8

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

June 24, 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Bromoxynil (Case #2070: PC Codes 035301 and 035302):** Revised Human Health Risk Assessment for Bromoxynil.
PRATS Data Barcode: D246944

FROM: Barbara Madden
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THRU: Steve Knizner, Branch Senior Scientist
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

TO: Linda Werrell
Special Review and Reregistration Division (7508W)

The revised Human Health Risk Assessment for bromoxynil is attached. This chapter supersedes all previous HED human health risk assessments, the last of which is dated April 23, 1998. This chapter includes the following revisions:

- Water and aggregate chronic risk estimates have been recalculated using a reasonable high end estimate of exposure of 0.05 ppb in response to EFED's memo (R.D. Jones, June 2, 1998).
- Footnote f from Table 11 has been revised.
- The discussion in the *Handler Risks* section on the "Estimates of Risks from Short-Term Exposures Using PHED Data" has been revised.
- Changes in the wording for application instructions for transgenic BXN cotton, and a change in the wording for rotational crop restrictions as follows:

  When application instructions to transgenic BXN cotton are discussed in Agency documents, the following should apply:

  "Apply from just prior to planting cotton until 75 days prior to harvest. Do not exceed 2 applications before cotton is 12 inches tall and 1 application after cotton exceeds 12 inches in height. Make the last application during bloom, but not later than 75 days before harvest."

When rotational crop restrictions are discussed in Agency documents, the following statements should be used:

"After applying up to 2 pints/A/season of [Buctril® or Buctril ® 4EC], wait a minimum of 30 days from the date of the application, and then plant any rotational crop."

"After applying more than 2 pints/A/season of [Buctril® or Buctril ® 4EC], only transgenic BXN cotton may be planted as a rotational crop."

- Revised bibliography and residue chemistry summary table (Table B).

HED also recommends that the end-use product labels for bromoxynil be revised and the paragraph below be **deleted** from the end-use product labels. This paragraph was previously required in response to the Special Review for bromoxynil but is no longer necessary since the risk estimates for the worker in the HED RED chapter are within HED's level of concern without the requirement of using a mechanical transfer system.

"If you handle a total of 60 gallons or more of this product per day, you must use a mechanical transfer system for all mixing and loading operations. If this product is packaged in a 30 gallon drum, you must use a mechanical transfer system which terminates in a drip-free hard coupling which may be used only with a spray or mix tank which has been fitted with a compatible coupling. If you do not presently own or have access to a mechanical transfer system with this type of coupling, contact your dealer for information on how to obtain such a system or to modify you present system. When using a mechanical transfer system, do not remove or disconnect the pump or probe from the container until the container has been emptied and rinsed. The pump or probe system must be used to rinse the empty container and to transfer the rinsate directly to the mixing or spray tank."

The following statement on the end-use product labels should also be revised:

"Application from a tractor with a completely enclosed cab or aerial application is required whenever this product is applied to 360 or more acres in a day... or repair."

Based on this current risk assessment enclosed cockpits are required for all aerial applications and enclosed cabs are not required for groundboom applications. As per your previous conversation with Alan Nielsen of RRB 2, HED recommends that the end-use product labels be sent to the contractor for review prior to the RED being issued for additional comments on labeling changes.

HUMAN HEALTH ASSESSMENT FOR BROMOXYNIL

JUNE 24, 1998

Table of Contents

HUMAN HEALTH ASSESSMENT FOR BROMOXYNIL

I. BACKGROUND

This RED chapter addresses issues and data related to bromoxynil phenol and its octanoic acid ester, bromoxynil octanoate, both of which are currently registered with EPA and have been supported for reregistration. Other chemical forms of "bromoxynil" are not addressed in this RED; these include bromoxynil butyrate, the butyric acid ester of bromoxynil, which was not supported for reregistration, and bromoxynil heptanoate, the heptanoic acid ester of bromoxynil, which is considered to be a new pesticide chemical and therefore not subject to reregistration.

During the preparation of the RED for bromoxynil, a permanent registration was requested for the use of bromoxynil on transgenic BXN cotton. A temporary tolerance was established, expired and was reestablished which expired in 1/98. Ordinarily, the temporary tolerance on cotton would not be included in the RED for this chemical, however, this use contributed so significantly to the dietary (food and water) cancer risk for bromoxynil it was necessary that it be included.

