana, Mississippi, Arkansas, and southern Missouri, and California in the Sacramento River Basin. The Gulf Coast estimate (the maximum estimate of the three growing regions) of 0.317 ppb was the reported surface water EEC. This EEC is a point estimate representing only peak or maximum concentrations. However, as no attempt has been made to determine average concentrations resulting in chronic exposure, and the concentration estimate should be less than

the peak concentration estimate, an EEC of 0.317 ppb was used for the chronic risk assessment. All the EEC values are less than the lowest drinking water level of comparison (DWLOC) value of 1000 ppb (specifically for both the "all infants (<1 year old)," and "children 1-6 years old" subpopulations) determined for the chronic scenario, and therefore do not exceed HED's level of concern.

### *Exposure Scenarios and Risk Conclusions*

For the proposed use on rice, human health risk assessments were conducted for the following scenarios: chronic dietary exposure (food only), aggregate chronic exposure (food and water), and short-term occupational exposure. Other scenarios were not evaluated for bispyribac-sodium because an acute dietary endpoint was not selected, there are no registered or proposed residential uses, bispyribac-sodium is not carcinogenic, and intermediate- and long-term occupational exposures are not expected. **All exposure estimates associated with the proposed use of bispyribac-sodium do not exceed HED's level of concern for the general U.S. population or any population subgroups.**

### *Recommendation for Tolerances and Registration*

Provided a revised Section B with the modifications specified in Section 8.1 of this risk assessment is submitted and a successful Agency petition method validation (PMV) of the analytical method is reported, the residue chemistry and toxicological databases support the establishment of a conditional registration and permanent tolerances for residues of bispyribac-sodium *per se* in/on the following RACs:

Rice, grain .....	0.02 ppm
Rice, straw .....	0.02 ppm

**HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following data:**

- OPPTS 860.1300: Storage stability data for the benzene-labeled rice metabolism study.
- OPPTS 860.1480: Poultry feeding study.
- OPPTS 870.3465: 28-Day inhalation toxicity study. The HIARC recommended that protocol for the existing 90-day inhalation toxicity study should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.
- OPPTS 870.5300: *In vitro* mammalian cell gene mutation assay.

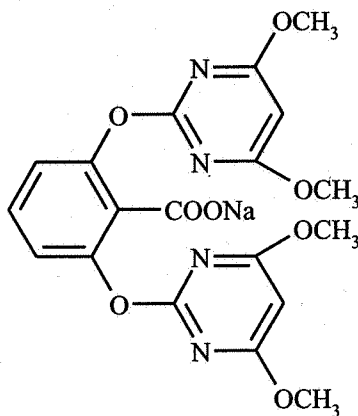


## 2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

### 2.1 Identification of Active Ingredient

- Chemical Name: Sodium 2,6-bis[(4,6-dimethoxypyrimidin-2-yl)oxy] benzoate
- Common Name: Bispyribac-sodium
- Chemical Class: Pyrimidinyloxybenzoic acid herbicides (bispyribac, pyriminobac)
- Chemical Type: Herbicide
- Trade Names: Regiment 80 S
- Mode of Action: Inhibition of the plant enzyme ALS
- PC Code Number: 078906
- CAS Registry No.: 125401-92-5
- Empirical Formula:  $C_{19}H_{17}N_4O_8Na$
- Molecular Weight: 452.36 g/mol

### 2.2 Structural Formula



### 2.3 Physical and Chemical Properties

The following data for bispyribac-sodium were taken from the product chemistry review conducted by RD (Memo, S. Malik, 4/26/01; D267318) (note that all property values are given at 25°C unless noted otherwise):

- Appearance: White, solid granular powder
- Vapor Pressure:  $3.79 \times 10^{-11}$  mmHg
- Water Solubility: 6.75 g/100 mL
- Partition Coefficient (Octanol/Water):  $K_{ow} = 0.0932$ ;  $\log K_{ow} = -1.03$  (pH 6.18)
- Melting Point Range: 223-224°C (decomposed)
- Relative Density: 1.29 g/ml at 20°C

Bispyribac-sodium is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal.

### 3.0 HAZARD CHARACTERIZATION

The existing toxicological database for bispyribac-sodium submitted in support of PP#9F06044 was reviewed by HED (Memo, G. Reddy, 9/18/01; D277168). The HIARC met on 7/26/01 to review the toxicological database for bispyribac-sodium with regard to the acute and chronic RfDs and the toxicological endpoint selection for use as appropriate in occupational/ residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to bispyribac-sodium was also evaluated as required by the FQPA of 1996 (Memo, G. Reddy, 8/2/01; HED DOC. NO. 014647). The HIARC determined that the toxicological database supports the conditional registration of the use of bispyribac-sodium on rice and the establishment of permanent tolerances for residues of bispyribac-sodium *per se* in/on rice RACs. However, the following 2 data gaps must be resolved prior to granting permanent registration. A 28-day rat inhalation study was requested by the HIARC for further characterization of inhalation exposure risk assessment. Due to the potential for inhalation exposure, there is concern for toxicity by inhalation route. The protocol for the existing 90-day inhalation toxicity study (OPPTS 870.3465) should be followed with the exposure (treatment) ending after 28 days, instead of 90 days. In addition, *in vitro* mammalian cell gene mutation assay is a data gap (OPPTS 870.5300).

#### 3.1 Hazard Profile

Bispyribac-sodium is an herbicide for postemergence treatment on rice. The herbicidal activity of bispyribac-sodium is due to inhibition of the plant enzyme ALS. The toxicological database for bispyribac-sodium is essentially complete with the exception of a 28-day inhalation toxicity study and an *in vitro* mammalian cell gene mutation assay. The acute toxicity battery of tests shows that bispyribac-sodium has a low acute toxicity profile (Categories III & IV) and is not a dermal sensitizer. The liver and bile duct were identified as the target organs in the subchronic and chronic toxicity studies in rats, mice and dogs and the reproduction toxicity study in rats. Males appear to be slightly more sensitive than females. Repeated dermal applications at the limit dose did not elicit systemic toxicity or dermal irritation.

Bispyribac-sodium is negative for carcinogenicity in feeding studies in rats and mice and was classified as a “**not likely human carcinogen**” by the HIARC. Bispyribac-sodium was negative for developmental and offspring effects in both the developmental studies in rats and rabbits and in the reproduction study in rats. The battery of mutagenicity studies on the parent and three major metabolites were all negative. Neurotoxicity data are not available nor required as the chemical is not a cholinesterase inhibitor and has shown no indications of central or peripheral nervous system effects in any other studies and does not appear to be structurally related to any other chemical that causes adverse nervous system effects.

In the rat metabolism study, pretreatment, dose level, sex and position of radiolabel had little effect on the absorption, distribution, elimination and metabolism. It was readily absorbed by male and female rats following intravenous or oral dosing. The total recovery of the administered radioactivity was 95.8 - 101.6% for all treatment groups. Most of the dose (> 43%) of the administered dose was excreted in feces within 48 hours and elimination was essentially

complete within 5 days. Less than 2% of the administered dose remained in the carcass and tissues and < 0.1% of the dose was recovered in air. The parent and five metabolites were identified in the excreta of male and females following administration of [<sup>14</sup>C-Py]-bispyribac-sodium. The parent and three metabolites were identified following administration of [<sup>14</sup>C-Bn]-bispyribac-sodium.