Originally, the transgenic BXN cotton use was based on a maximum 4.5 lbs ai/A/year (based on 3 banded applications a year at 1.5 lbs ai/A). Rhone-Poulenc has since proposed:

- a reduction in the rate applied to BXN cotton by 67% to a the maximum of 1.5 lbs ai/A/year;
- to increase the pre-harvest interval (PHI) from 60 to 75 days following application to cotton;
- to increase the pre-grazing interval (PGI) from 30 to 45 days for sorghum forage;
- to increase the PHI from 30 to 45 days for corn and small grains forages;
- preparation of anticipated residues in swine commodities using anticipated swine diets (rather than translating anticipated residues directly from cattle to swine); and
- to include cotton gin by-products (gin trash) in ruminant diets at 1% of the diet for dairy cattle and 5% of the diet for beef cattle.

The proposed use rate reduction was incorporated into Agency risk assessments conducted in conjunction with the extension of the time-limited tolerances in June, 1997. However, additional confirmatory field trial studies conducted at the proposed reduced rate were required. These data have been submitted, and are included in the current assessment (see below for discussion). The new field trials were conducted at the new proposed PHI of 75 days.

The registrant's request to increase the pre-grazing interval (PGI) for sorghum was denied. In general, the Agency does not consider pre-grazing intervals to be practical for grasses and sorghum, but the PGI for sorghum/grasses was permitted due to application timing. The registrant's request to increase the PHI for corn and small grain forages was acceptable; adequate residue data have been submitted to the Agency in conjunction with reregistration. As a result tolerances for residues in forages have been reassessed, and these revised tolerances have been included in the Tolerance Reassessment Summary.

The registrant's refinements to the livestock diets were acceptable to the Agency with respect to swine diets and the proposed percentages of gin trash contributing to ruminant diets.

II. USE SUMMARY

Bromoxynil is a selective contact foliage applied herbicide used to control broadleaf weeds. Bromoxynil inhibits photosynthetic electron transport and also uncouples oxidative phosphorylation

in mitochondria, thereby stopping energy production and negatively affecting plant respiration. Agricultural crop use sites include: food crops (e.g., garlic/onions), food and feed crops (e.g., mint, wheat, sorghum, corn, cotton), feed crops (e.g., fodder/hay), non-food crops (e.g., fallow/idle land, golf course turf, and sod farms). Bromoxynil is formulated as an emulsifiable concentrate, soluble concentrate and a gel formulation (in water soluble packages). The application rates for crop uses range from 0.25 lb ai/acre to 0.5 lb ai/acre for all crops.

Currently the end-use products containing bromoxynil phenol and bromoxynil octanoate are intended for agricultural uses only and not for homeowner uses. Therefore, residential exposure is not expected.

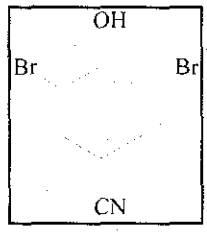
III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

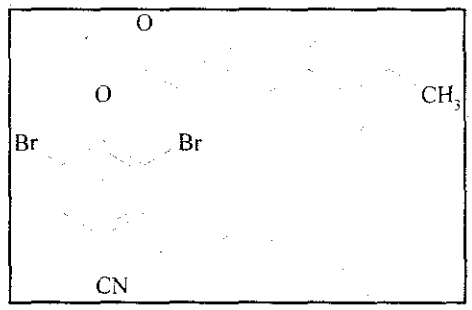
1. Description of Chemical

Bromoxynil [3,5-dibromo-4-hydroxybenzonitrile] is a selective herbicide which is registered for application as the octanoic or heptanoic acid esters for postemergence control of broadleaf weeds in various crops.

Bromoxynil
Empirical Formula: $C_7H_3Br_2NO$
Molecular Weight: 276.9
CAS Registry No.: 1689-84-5
Shaughnessy No.: 035301



Bromoxynil octanoate
Empirical Formula: $C_{15}H_{17}Br_2NO_2$
Molecular Weight: 403.0
CAS Registry No.: 1689-99-2
Shaughnessy No.: 035302



2. Identification of Active Ingredient

Bromoxynil is a white to slightly yellow crystalline solid with a melting point of approximately 190 C. Bromoxynil is slightly soluble in water at 211 ppm and in hexane at 178 ppm, and is soluble in 1-octanol (4.97 g/100 L) and methanol (8.51 g/100 mL) at 25 C.