**Table 1. Acute Toxicity Data on Bispyribac-sodium Technical.**

Guideline No./Study Type	MRID #s	Results	Toxicity Category
870.1100 Acute Oral- Rat	44889127	LD <sub>50</sub> = 4111 (male), 2365 (female), 3565 (combined) mg/kg	III
870.1200 Acute Dermal- Rabbit	44889128	LD <sub>50</sub> > 2000 mg/kg	III
870.1300 Acute Inhalation- Rat	44889130	LC <sub>50</sub> > 4.48 mg/L	IV
870.2400 Primary Eye Irritation- Rabbit	44929911 44929912	Moderate irritant (unwashed) Not an irritant (washed)	III IV
870.2500 Primary Skin Irritation- Rabbit	44929913	Not an irritant	IV
870.2600 Dermal Sensitization	44929914	Not a sensitizer	NA <sup>1</sup>

1. NA = Not Applicable

**Table 2. Toxicity Profile of Bispyribac-sodium Technical.**

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents (rat)	44929916 (1991) <b>Acceptable/guideline</b> 0, 100, 1000, 10,000 or 20,000 ppm M : 0, 8.1, 79.7, 790.8, or 1582.5 mg/kg/day F: 0, 7.2, 71.9, 724.0, or 1456.5 mg/kg/day	NOAEL = 71.9/79.9 mg/kg/day (M/F) LOAEL = 724.0/790.8 mg/kg/day (M/F), based on decreased body wt. gain, increased absolute and relative liver wts., increased alkaline phosphatase and gamma-GTP, and increased incidence of grossly dilated bile duct lumen in males, and microscopic lesions in the liver, biliary system and urinary bladder in both sexes.
870.3100 90-Day oral toxicity rodents (mouse)	44929917 (1991) <b>Acceptable/guideline</b> 0, 35, 350, 3500, or 7000 ppm M: 0, 6.8, 68.6, 699.1 or 1478.9 mg/kg/day F: 0, 8.0, 79.0, 806.1 or 1590.5 mg/kg/day	NOAEL = 68.6/79.0 mg/kg/day (M/F) LOAEL = 699.1/806.1 mg/kg/day (M/F), based on liver cell swelling and slight liver cell granulation in females.

<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
870.3150 90-Day oral toxicity in nonrodents (dog)	44889132 (1992) <b>Acceptable/guideline</b> M & F: 0, 30, 100, or 600 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 600 mg/kg/day (M/F), based on increased salivation and slight proliferation of intrahepatic bile duct.
870.3200 21/28-Day dermal toxicity (rat)	44889133 (1996) <b>Acceptable/guideline</b> M & F: 0, 10, 100, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day (M/F) LOAEL > 1000 mg/kg/day (M/F). No systemic toxicity or dermal irritation noted
870.3250 90-Day dermal toxicity	NA <sup>1</sup>	NA
870.3465 90-Day inhalation toxicity	NA	NA
870.3700a Prenatal developmental in rodents (rat)	44929921 (1991) <b>Acceptable/guideline</b> F: 0, 100, 300, or 1000 mg/kg/day	<b>Maternal</b> NOAEL = 1000 mg/kg/day LOAEL > = 1000 mg/kg/day <b>Developmental</b> NOAEL = 1000 mg/kg/day LOAEL > 1000 mg/kg/day
870.3700b Prenatal developmental in nonrodents (rabbit)	44889201 (1992) 44889136 (1990) <b>Acceptable/guideline</b> F: 0, 30, 100, 300 or 500 Range-finding F: 0, 75, 150, 300, or 500	<b>Maternal</b> NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day, based on lethargy, diarrhea, and decreased body weight gain in the range-finding study <b>Developmental</b> NOAEL = 300 mg/kg/day LOAEL was not established
870.3800 Reproduction and fertility effects (rats)	44929923 (1994) <b>Acceptable/guideline</b> 0, 20, 1,000, or 10,000 ppm M: 0, 1.5, 75.7, or 759.0 mg/kg/day F: 0, 1.72, 86.3, or 874.0 mg/kg/day	<b>Parental/Systemic</b> NOAEL = 1.5 mg/kg/day LOAEL = 75.7 mg/kg/day (M/F), based on trace to mild choledochus <b>Reproductive</b> NOAEL = 759.0 mg/kg/day LOAEL >759 mg/kg/day <b>Offspring</b> NOAEL = 75.7 mg/kg/day LOAEL = 759 mg/kg/day (M/F), based on decreased body weights, body weight gains, and liver weights, and increased incidence of consolidation and circumscribed areas in the liver
870.4300 Combined chronic toxicity/carcinogeni city rodents (rat)	44929924 (1995) <b>Acceptable/guideline</b> M: 0, 20, 200, 3500, or 7000 ppm (0, 1.1, 10.9, 194.5, or 404.5 mg/kg/day, respectively) F: 0, 20, 200, 5000, or 10,000 ppm (0, 1.4, 13.8, 352.2, or 714.9 mg/kg/day, respectively)	NOAEL = 10.9 mg/kg/day LOAEL = 194.5 mg/kg/day (M), based on macroscopic (yellowish liver, dilated choledochus lumen), microscopic (cellular infiltration, vacuolic changes in the bile ducts), and clinical signs (moribundity, wasting, piloerection, subnormal temperature, and decreased spontaneous motor activity).  <b>No evidence of carcinogenicity</b>

<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
870.4100b Chronic toxicity dogs	44889134 (1998) <b>Acceptable/guideline</b> M & F: 0, 10, 100, or 750 mg/kg/day	NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day (M/F), based on dose-related increase in intrahepatic bile duct hyperplasia and liver granulation in females
870.4300 Carcinogenicity mice	44929920 (1995) <b>Acceptable/guideline</b> 0, 10, 100, 2,500, or 5,000 ppm M: 0, 1.4, 14.1, 353.0, 728.9 mg/kg/day F: 0, 1.7, 17.4, 447.8, or 902.9 mg/kg/day	NOAEL = 14.1/17.4 (M/F) mg/kg/day LOAEL = 353.0/447.8 mg/kg/day (M/F), based on decreased body weight gain, and food efficiency, and increased incidence of microscopic lesions in the liver and gall bladder (M)  <b>No evidence of carcinogenicity</b>
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44889210 (1990) <b>Acceptable/guideline</b> 0, 333, 667, 1000, 3330, 6670, or 10000 µg/plate	There was <i>no evidence</i> of induced mutant colonies over background
Cytogenetics 870.5375 <i>in vitro</i> mammalian cytogenetic assay	44889208 (1990) <b>Acceptable/guideline</b> 0, 250, 500, 750, 1000, 1500, 2000, 3000, or 4000 µg/ml w/o S9 0, 500, 1250, 2500, 3750, or 5000-5010 µg/ml w/ S9	Not clastogenic with or without S9 activation, at any dose tested
Other Effects 870.5395 <i>in vivo</i> mammalian cytogenetic assay	44889211 (1991) <b>Acceptable/guideline</b> 0, 1250, 2500, or 5000 mg/kg	Did not induce micronucleated polychromatic erythrocytes (PMCEs) in bone marrow at any dose
Other Genotoxic Effects 870.5500 bacterial DNA damage and repair test	44929925 (1997) <b>Acceptable/guideline</b> 0, 50, 150, 500, 1500, or 5000 µg/ml	No zones of inhibition and the differential killing index suggesting potential DNA damage
Other Genotoxic Effects 870.5550 UDS synthesis in mammalian cell culture	44889209 (1990) <b>Acceptable/guideline</b> 0, 0.5 to 5000 µg/ml	Did not induce UDS at any dose
870.6200a Acute neurotoxicity screening battery	NA	NA

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.6200b Subchronic neurotoxicity screening battery	NA	NA
870.6300 Developmental neurotoxicity	NA	NA
870.7485 Metabolism and pharmacokinetics (rat)	44889216 (1993) 44889213 (1991) 44889214 (1991) 44889215 (1994) <b>Acceptable/guideline</b> M & F: 30 or 600 mg/kg single oral dose, -single gavage dose of 30 mg/kg for 14 days followed by labeled 30 mg/kg, -single IV dose of 30 mg/kg, -in bile duct cannulated, single dose of 10 or 100 mg/kg	A series of rat metabolism studies with [ <sup>14</sup> Cpy]-bispyribac-sodium and [ <sup>14</sup> C-Bn]-bispyribac-sodium indicated that pretreatment, dose level, sex and position of the radiolabel made little effect on the absorption, distribution, elimination and metabolism. It was readily absorbed by male and female rats following intravenous or oral dosing. The total recovery of the administered radioactivity was 95.8 - 101.6% for all treatment groups. Most of the dose (> 43%) of the administered dose was excreted in feces within 48 hours and essentially complete within 5 days. Less than 2% of the administered dose remained in the carcass and tissues and < 0.1% of the dose was recovered in air. Parent and 5 metabolites were identified in the excreta of male and females following administered [ <sup>14</sup> Cpy]-bispyribac-sodium and parent and 3 metabolites identified with [ <sup>14</sup> C-Bn]-bispyribac-sodium administration. The parent compound, bispyribac-sodium, was the major component identified in the feces (37 - 69% of the dose) and urine (5 - 41% of the dose), in both sexes. Metabolites identified in the excreta constituted 8.3 - 14.6% and unknown metabolites constituted 0.7 - 5.2% of the dose.
870.7600 Dermal penetration	NA	NA
Non-guideline - mice serum bile acids	44929929 (1995) <b>Acceptable/nonguideline</b> 0, or 7000 ppm equivalent to 0 or 1050 mg/kg/day in males	Bile acids increased 115% and slight cecal enlargement in 9/10 treated mice
Non-guideline - mice reversibility	44929930 (1994) <b>Unacceptable</b> 0, 100, or 5000 ppm M: 0, 15.3, or 854.1 mg/kg/day F: 0, 19.6, or 1025.9 mg/kg/day	Bispyribac-sodium was associated with liver lesions, bile duct hyperplasia and dilated gall bladders in subchronic and oncogenicity studies were not replicated in this reversibility study

<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
Non-guideline - rat serum bile acids	44979001 (1995) <b>Acceptable/nonguideline</b> 0, or 20,000 ppm equivalent to 0, or 1792 mg/kg/day in males	Total bile acids increased 1072% (12-fold). The concentration of glycocholic acid, taurocholic acid, deoxycholic acid increased 2127%, 2991% and 138%, respectively, where as chenodeoxy cholic acid levels were similar to controls. Hyodeoxycholic acid was reduced from 34.0% to 3.3 of the total bile acids. Treatment altered the degree of conjugation; hyodeoxycholic acid increased 84% and deoxycholic acid increased 1133%.
Non-guideline - rat reversibility	44979002 (1994) <b>Acceptable/nonguideline</b> M: 0, 200, or 7000 ppm (0, 12.3, or 446.8 mg/kg/day) F: 0, 200, or 10000 ppm (0, 13.8, or 724.2 mg/kg/day)	Bispyribac-sodium was associated with urinary bladder epithelial hyperplasia in subchronic study and bile duct hyperplasia, enlarged bile ducts, and liver cell hypertrophy and fibrosis in chronic study. Upon removal of bispyribac-sodium from the diet, complete recovery in liver enzymes, food consumption, food efficiency, body weights were observed. Muscular hypertrophy of choledocus was still evident. The study did not duplicate urinary bladder lesions noted in the subchronic study.
<b>Metabolites</b>		
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44889203 (1991) <b>Acceptable/guideline</b> 0, 66.7, 100, 333, 667, 1000, 3330, or 6670 µg/plate	DesMe-2023 did not induce mutant colonies over background
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44889204 (1995) <b>Acceptable/guideline</b> 0, 50, 158, 500, 1580, or 5000 µg/plate	2,4-dihydroxy-6-mehtoxy pyrimidine did not induce mutant colonies over background
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44889205 (1995) <b>Acceptable/guideline</b> 0, 50, 158, 500, 1580, or 5000 µg/plate	KIH-2023-M-8-Na did not induce mutant colonies over background
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44889206 (1995) <b>Acceptable/guideline</b> 0, 50, 158, 500, 1580, or 5000 µg/plate	KIH-2023-M-9-Na did not induce mutant colonies over background
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44889207 (1991) <b>Acceptable/guideline</b> 0, 100, 333, 667, 1000, 3330, 6670, or 10,000 µg/plate	BIX-180 did not induce mutant colonies over background

<b>Guideline No./ Study Type</b>	<b>MRID No. (year)/ Classification /Doses</b>	<b>Results</b>
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44889212 (1991) <b>Acceptable/guideline</b>  0, 100, 333, 667, 1000, 3330, or 5000 µg/plate	Me <sub>2</sub> BA did not induce mutant colonies over background
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44929926 (1992) <b>Acceptable/guideline</b>  0, 8, 40, 200, 312.5, 625, 1000, 1250, 2500, or 5000 µg/plate	KIH-2023-I-1 did not induce mutant colonies over background
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44929927 (1995) <b>Acceptable/guideline</b>  0, 50, 150, 500, 1500, or 5000 µg/plate	KIH-2023-I-2 did not induce mutant colonies over background
Gene Mutation 870.5100 reverse gene mutation assay in bacteria	44929928 (1995) <b>Acceptable/guideline</b>  0, 50, 150, 500, 1500, or 5000 µg/plate	KIH-2023-I-4 did not induce mutant colonies over background

1. NA = Not Applicable

### 3.2 FQPA Considerations

The FQPA SFC recommended that the FQPA safety factor to account for enhanced sensitivity of infants and children to be used in human health risk assessments (as required by FQPA of August 3, 1996) be reduced to 1x for the general U.S. Population and all population subgroups and scenarios in assessing the risk posed by this chemical (HED Document Number 014648, B. Tarplee, 8/14/01). This decision was based on the following: 1) there is no indication of quantitative or qualitative increased susceptibility of rats or rabbits to *in utero* or postnatal exposure; 2) a DNT with bispyribac-sodium is not required; 3) the dietary food and drinking water exposure assessments will not underestimate the potential exposures for infants and children; and 4) there are currently no registered or proposed residential (non-occupational) uses of bispyribac-sodium.

### 3.3 Dose-Response Assessment

*Acute Dietary Endpoint:* No appropriate endpoint was available to quantitate risk to the general U.S. population or to females 13-50 years old from a single-dose administration of bispyribac-sodium.



*Chronic Dietary Endpoint:* The chronic dog study was used to select the endpoint for establishing the chronic RfD of 0.1 mg/kg/day. The standard 100x uncertainty factor (UF) was applied to account for interspecies extrapolation and intraspecies variation. The NOAEL of 10 mg/kg/day was based on dose-related increase in hyperplasia of the intrahepatic bile ducts in both sexes and granulation of liver in females observed at a LOAEL of 100 mg/kg/day. The FQPA SFC determined that an FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Thus, the cPAD is 0.1 mg/kg/day. The same effects (mild choledochus and liver consolidation) were seen in the parental and offspring in a 2-generation reproduction study. The reproduction study in rats was not selected for this risk assessment because of the dose spread between the LOAEL and NOAEL (75.7 mg/kg/day and 1.5 mg/kg/day), as compared to the chosen study (75 fold vs 10 fold, respectively).

*Carcinogenicity:* In accordance with the Draft Carcinogenicity Risk Assessment Guideline (July 1999) the HIARC classified bispyribac-sodium as a "not likely human carcinogen" based on the lack of evidence of carcinogenicity in rats and mice; therefore, a cancer risk assessment is not required.