Bromoxynil octanoate is a brown crystalline solid with a melting point of approximately 44 C. The octanoic esters are virtually insoluble in water. Bromoxynil octanoate is soluble in acetone or ethanol (10 g/100 mL), benzene or xylene (70 g/100 mL), chloroform or dichloromethane (80 g/100 mL), and cyclohexanone (55 g/100 mL). The octanoic acid esters are readily hydrolyzed to

bromoxynil under alkaline conditions.

3. Manufacturing-Use Products

A search of the Reference Files System (REFS) conducted 10/18/95 identified three bromoxynil manufacturing-use products (MPs) registered under Shaughnessy No. 035301 and three bromoxynil octanoate MPs registered under Shaughnessy No. 035302. The registered bromoxynil and bromoxynil ester MPs are presented below. An additional bromoxynil octanoate 70% formulation intermediate (FI) manufactured by an integrated system is in the process of being registered.

Table 1: Summary of Technical Registrations for Bromoxynil

Formulation	EPA Reg. No.	Registrant	Comments
Bromoxynil (035301)			
95% T	264-229	Rhone-Poulenc AG Company	TGAI produced by Rhone-Poulenc in the United States and by an alternate producer (CFPI Co., France).
95% T	264-473		
94% T	51036-250	Micro-Flo Company	Repackaged from a registered product.
Bromoxynil octanoate (035302)			
95% T	264-442	Rhone-Poulenc AG Company	Produced by the UK manufacturing process. We note that, based on a statement of formula, the 87.3% T is properly identified as a 95% T formulation.
87.3% T	264-395		
70% FI	264-XXX		Produced by the TN process using an integrated system. We note that the EPA Reg. No. referenced in CBRS No. 14100 (D205877; C. Swartz, 2/22/96) is incorrect; a registration number has not yet been assigned.
87.3% FI	51036-251	Micro-Flo Company	Repackaged from a registered product. We note that, based on the product name and a CSF from the product jacket, this product is properly identified as a 95% T formulation.

B. Human Risk Assessment

1. Hazard Assessment

The hazard assessment addresses issues and data related to bromoxynil phenol and its octanoic acid ester, bromoxynil octanoate, both of which are currently registered with EPA and have been supported for reregistration. Technically, the term "bromoxynil phenol" is a misnomer, the phenolic form of bromoxynil being known more properly simply as "bromoxynil". Nevertheless, the term "bromoxynil phenol" will be used throughout this section to eliminate possible confusion and to clearly distinguish the phenolic form of the compound from all other forms of the compound. The toxicology data in support of the reregistration of bromoxynil phenol and bromoxynil octanoate are complete and adequate.

a. Acute Toxicity

Table 2a. Acute Toxicity Results for Bromoxynil Phenol

Study	Result	Tox Category
Acute Oral LD_{50} (rat)[1,a]	81 mg/kg (M) 93 mg/kg (F)	II
Acute Dermal LD_{50} (rabbit)[2,a]	>2000 mg/kg (M and F)[b]	III
Acute Inhalation LC_{50} (rat)[3,a]	0.269 mg/L (M) 0.150 mg/L (F)	II
Eye Irritation (rabbit)[4,a]	corneal opacity, iritis, conjunctival irritation	II
Dermal Irritation (rabbit)[5,a]	no irritation	IV
Skin Sensitization (guinea pig)[6,a]	negative	N/A

[1-6] MRIDs 00124758, 00124758, 43014701, 00124758, 00124758 and 42718701
[a] Test material was technical grade bromoxynil phenol (94.0%).
[b] Abraded skin
N/A = not applicable