*Short-Term Incidental Oral Endpoint:* A short-term incidental oral endpoint was selected from a rabbit developmental study in combination with a range finding study. The maternal NOAEL of 100 mg/kg/day was based on lethargy, diarrhea and decreased body weight gain observed at 300 mg/kg/day in a range-finding study. The endpoint (systemic toxicity) is appropriate for the population (infants and children) and duration of exposure.

*Intermediate-Term Incidental Oral Endpoint:* An intermediate-term incidental oral endpoint was selected from a subchronic oral toxicity dog study. The NOAEL of 100 mg/kg/day was based on increased salivation and slight proliferation of intrahepatic bile duct in both sexes at 600 mg/kg/day. This endpoint was seen consistently between the 90-day dog and the 1-year dog and it is appropriate for this exposure period and the population (infants and children) of concern. This study was selected because the dose spread (LOAELs and NOAELs) in the mouse and rat study is wide. The NOAELs were 68.6, 100 and 72 mg/kg/day for mouse, dog and rat respectively. The LOAELs were observed at 699.1, 600 and 724 mg/kg/day in mouse dog and rat respectively. The LOAEL (600 mg/kg/day) in selected study is lower than the LOAELs in subchronic rat (724 mg/kg/day) and mouse (699.9 mg/kg/day) studies.

*Dermal Endpoint:* The HIARC did not identify hazards for dermal risk assessment for any durations since no systemic toxicity was observed at the limit dose (1000 mg/kg) via dermal route in a 21-day rat dermal toxicity study. In addition no maternal developmental toxicity was seen in the rat. Further, based on the physical and chemical properties (large molecular weight = 452.36, and  $\log k_{ow} = 0.092$ ), this compound is not likely to be significantly absorbed through the skin.

*Short-Term Inhalation Endpoint:* A short-term inhalation endpoint was selected from a rabbit developmental study in combination with a range finding study. The maternal NOAEL of 100 mg/kg/day was based on lethargy, diarrhea and decreased body weight gain observed at 300 mg/kg/day in a range-finding study. An oral study was selected since no appropriate inhalation study is available in the database. A 100% inhalation factor should be used to convert to an oral

equivalent dose. This dose/endpoint is appropriate for short-term exposure risk assessment.

*Intermediate-Term Inhalation Endpoint:* An intermediate-term inhalation endpoint selected from a subchronic oral toxicity dog study. The NOAEL of 100 mg/kg/day was based on increased salivation and slight proliferation of intrahepatic bile duct in both sexes seen at 600 mg/kg/day. This endpoint was seen consistently between the 90-day dog and the 1-year dog. An oral study was selected since no appropriate inhalation study is available in the database. A 100% inhalation factor should be used to convert to an oral equivalent dose. This dose/endpoint is appropriate for intermediate-term exposure risk assessment since the treatment period extends into the exposure period of concern (1-6 months). This study was selected because the dose spread (LOAELs and NOAELs) in the mouse and rat study is wide. The NOAELs were 68.6, 100 and 72 mg/kg/day for mouse, dog and rat respectively. The LOAELs were observed at 699.1, 600 and 724 mg/kg/day in mouse dog and rat respectively. The LOAEL (600 mg/kg/day) in selected study is lower than the LOAELs in subchronic rat (724 mg/kg/day) and mouse (699.9 mg/kg/day) studies.

*Long-Term Inhalation Endpoint:* A long-term inhalation endpoint was selected from the chronic dog study. The NOAEL of 10 mg/kg/day was based on dose-related increase in the hyperplasia of the intrahepatic bile ducts in both sexes and granulation of liver in females observed at a LOAEL of 100 mg/kg/day. An oral study was selected since no appropriate inhalation study is available in the database. A 100% inhalation factor should be used to convert to an oral equivalent dose. This dose/endpoint is appropriate for long-term exposure risk assessment. The same effects (mild choledochus and liver consolidation) were seen in the parental and offspring in a 2-generation reproduction study. The reproduction study in rats was not selected for this risk assessment because of the dose spread between the LOAEL and NOAEL (75.7 mg/kg/day and 1.5 mg/kg/day), as compared to the chosen study (75 fold vs 10 fold, respectively).

*MOE for Occupational/Residential Risk Assessments:* A MOE of 100 is adequate for dermal and inhalation occupational exposure. This includes the standard 100x UF to account for interspecies extrapolation and intraspecies variation. At the present time there are no residential uses.

Table 3 summarizes the toxicological dose and endpoints for bispyribac-sodium for use in human risk assessment.

**Table 3. Summary of Toxicological Dose and Endpoints for Bispyribac-sodium for Use in Human Risk Assessment<sup>1</sup>.**

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary <u>all populations</u>	Not Applicable	Not Applicable	No appropriate endpoint attributable to single exposure was identified.
Chronic Dietary <u>all populations</u>	NOAEL= 10 mg/kg/day UF = 100 <b>Chronic RfD</b> = 0.1 mg/kg/day	FQPA SF = 1x <b>cPAD</b> = <u>chronic RfD</u> FQPA SF = 0.1 mg/kg/day	Chronic Toxicity Study - Dog LOAEL = 100 mg/kg/day based on dose-related increases in hyperplasia of the intrahepatic bile ducts in males and females and granulation of the liver in the females.
Short-Term Incidental Oral (1-30 days)  (Residential)	NOAEL = 100 mg/kg/day	<b>LOC for MOE</b> = 100 (Residential, includes the FQPA SF = 1)	Developmental Toxicity Study - Rabbit Maternal LOAEL = 300 mg/kg/day based on lethargy, diarrhea and decreased body weight gain in the range-finding study.
Intermediate-Term Incidental Oral (1-6 months)  (Residential)	NOAEL = 100 mg/kg/day	<b>LOC for MOE</b> = 100 (Residential, includes the FQPA SF = 1)	90-Day Feeding Study - Dog LOAEL = 600 mg/kg/day based upon salivation and slight proliferation of intrahepatic bile duct.
Dermal, All Durations  (Occupational/ Residential)	Not Applicable	Not Applicable	No hazard via the dermal route was identified; therefore, risk quantification is not required. No systemic toxicity was seen at the limit dose in the 21-day dermal toxicity study in rats. In addition no developmental toxicity was seen. Further, based on the physical and chemical properties (large molecular weight = 452.36, and log kow = 0.092), this compound is not likely to be significantly absorbed through the skin.
Short-Term Inhalation (1-30 days)  (Occupational/ Residential)	Oral study NOAEL= 100 mg/kg/day (inhalation absorption rate = 100%)	<b>LOC for MOE</b> = 100 (Occupational)  <b>LOC for MOE</b> = 100 (Residential, includes the FQPA SF = 1)	Developmental Toxicity Study - Rabbit Maternal LOAEL = 300 mg/kg/day based on lethargy, diarrhea and decreased body weight gain in the range-finding study.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF and LOC for Risk Assessment	Study and Toxicological Effects
Intermediate-Term Inhalation (1-6 months)  (Occupational/ Residential)	Oral study NOAEL= 100 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 100 (Occupational)  LOC for MOE = 100 (Residential, includes the FQPA SF = 1)	90-Day feeding study - Dog LOAEL = 600 mg/kg/day based upon salivation and slight proliferation of intrahepatic bile duct.
Long-Term Inhalation (>6 months)  (Occupational/ Residential)	Oral study NOAEL= 10 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 100 (Occupational)  LOC for MOE = 100 (Residential, includes the FQPA SF = 1)	Chronic Toxicity Study - Dog LOAEL = 100 mg/kg/day based on dose-related increases in hyperplasia of the intrahepatic bile ducts in males and females and granulation of the liver in the females.
Cancer (oral, dermal, inhalation)	"not likely"	Not Applicable	No evidence of carcinogenic or mutagenic potential. A cancer risk assessment is not required.