Table 2b. Acute Toxicity Results for Bromoxynil Octanoate

Study	Result	Tox Category
Acute Oral LD_{50} (rat)[1,a]	400 mg/kg (M) 238 mg/kg (F)	II
Acute Dermal LD_{50} (rabbit)[2,a]	>2000 mg/kg (M)[b] 1310 mg/kg (F)[c]	II
Acute Inhalation LC_{50} (rat)[3,a]	0.81 mg/L (M) 0.79 mg/L (F)	III
Eye Irritation (rabbit)[4,a]	corneal opacity, conjunctival irritation	III
Dermal Irritation (rabbit)[5,a]	slight erythema	IV
Skin Sensitization (guinea pig)[6,a]	positive (modified draize test)	N/A

[1-6] MRIDs 00124112, 00124112, 42167101, 00124112, 00124112 and 41879801
[a] Test material was technical grade bromoxynil octanoate (87.3%).
[b] Abraded skin
[c] Intact skin
N/A = not applicable

b. Subchronic Toxicity

i. Bromoxynil Phenol

In a 13-week subchronic feeding study, technical grade bromoxynil phenol was administered in the diet to groups of 15 male and 15 female Sprague Dawley rats at dose levels of 0 (control), 400, 755 or 1456 ppm (0, 28, 58 or 168 mg/kg/day in males and 0, 35, 76 or 250 mg/kg/day in females). Decreased body weight gain (22%), increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased alkaline phosphatase were

observed in males at 755 ppm. At 1456 ppm, signs of severe toxicity and excessive mortality (10/15 died) were also observed in males. Treatment-related effects were recorded in females at all dose levels. These effects were decreased body weight gain at 400 ppm (19%) and at 755 ppm (34%), increased alkaline phosphatase at 755 and 1456 ppm, and signs of severe toxicity and excessive mortality (15/15 died) at 1456 ppm. For male rats, the NOEL is 400 ppm (28 mg/kg/day) and the LOEL is 755 ppm (58 mg/kg/day), based on decreased body weight gain, increased ALT, increased AST and increased alkaline phosphatase. For female rats, no NOEL was determined in this study (<400 ppm; <35 mg/kg/day). The LOEL is 400 ppm (35 mg/kg/day), based on decreased body weight gain. This study is of limited usefulness because a NOEL was not determined for females, excessive mortality occurred in males and females at the highest dose level tested, and an insufficient number of tissues was microscopically examined. (MRID 41469101)

In a 12-week range-finding study, technical grade bromoxynil phenol was administered in the diet to groups of 10 male and 10 female CD-1 mice at dose levels of 0 (control), 10, 30, 100, 300, 1000 or 3000 ppm (equivalent to 0, 1.3, 3.9, 13, 39, 130 or 390 mg/kg/day). Increased liver weights and hepatocellular (HC) hypertrophy were observed in males at 100 ppm and higher. Degeneration and vacuolization were also observed in the hepatocytes of males at 300 ppm and higher and decreased body weight gain and additional pathological effects in the liver were observed at 1000 ppm and higher. At the highest dose level tested (3000 ppm), all male mice died during the first week of testing. For female mice, increased liver weights, HC hypertrophy, HC degeneration and HC vacuolization were observed at 300 ppm and higher. At dose levels of 1000 and 3000 ppm, effects for females were the same as for males. For male mice, the NOEL is 30 ppm (3.9 mg/kg/day) and the LOEL is 100 ppm (13 mg/kg/day), based on increased liver weights and HC hypertrophy. For female mice, the NOEL is 100 ppm (13 mg/kg/day) and the LOEL is 300 ppm (39 mg/kg/day), based on increased liver weights, HC hypertrophy, HC degeneration and HC vacuolization. This study was a range-finding study. Ophthalmologic, hematologic, clinical chemistry and urinalyses examinations were not conducted. In addition, a complete histopathologic examination was not performed. (MRID 42553401)

In a 13-week range-finding study, technical grade bromoxynil phenol was administered orally in gelatin capsules to groups of 2 male and 2 female beagle dogs at dose levels of 0 (control), 1, 5, 8, 12, 16, 20, 30, 40 or 50 mg/kg/day. Treatment-related decreased body weight gain was observed in males at all dose levels tested. At 5 mg/kg/day, occasional panting and liquid feces were also noted and at 8 and 12 mg/kg/day, frequent panting, occasional salivation, unsteady gait, decreased erythrocyte count, decreased hemoglobin, decreased packed cell volume, and increased urea nitrogen were observed. Dose levels of 16 mg/kg/day and higher were clearly excessive and caused mortality and/or signs of severe toxicity. Decreased body weight gain, occasional panting and liquid feces were observed in females at 5 mg/kg/day. At 8 mg/kg/day and higher, effects in females were the same as in males. For males, no NOEL was determined in this study (<1 mg/kg/day). The LOEL is 1 mg/kg/day for males, based on decreased body weight gain. For females, the NOEL is 1 mg/kg/day and the LOEL is 5 mg/kg/day, based on decreased body weight gain, panting and liquid feces. This study was a range-finding study. Only 2 dogs/sex/dose level were used and an insufficient number of tissues was microscopically examined in the control group and at dose levels of 12 mg/kg/day and lower. (MRID 43166701)

In a 21-day subchronic dermal study, technical grade bromoxynil phenol was applied to the shaved dorsal skin of groups of 5 male and 5 female New Zealand white rabbits at dose levels of 0 (deionized water control), 30, 300 or 1000 mg/kg/day for 6 hours/day, 5 days/week, for 3 weeks (24-25 days). Treatment with bromoxynil phenol did not produce any observable dermal or systemic toxicity. The NOEL for dermal irritation and systemic toxicity is 1000 mg/kg/day, the limit dose for a 21-day study. (MRID 42272301)

ii. Bromoxynil Octanoate

In a 13-week subchronic feeding study, technical grade bromoxynil octanoate was administered in the diet to groups of 20-30 male and 20-30 female Sprague Dawley rats at dose levels of 0 (control), 150, 600 or 1100 ppm (0, 11, 45 or 91 mg/kg/day in males and 0, 13, 55 or 111 mg/kg/day in females). An additional group of 30 male and 30 female rats was started at a dose level of 2100 ppm, but was sacrificed during the first week of the study due to high mortality and signs of severe toxicity. No treatment-related signs of toxicity were observed in males at 150 or 600 ppm. At 1100 ppm, the following effects were observed in males: decreased body weight gain, decreased serum total protein, decreased globulins, possibly increased thymic lymphocyte necrosis, and increased degeneration/necrosis of cardiac myofibers. No treatment-related effects were observed in females at 150 ppm. At 600 ppm, decreased body weight gain and increased liver weights were observed in females. At 1100 ppm, the following additional effects were also noted in females: decreased serum total protein, decreased globulins, possibly increased thymic lymphocyte necrosis, and increased degeneration/necrosis of cardiac myofibers. For male rats, the NOEL is 600 ppm (45 mg/kg/day) and the LOEL is 1100 ppm (91 mg/kg/day), based on decreased body weight gain, decreased serum total protein, decreased globulins and increased degeneration/necrosis of cardiac myofibers. For female rats, the NOEL is 150 ppm (13 mg/kg/day) and the LOEL is 600 ppm (55 mg/kg/day), based on decreased body weight gain and increased liver weights. (MRID 42411901)

In a 13-week subchronic oral study, technical grade bromoxynil octanoate was administered orally in gelatin capsules to groups of 2 male and 2 female beagle dogs at dose levels of 0 (control), 0.43, 1.43 or 7.14 mg/kg/day. The only treatment-related effect observed in males and females in this study was decreased body weight gain. For males, mean absolute body weight gains from 0 to 13 weeks were +3.60, +2.80, +2.20 and +1.15 kg for the control, low, mid and high dose level groups respectively. These gains corresponded to 78%, 61% and 32% of the male control group (100%) for the low, mid and high dose level groups respectively. For females, the comparable mean absolute body weight gains were +2.90, +2.05, +1.75 and +0.55 kg. These gains corresponded to 71%, 60% and 19% of the female control group (100%). Although the % of body weight gain compared to controls was 78% for low dose level males and 71% for low dose level females, the corresponding differences in absolute body weight gains were actually less than 1 kg and since the low dose level animals appeared healthy throughout the entire study and showed no other sign of toxicity, it was concluded that the NOEL for both males and females in this study is 0.43 mg/kg/day and the LOEL is 1.43 mg/kg/day, based on decreased body weight gain. (MRID 42869701, 43700201)