1. UF = uncertainty factor, FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, cPAD = chronic population adjusted dose, RfD = reference dose, MOE = margin of exposure, LOC = level of concern.

### 3.4 Endocrine Disruption

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

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

## 4.0 EXPOSURE ASSESSMENT

### 4.1 Summary of Proposed Uses

The petitioner provided a proposed label for the bispyribac-sodium end-use product, Regiment™ Herbicide, a WP formulation in water-soluble bags. The WP formulation is proposed for use on rice to control grass and broadleaf weeds. The proposed product label lists the active ingredient bispyribac-sodium at 81.6%; however, the petitioner references the product as an 80% bispyribac-sodium formulation. An examination of the Confidential Statement of Formula indicates that the active ingredient percentage is actually 80%; therefore, the product label should be modified. **A revised Section B should be submitted.**

The WP formulation is proposed for multiple post-emergence applications to dry-seeded or water-seeded rice at 9-14.4 g ai/A/application (0.020-0.032 lb ai/A/application) except in California (CA). In CA, multiple post-emergence applications may be made at 9.6-18 g ai/A/application (0.021-0.040 lb ai/A/application). In all rice growing regions, applications may be made with three-week retreatment intervals. The proposed maximum seasonal rate is 24 g ai/A (0.053 lb ai/A). Applications may be made to rice after the 3-leaf growth stage up to panicle initiation (green ring). No numerical preharvest interval (PHI) is specified. Applications may be made in a minimum of 10 gal using ground or aerial equipment. Use of a surfactant with the applications is required.

Pre-flood and post-flood applications may be made to rice. Following pre-flood applications, one day is to be allowed for herbicide uptake prior to establishing permanent flood. For post-flood applications, the flood-water must be lowered prior to application so that 70% of the weed plant surface is above the flood-water, and the field should be returned to normal flood level 2-3 days following application. The label prohibits use on second crop (stubble/ratoon) rice, and prohibits the use of water drained from treated fields for irrigation of other crops. No rotational crop restrictions are specified. A restricted entry interval (REI) of 4 hours is specified.

### 4.2 Dietary Exposure/Risk Pathway

#### 4.2.1 Residue Profile

##### *Background*

The rice petition (PP#9F6044) represents the first petition for use of bispyribac-sodium in the U.S., and there are currently no tolerances established for the use of bispyribac-sodium. The residue chemistry data submitted in support of PP#9F6044 were reviewed in the HED memorandum dated 8/23/01 (Memo, J. Tyler; D267306).

Valent U.S.A. Corporation has submitted a registration application for use of bispyribac-sodium on rice, along with a petition to establish permanent tolerances on these commodities. Section F of the current petition proposes the establishment of permanent tolerances for residues of bispyribac-sodium in/on rice grain at 0.02 ppm and rice straw at 0.02 ppm.

### *Nature of the Residue*

Plants: Provided adequate storage stability data for the benzene-labeled rice metabolism study are submitted, the nature of the residue in rice is adequately understood. The results of a rice metabolism study were presented to the HED Metabolism Assessment Review Committee (MARC) on 7/31/01 (Memo, J. Tyler and G. Reddy, 7/30/01; D275456). The Committee concluded that for the tolerance expression and risk assessment purposes the residue of concern in/on rice is bispyribac-sodium *per se* (Memo, J. Tyler, 8/20/01; D276560). The Committee based this decision on the following: 1) all metabolites identified were present at low levels relative to the parent in the plant, and livestock metabolism studies, 2) bispyribac-sodium has a low toxicity profile and the metabolites are not expected to be more toxic than the parent, and 3) the identified metabolites are also metabolites in rats and their toxicity is assessed in the rat metabolism studies.

Livestock: The nature of the residue in livestock is adequately understood. The results of ruminant and poultry metabolism studies were presented to the HED MARC on 7/31/01 (Memo, J. Tyler and G. Reddy, 7/30/01; D275456). The Committee concluded that for the tolerance expression and risk assessment purposes the residue of concern in livestock is bispyribac-sodium *per se* (Memo, J. Tyler, 8/20/01; D276560). The Committee based this decision on the following: 1) all metabolites identified were present at low levels relative to the parent in the plant, and livestock metabolism studies, 2) bispyribac-sodium has a low toxicity profile and the metabolites are not expected to be more toxic than the parent, and 3) the identified metabolites are also metabolites in rats and their toxicity is assessed in the rat metabolism studies.

### *Residue Analytical Methods*

Plants: The petitioner has proposed gas chromatography (GC) method RM-35R-2 for the enforcement of tolerances on rice grain and straw. The reported method limits of detection and quantitation (LOD and LOQ) for residues of bispyribac-sodium are 0.01 ppm and 0.02 ppm, respectively, in/on rice grain and straw. Adequate radiovalidation and independent laboratory validation (ILV) data have been submitted for this method. The GC method RM-35R-2 has been forwarded to the Analytical Chemistry Branch (ACB) of the Biological Economic Analysis Division (BEAD) for a PMV (Memo, J. Tyler 3/5/01; D272600). The method includes procedures for confirmation of residues (analysis using a different GC column, and/or analysis by GC with mass selective detection). **Provided that the method is successfully validated by the Agency**, HED concludes that the requirements for a plant enforcement method have been fulfilled for the purpose of permanent tolerances for residues of bispyribac-sodium *per se* in/on rice commodities.

Rice commodity samples collected from the field trials and processing studies and beet tops and roots, bok choy, and tomato from the irrigated crop trials were analyzed for residues of bispyribac-sodium using GC method RM-35R-3. Method RM-35R-3 is the same as the proposed enforcement method (RM-35R-2), except that diazomethane was substituted for TMS-diazomethane as the methylating agent. The concurrent method recoveries indicate that the GC method is adequate for data collection.

Livestock: The petitioner has not proposed tolerances for livestock commodities and therefore did not submit any tolerance enforcement methods for livestock commodities. When a decision regarding the need for tolerances in poultry commodities has been made, the need for enforcement methods for livestock commodities will be addressed.

#### *Multiresidue Method (MRM)*

The petitioner submitted data pertaining to the multiresidue methods testing of bispyribac-sodium. These results indicate that bispyribac-sodium is not likely to be recovered through the Food and Drug Administration (FDA) MRM protocols. The results of the multiresidue testing for bispyribac-sodium have been forwarded to the FDA for inclusion in the Pesticide Analytical Method Volume I (PAM I) (J. Tyler 3/27/01; D273621).

#### *Magnitude of Residues in Water, Fish, and Irrigated Crops*

The submitted irrigated crop study indicates that there is a possibility of detectable residues of bispyribac-sodium in crops irrigated with water drained from treated rice fields; however, the proposed label includes a restriction against the use of water from treated fields for irrigation purposes due to phytotoxicity. Therefore, tolerances for residues in/on irrigated crops are not needed at this time.

The petitioner has requested a waiver from conducting potable water and fish studies because bispyribac-sodium: (i) is used at a low rate (0.053 lb ai/A proposed maximum seasonal rate); (ii) dissipates rapidly by biotic degradation from rice paddy environments (water dissipation half-life of 9 days from aquatic field dissipation studies), and (iii) has an octanol/water partition coefficient of 0.0932 suggesting it will not bioaccumulate in organisms. The regulation of pesticide levels in potable water is no longer under the purview of HED. The Office of Water has not set a Maximum Contaminant Level (MCL) for bispyribac-sodium. Although water from treated fields may be used in catfish ponds, due to the low use rate, short water dissipation half-life of bispyribac-sodium, and the dilution of bispyribac-sodium residues in the pond water, HED agrees with the waiver request. HED will not require a label restriction prohibiting using water from treated fields in catfish ponds. However, crayfish can be raised in treated water. **In the absence of magnitude of residue data on shellfish, the petitioner should submit a revised Section B to include a statement prohibiting the farming of crayfish in treated fields.**

#### *Magnitude of Residues in Plants*

Adequate residue field trial data in support of the proposed use on rice have been submitted. The available data indicate that residues of bispyribac-sodium were less than the LOD (<0.005 ppm) and <0.005-0.013 ppm in/on rice grain and straw, respectively, harvested 50-84 days following either a single broadcast foliar application of the WP formulation made at the panicle initiation growth stage at 0.053 lb ai/A (1x the proposed maximum seasonal application rate), or two post-emergence broadcast applications made at the 4- to 5-leaf growth stage and again at panicle initiation at 0.026 lb ai/A/application for a total application rate of 0.053 lb ai/A (1x the proposed maximum seasonal application rate). In addition, residues of bispyribac-sodium were less than the LOD (<0.005 ppm) in/on rice grain and straw treated with either a single or two broadcast

applications of the WP formulation for a total of 0.106 lb ai/A (2x the proposed maximum seasonal application rate).

Based on the rice field trial data, the following proposed tolerances for residues of bispyribac-sodium *per se* in/on rice are adequate: rice, grain at 0.02 ppm and rice, straw at 0.02 ppm. The proposed tolerances are set at the LOQ for the proposed enforcement method.

#### *Magnitude of Residues in Processed Commodities*

The rice processing study is adequate. The submitted data indicate that residues of bispyribac-sodium do not concentrate in polished grain, rice hulls or bran. Residues of bispyribac-sodium were less than the method LOD (<0.005 ppm) in/on rice grain treated at 1x and 2x the proposed maximum seasonal application rate, and residues were less than the method LOD (<0.005 ppm) in polished grain, hulls, or bran processed from the rice grain.

Based on the results of the current processing study, tolerances for residues of bispyribac-sodium in the processed commodities of rice are not required. Although the 2x exaggeration rate of the study did not result in quantifiable residues in rice grain, HED concludes that it is unlikely that higher exaggeration rates would result in quantifiable residues in processed commodities.

#### *Magnitude of Residues in Meat, Milk, Poultry and Eggs (MMPE)*

No ruminant feeding studies were submitted with this petition. Based on the MTDB to beef and dairy cattle (0.017 ppm) and hogs (0.018 ppm) and the results of the goat metabolism study, the use of bispyribac-sodium on rice falls under Category 3 of 40 CFR §180.6(a) for ruminant commodities; there is no expectation of finite residues of bispyribac-sodium in ruminant commodities. No ruminant feeding studies or tolerances for residues in ruminant commodities are required. The petitioner should note that if additional uses of bispyribac-sodium are requested in the future which significantly increase the dietary burden, a ruminant feeding study may be required.

No poultry feeding studies were submitted with this petition. Based on the MTDB to poultry (0.020 ppm) and the results of the poultry metabolism study, there is a possibility of finite residues of bispyribac-sodium in liver and the potential for higher residue levels in poultry commodities following dosing at intervals longer than those used in the metabolism study. Therefore, HED cannot conclude that there is no expectation of finite residues of bispyribac-sodium in poultry commodities based on the results of the poultry metabolism study. **The petitioner should submit a poultry feeding study. The need for tolerances for poultry commodities will be determined when an adequate poultry feeding study has been submitted.**

In order to account for possible dietary exposure to bispyribac-sodium residues in poultry commodities, anticipated residues were calculated by extrapolating the results of the poultry metabolism study (610x MTDB) to 10x the MTDB. A level of 10x was chosen rather than 1x to account for differences in the durations of dosing in poultry feeding and poultry metabolism studies. Using the equation below, the appropriate residue levels (parent only) to be used in the



dietary exposure assessment of HED's human health risk assessment were determined. Table 4 is a summary of the calculated anticipate residues for poultry commodities.

**Table 4. Summary of Anticipated Bispyribac-sodium Residues in Poultry Commodities.**

Poultry Commodity	Bispyribac-sodium Residues (ppm)	
	610x MTDB <sup>a</sup>	10x MTDB
Eggs	0.003	0.000049
Liver	4.819	0.079
Fat	0.011	0.00018
Muscle	<0.01 <sup>b</sup>	0.00016

a. Taken from the results of the poultry metabolism study.

b. Because the TRR in muscle was <0.01 ppm, the residues were not further characterized. Therefore, a TRR value of 0.01 was used.

#### *Confined Accumulation in Rotational Crops*

The submitted confined rotational crop study is adequate. The total radioactive residues (TRR) did not accumulate at levels  $\geq 0.01$  ppm in/on the RACs of radish, soybean, and spring wheat planted in loam soil 28-46 days after treatment of the soil with [<sup>14</sup>C-pyrimidine-2]bispyribac-sodium at 0.061 lb ai/A (~1.2x the proposed maximum seasonal rate for rice). Because the TRR in all 30-day PBI crops were <0.01 ppm, the samples were not extracted for characterization/identification of residues. Based on the submitted pyrimidine-labeled study, no rotational crop restrictions or tolerances for rotational crop commodities are required for the proposed use of bispyribac-sodium on rice.

The nature of the residue in rotational crops is adequately understood. The results of the confined rotational crop study were presented to the HED MARC on 7/31/01. The Committee concluded that the residue of concern in rotational crops is bispyribac-sodium *per se* (Memo, J. Tyler, 8/20/01; D276560). Because the TRR in the samples from the confined rotational crop study were present at levels <0.01 ppm, the samples were not further characterized. Due to the results of the confined rotational crop study, tolerances on rotational crop are not required at this time. However, the Committee concluded that additional confined rotational crop data will be necessary if in the future new uses with significantly higher use rates are submitted.

#### *International Harmonization of Tolerances*

There are currently no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for residues of bispyribac-sodium in/on plant or livestock commodities. Therefore, no compatibility issues exist with regard to the proposed U.S. tolerances discussed in this petition review.

## 4.2.2 Dietary Exposure Analyses

Bispyribac-sodium chronic dietary exposure assessments were conducted using the DEEM™ software Version 7.73, which incorporates consumption data from USDA's CSFII, 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days; and, therefore, represent more than 30,000 unique "person days" of data. Foods "as consumed" (e.g., apple pie) are linked to raw agricultural commodities and their food forms (e.g., apples-cooked/canned or wheat-flour) by recipe translation files internal to the DEEM software. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessment, but are retained as individual consumption events for acute exposure assessment.

For chronic exposure and risk assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange-juice) on the commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate for each food/food form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup.

### 4.2.2.1 Acute Dietary Exposure Analysis

An appropriate endpoint attributable to a single oral dose was not selected for either the general U.S. population (including infants and children) or the females 13-50 years old population subgroup for bispyribac-sodium; therefore, an acute dietary exposure analysis was **not** performed.

### 4.2.2.2 Chronic Dietary Exposure Analysis

A conservative, deterministic chronic dietary exposure analysis for bispyribac-sodium was performed for the general U.S. population and all population subgroups using proposed tolerance level residues and 100% CT information for all rice commodities (Memo, J. Tyler 8/15/01; D276558). There is no reasonable expectation of finding finite bispyribac-sodium residues of concern in milk, meat, fat, or meat byproducts of ruminants as a result of the proposed uses on rice [Category 180.6(a)(3)]. No poultry feeding study was submitted. However, based on the results of the poultry feeding study and the calculated poultry MTDB (See Table 4), dietary exposure to bispyribac-sodium residues in poultry commodities is expected to be minimal (Memo, J. Tyler 9/24/01; D277811). The need for poultry tolerances will be determined upon submission of an adequate poultry feeding study. Chronic dietary exposure estimates for the general U.S. population and other population subgroups are presented in Table 5. For chronic dietary risk estimates, HED's level of concern is >100% cPAD. The results of the analysis indicate that the estimated chronic dietary risks associated with the proposed use of bispyribac-sodium do not exceed HED's level of concern for the general U.S. population or any population subgroups.