In a 13-week subchronic oral study, technical grade bromoxynil octanoate was administered orally in gelatin capsules to groups of 3 male and 3 female beagle dogs at dose levels of 0 (control), 1, 5 or 25 mg/kg/day. No treatment-related effects were observed in either sex at 1 mg/kg/day. At 5 mg/kg/day, occasional panting was noted in both males and females. At 25 mg/kg/day, additional signs of toxicity, observed in both males and females, were panting (after each dose) throughout the study; decreased body weight gain; possibly decreased erythrocyte counts, hemoglobin, and packed cell volume; and increased serum urea nitrogen. The NOEL for both males and females was reported as just under 5 mg/kg/day. (MRID 00061179)

In a 21-day subchronic dermal study, technical grade bromoxynil octanoate was applied to the shaved dorsal skin of 10 male and 10 female New Zealand white rabbits at dose levels of 0 (deionized water control), 30, 300 or 1000 mg/kg/day for 6 hours/day, 5 days/week, for 3 weeks (24-26 days). Treatment with bromoxynil octanoate did not produce any observable systemic effects. Significant dermal irritation, consisting of slight to moderate redness and swelling, cracking and flaking of the skin, was observed at 300 and 1000 mg/kg/day. The NOEL for

systemic toxicity is 1000 mg/kg/day, the limit dose for a 21-day study. The NOEL for dermal irritation is 30 mg/kg/day and the LOEL is 300 mg/kg/day. (MRID 42346201)

c. Chronic Toxicity and Carcinogenicity

i. Bromoxynil Phenol

In a 12-month chronic oral toxicity study, technical grade bromoxynil phenol was administered in gelatin capsules to groups of 6 male and 6 female beagle dogs at dose levels of 0 (control), 0.1, 0.3, 1.5 or 7.5 mg/kg/day. At the highest dose level tested (7.5 mg/kg/day), the following treatment-related effects were observed in both male and female dogs: increased incidences of salivation, panting, liquid feces and pale gums; statistically significant decreased body weight gain over entire duration of study, but particularly during first 8 weeks of study; statistically significant decreased erythrocytes (RBC), hemoglobin (Hb) and packed cell volume (PCV); statistically significant increased urea nitrogen; increased absolute liver weights and liver/body weight ratios. At 1.5 mg/kg/day, a statistically significant decreased body weight gain over the entire duration of study was observed in the male dogs. Other "effects" at this same dose level were marginal, inconsistent and of equivocal toxicological significance. These effects included panting; decreased RBC, Hb and PCV; increased urea nitrogen; and increased absolute and relative liver weights in males and panting and increased absolute and relative liver weights in females. No treatment-related gross or histo-pathological changes were observed in any organs in this study. The dose level of 1.5 mg/kg/day is considered to be a threshold NOEL/LOEL for both male and female dogs in this study. (MRID #40780301, 41304701)

In a 120-week combined chronic feeding/carcinogenicity study, technical grade bromoxynil phenol was administered in the diet to groups of 60 male and 60 female Fischer 344 rats at dose levels of 0 (control), 10, 30 or 100 ppm (equivalent to 0, 0.5, 1.5 or 5 mg/kg/day). Ten rats/sex/dose level were sacrificed and examined at 12 months. An increase in absolute liver weights of the high dose female rats at the 12-month interim sacrifice was considered to be of little concern since a similar increase was not observed at the 120-week terminal sacrifice. No other effects of any kind in either the male or female rats were observed. The NOEL for systemic effects is 100 ppm (5 mg/kg/day) for both male and female rats. An increased incidence of neoplasms was not observed in the male or female rats in this study; however, the dose levels were determined to be too low to assess carcinogenic potential. (MRID 00096521)