**Table 5. Summary of Results from Chronic DEEM™ Analysis of Bispyribac-Sodium.**

<b>Population Subgroup</b>	<b>Dietary Exposure (mg/kg/day)</b>	<b>% cPAD</b>
U.S. Population (total)	0.000005	<1
All Infants (< 1 year old)	0.000019	<1
Children 1-6 years old	0.000010	<1
Children 7-12 years old	0.000006	<1
Females 13-50 years old	0.000004	<1
Males 13-19 years old	0.000003	<1
Males 20+ years old	0.000004	<1

HED notes that there is a degree of uncertainty in extrapolating exposures for certain population subgroups which may not be sufficiently represented in the consumption surveys (e.g., nursing infants). Therefore, risks estimated for these subpopulations were included in representative populations having sufficient numbers of survey respondents (e.g., all infants or females, 13-50 years old). Thus, the population subgroups listed in Table 5 include those subgroups having sufficient numbers of survey respondents in the CSFII food consumption survey.

#### **4.2.2.3 Cancer Dietary Exposure Analysis**

The HIARC classified bispyribac-sodium as a "not likely human carcinogen" according to EPA *Proposed Guidelines for Carcinogenic Risk Assessment* (April 10, 1996) (HED Doc. No. 014647, G. Reddy, 8/2/01). Therefore, a cancer dietary risk assessment was not performed.

### **4.3 Water Exposure/Risk Pathway**

#### *Environmental Fate Assessment*

The following information concerning the environmental fate and drinking water assessment of bispyribac-sodium was provided by EFED (Memo, L. Shanaman, 7/6/01). Bispyribac-sodium is a moderately persistent, mobile compound on most soils. The primary degradation pathway is aerobic and anaerobic degradation through fragmentation and hydrolysis to form six major and multiple minor metabolites monitored in the laboratory studies. These metabolites break down further, eventually transforming into CO<sub>2</sub> and low weight, soil-bound residues. Batch adsorption studies, when considered together with model simulation results, indicate a limited potential for leaching and runoff. K<sub>d</sub> values varied between 0.604 and 2.01 mL/g, with an overall K<sub>oc</sub> value of 114. Soil characteristics such as organic carbon content, cation exchange capacity and clay content, indicate a good correlation between the partitioning constant and all three physical factors. Additionally, due to the aquatic nature of rice cultivation, irrigation canals and flood water holding ponds associated with rice paddies are particularly vulnerable to both spray drift and potential runoff. However, this risk is mitigated by the low application rate (0.053 lbs a.i./A).

In a meeting on 7/31/01, the HED MARC concluded that the residue of concern in drinking water is bispyribac-sodium *per se* (Memo, J. Tyler, 8/20/01; D276560). All metabolites identified were present at low levels, and are not expected to be more toxic than the parent.

EFED provided Tier 1 estimated EECs in water from rice culture for bispyribac sodium (Memo, R. David Jones 5/16/01; D275614). EECs were calculated for drinking water risk from surface water and groundwater.

#### *Ground Water EEC*

The groundwater EEC was estimated with SCI-GROW. It is based on a regression approach which relates the concentrations found in ground water from Prospective Ground Water studies to aerobic soil metabolism rate and soil-water partitioning properties of the chemical.

*ground water EEC:*                    0.0072 ppb (7.2 ng L<sup>-1</sup>)

#### *Surface Water EEC*

Because OPP currently has no official model for estimating EECs in surface water due to rice culture, a screening calculation method was developed; thus, these EECs are provisional only. Estimates were done for each of the three major rice growing regions in the United States, the Gulf Coast of Louisiana and Texas, the Mississippi Valley including parts of northern Louisiana, Mississippi, Arkansas, and southern Missouri, and California in the Sacramento River Basin. The following surface water EEC reflect soils and management practices prevalent in the Gulf Coast (the maximum estimate of the three growing regions) for rice culture.

*surface water EEC:*                    0.317 ppb (317 ng L<sup>-1</sup>)

The surface water EEC is a point estimate representing only peak or acute concentrations. However, as no attempt has been made to determine average exposure and the average exposure should be less than the acute exposure, an EEC of 0.317 ppb was used for the chronic risk assessment.

### **4.4 Residential Exposure/Risk Pathway**

There are no products containing bispyribac-sodium proposed or registered for residential use or that may be applied by commercial applicators to residential sites. Therefore, a residential exposure assessment was not performed.

#### **4.4.1 Non-occupational Off-Target Exposure**

This assessment for bispyribac-sodium reflects the Agency's current approaches for completing residential exposure assessments based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines*, the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment*, and the *Overview of Issues Related to the Standard Operating Procedures*

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

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

## **5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION**

An aggregate exposure risk assessment was performed for the following scenario: chronic aggregate exposure (food + drinking water). Acute, short- and intermediate-term and cancer aggregate risk assessments were not performed because an acute dietary endpoint was not selected, there are no registered or proposed residential non-food uses, and bispyribac-sodium is not carcinogenic, respectively. Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, DWLOCs were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

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

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

### 5.1 Chronic Aggregate Risk Assessment

The Tier 1 (conservative, deterministic assessment using tolerance level residues and 100% CT information) chronic dietary exposure estimates for the general U.S. population and all population subgroups accounted for <1% of the cPAD. The EECs generated by EFED are less than HED's calculated chronic DWLOCs for chronic exposure to bispyribac-sodium in drinking water. Therefore, the chronic aggregate risk associated with the proposed use of bispyribac-sodium does not exceed HED's level of concern for the general U.S. population or any population subgroups. Table 6 summarizes the chronic aggregate exposure estimates to bispyribac-sodium residues.

**Table 6. Chronic Aggregate Exposures to Bispyribac-sodium Residues.**

Population Subgroup	cPAD, mg/kg/day	Chronic Food Exposure, mg/kg/day	Maximum Chronic Water Exposure <sup>1</sup> , mg/kg/day	Ground Water EEC <sup>2</sup> , ppb	Surface Water EEC <sup>2</sup> , ppb	Chronic DWLOC <sup>3</sup> , (µg/L)
U.S. Population	0.1	0.000005	0.1	0.0072	0.317	3500
All infants (< 1 year old)	0.1	0.000019	0.1	0.0072	0.317	1000
Children (1-6 years old)	0.1	0.000010	0.1	0.0072	0.317	1000
Children (7-12 years old)	0.1	0.000006	0.1	0.0072	0.317	1000
Females (13-50 years old)	0.1	0.000004	0.1	0.0072	0.317	3000
Males (13-19 years old)	0.1	0.000003	0.1	0.0072	0.317	3500
Males (20+ years old)	0.1	0.000004	0.1	0.0072	0.317	3500
Seniors (55+ years old)	0.1	0.000003	0.1	0.0072	0.317	3500

1. Maximum chronic water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure from DEEM™ (mg/kg/day).

2. Ground water EEC resulting from the maximum proposed application rate (0.053 lbs a.i./A/season); provisional surface water EEC point estimate representing acute concentration, however can be used for both acute and chronic assessments.

3. Because there are no residential uses, the chronic DWLOCs were calculated as follows:

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

## 6.0 CUMULATIVE RISK

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

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

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether bispyribac-sodium shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for bispyribac-sodium need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with bispyribac-sodium, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment once the final guidance HED will use for conducting cumulative risk assessments is available.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on June 30, 2000 (65 FR 40644-40650) and is available from the OPP Website at: <http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf>

In the draft guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The proposed guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity is expected to be finalized by the summer of 2001.

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

## 7.0 OCCUPATIONAL EXPOSURE

An occupational exposure assessment for bispyribac-sodium was prepared in an HED memo dated 8/24/01 (Memo, M. Dow; D276686).

Valent USA Corporation, as agent for K-1 Chemical USA, Inc. has submitted an application to register the herbicide bispyribac-sodium (sodium 2,6-bis[(4,6-dimethoxypyrimidin-2-yl)oxy]benzoate) for use on rice. It will be marketed as Regiment™ Herbicide. It is an 80% WP only marketed in water soluble packages. Bispyribac-sodium is a broad-spectrum herbicide effective against many grass and broadleaf weed species. It acts through the inhibition of the plant enzyme ALS. It is relatively slow acting with complete control in 14-21 days. Early signs of wilting and necrosis are evident at 3-7 days. It is not a residual soil active herbicide and will not control weeds that germinate after application. It may be applied by ground or aerial equipment. See Table 7 for a summary of the proposed use pattern.

**Table 7. Summary of Proposed New Use of Bispyribac-sodium on Rice.**

<b>Formulation</b>	<b>80 % Wettable Powder in Water Soluble Bags</b>
Use Site	Rice
Method of Application	Ground and Air
Pest	Grass and Broadleaf Weed Species
Maximum Application Rate	0.032 lb a.i./A (0.040 lb a.i./A in California)
Frequency/Timing	Multiple applications permitted. Max. Rate/Acre/Season 0.053 lb a.i. with 3 week minimum application interval.
PHI	None stated on label
REI	<b>Proposed label REI = 4 hours</b>
Manufacturer	Valent, agent for K-1 Chemical USA

The exposure estimates are based on toxicological endpoints identified in HED's HIARC document dated 8/2/01. The acute toxicity of bispyribac-sodium and the doses and toxicological endpoints selected for various occupational exposure scenarios are in Tables 1 and 3.

### 7.1 Occupational Handler

Due to the proposed use patterns, HED believes that the most highly exposed pesticide handler activities are likely to be a mixer/loader supporting aerial application operations and an applicator using ground boom apparatus. These activity functions are assessed at the maximum rate of application i.e., 0.04 lb a.i./Acre (limited to California - the maximum rate for other rice producing states is 0.032 lb a.i./Acre). In light of the proposed use patterns, HED expects commercial and private mixer/loaders and applicators to be exposed to short-term exposures (1-



30 days). Private (i.e., grower) applicators may perform both functions, that is, mix, load and apply the material. HED Science Advisory Council for Exposure draft Policy (29 March 2000) "Combining Mixer/Loader/Applicator Data" directs that although the same individual may perform both tasks, they shall be assessed separately. "By separating the two job functions, HED determines the most appropriate levels of personal protection equipment (PPE) for each aspect of the job without requiring the applicator to wear unnecessary PPE that may be required for the mixer/loaders (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation)."

Chemical specific data were not available with which to assess pesticide handler exposure. Therefore surrogate data from studies in the Pesticide Handler Exposure Database Version 1.1 (August 1998) PHED SURROGATE EXPOSURE GUIDE were used to estimate mixer/loader and applicator exposure. The proposed label directs pesticide handlers to wear long-sleeved shirt, long pants, waterproof gloves, shoes plus socks. See Table 8 for estimates of exposure and risk to pesticide handlers.

**Table 8. Estimated Exposures and Risks to Pesticide Handlers Applying Bispyribac-sodium to Rice.**

Unit Exposure <sup>1</sup>	Application Rate <sup>2</sup>	Units Treated <sup>3</sup>	Avg. Daily Dose <sup>4</sup>	NOAEL <sup>5</sup>	MOE <sup>6</sup>
<i>Mixer/Loader - Wettable Powder - Water Soluble Packages - Supporting Aerial Application</i>					
Inhalat 0.00024 LC	0.040	1200 A	ST = 0.00019	100	> 520 K
<i>Applicator - Groundboom - Open Cab</i>					
Inhalat. 0.00074 HC	0.040	200 A	ST = 0.000098	100	> 1 M

1. Unit Exposure = mg a.i./lb a.i. handled; taken from the Pesticide Handler's Exposure Database PHED Surrogate Exposure Guide version 1.1; August 1998; Inhalat. = Inhalation. HC = high confidence data; LC = low confidence data
2. Application Rate from proposed "Regiment"<sup>TM</sup> label (Valent 10029-TOL1 pages 38-46)
3. Acres Treated are derived from Sci.Adv.Coun Pol. No. 9.
4. Average Daily Dose (ADD) = Unit Exposure \* Application Rate \* Units Treated ÷ 60 kg body weight\*. Inhalation exposure assumes 100% inhalation absorption. \* The short term inhalation NOAEL is based upon a developmental study in the rabbit therefore MOE is calculated using 60 kg bw. Short Term Exposure (1-30 days)
5. NOAEL = No Adverse Effect Level (mg a.i./kg bw/day)
6. Margin of Exposure (MOE) = NOAEL ÷ ADD. K = 1000. M = 1,000,000

HED's level of concern for bispyribac-sodium is for MOEs below 100. The MOEs for pesticide handler exposure are greater than  $5.2 \times 10^5$ , and, therefore, do not exceed HED's level of concern.

## 7.2 Occupational Postapplication

Since no dermal toxicological endpoints have been identified, it is not necessary to assess post-application worker exposure. HED does not expect any post-application agricultural operations will occur until after the REI. At that point in time, sprays are expected to have dried. Further, the vapor pressure of bispyribac-sodium is  $3.79 \times 10^{-11}$  mm Hg. HED expects any inhalation exposure that might occur will be negligible. Therefore, assessment of post-application inhalation exposure is also not necessary.

## REI

The proposed label lists a 4-hour REI. There are specific criteria that must be met in order to establish a 4-hour REI. On 11 January 1995 the Agency published a draft policy statement on "Reduced Restricted Entry Intervals for Certain Pesticides," in the Federal Register. The final policy was published in the FR 3 May 1995. The policy provides for reductions of REIs from 12 to 4 hours for certain low risk Toxicity Category III and IV active ingredients. A list was published at that time for those active ingredients which were approved for 4-hour REIs. Bispyribac sodium is **not** included in that list. The policy also established an application procedure for registrants to request a reduction in the Worker Protection Standard (WPS) interim REIs. **HED suggests verification of the 4-hour REI on the proposed label.**

### 7.3 Incidents

Since bispyribac-sodium is a new a.i., no incident data are available.

## 8.0 DATA NEEDS/LABEL REQUIREMENTS

### 8.1 Chemistry

- OPPTS 860.1200: Revised Section B which lists the active ingredient bispyribac-sodium at 80% rather than 81.6% and includes a statement prohibiting the farming of crayfish in treated fields.
- OPPTS 860.1300: Storage stability data for the benzene-labeled rice metabolism study.
- OPPTS 860.1480: Poultry feeding study.
- OPPTS 860.1340: Agency PMV of the plant analytical enforcement method.

### 8.2 Toxicology

- OPPTS 870.3465: 28-Day inhalation toxicity study. The protocol for the existing 90-day inhalation toxicity study should be followed with the exposure (treatment) ending after 28 days, instead of 90 days.
- OPPTS 870.5300: *In vitro* mammalian cell gene mutation assay.

### 8.3 Occupational Exposure

- Verification of the 4-hour REI on the proposed label.