In a 2-year combined chronic feeding/carcinogenicity study, technical grade bromoxynil phenol was administered in the diet to Sprague Dawley rats at dose levels of 0 (control), 60, 190 or 600 ppm (0, 2.6, 8.2 or 28 mg/kg/day in males and 0, 3.3, 11.0 or 41 mg/kg/day in females). Groups of 105 male and 105 female rats were given the control diet and groups of 70 male and 70 female rats were given diets containing bromoxynil phenol. Fifteen rats/sex/dose level were sacrificed and examined at 12 months. In male rats, histopathological changes were observed in the liver at 190 ppm (spongiosis hepatis) and at 600 ppm (spongiosis hepatis and foci of eosinophilic cellular alteration). Decreased body weight gain was also noted in male rats at 600 ppm. In female rats, decreased body weight gain was observed at 190 ppm and 600 ppm. No neoplastic lesions were associated with treatment. For male rats, the systemic NOEL is 60 ppm (2.6 mg/kg/day) and the systemic LOEL is 190 ppm (8.2 mg/kg/day), based on an increased incidence of spongiosis hepatis in the liver. For female rats, the systemic NOEL is 60 ppm (3.3 mg/kg/day) and the systemic LOEL is 190 ppm (11.0 mg/kg/day), based on decreased body weight gain. An increased incidence of neoplasms were not observed in the male or female rats. Dose levels used in this study were determined to be sufficiently high to assess carcinogenic potential. (MRID 40612501, 41374801)

In an 18-month carcinogenicity study, technical grade bromoxynil phenol was administered in the diet to groups of 60 male and 60 female Swiss albino mice at dose levels of 0 (control), 10, 30 or 100 ppm (equivalent to 0, 1.3, 3.9 or 13 mg/kg/day). A dose-related increased incidence of liver adenomas/carcinomas combined was observed in the male mice. The increase was statistically significant at 100 ppm. The liver tumor response in male mice was based on both benign and malignant tumors with the carcinomas contributing to almost one-half of the total adenomas/carcinomas at the mid- and high-dose levels. For male mice, the percentage incidences of adenomas were 4%, 8%, 6% and 9%; the percentage incidences of carcinomas were 0%, 0%, 4% and 8%; and the percentage incidences of adenomas/carcinomas combined were 4%, 8%, 10% and 17% for the 0, 10, 30 and 100 ppm groups, respectively. The incidences of hyperplastic nodules in male mice, some of which may have been adenomas, were also increased at the mid- and high-dose levels. Percentage incidences were 4%, 4%, 10% and 9% for the 0, 10, 30 and 100 ppm groups, respectively. An increased incidence of neoplasms was not observed in female mice; however, dose levels for the female mice in this study were determined to be too low to assess carcinogenic potential. (MRID 00068077)

In an 18-month carcinogenicity study, groups of 60 male and 60 female CD-1 mice were given technical grade bromoxynil phenol in the diet at dose levels of 0 (control), 20, 75 or 300 ppm (0, 3.1, 12 or 46 mg/kg/day in males and 0, 3.7, 14 or 53 mg/kg/day in females). Mortality, body weights and food consumption were not affected by treatment. The liver was the target organ. At 300 ppm, treatment-related increased liver weights, increased incidences of diffusely dark livers, and increased incidences of non-neoplastic microscopic lesions in the livers of both male and female mice were observed. Histopathologic lesions in the liver included hepatocellular centrilobular hypertrophy, hepatocellular degeneration/necrosis, and pigment in hepatocytes and Kupffer cells. Similar non-neoplastic lesions were also observed in the livers of some male and female mice at 75 ppm. The LOEL for non-carcinogenic effects in this study for both male and female mice is 75 ppm and the NOEL is 20 ppm. Treatment-related increased incidences of hepatocellular adenomas, carcinomas, and adenomas/carcinomas combined were observed in the male mice at all dose levels in this study. For male mice, the percentage incidences of adenomas were 6%, 16%, 20% and 19%; the percentage incidences of carcinomas were 4%, 16%, 4% and 21%; and the percentage incidences of adenomas/carcinomas combined were 9%, 31%, 24% and 40% for the 0, 20, 75 and 300 ppm groups, respectively. Subsequent to the original pathology reading, liver sections from all male mice in the study were also evaluated by a second independent pathologist. Similar results were obtained in the second pathology evaluation. For female mice given 300 ppm, slightly increased incidences of hepatocellular carcinomas and of adenomas/carcinomas combined also were considered to be related to treatment with bromoxynil phenol. For female mice, the percentage incidences of carcinomas were 0%, 2%, 0% and 10%; and the percentage incidences of adenomas/carcinomas combined were 4%, 4%, 4% and 17% for the 0, 20, 75 and 300 ppm groups, respectively. Liver sections from female mice in this study were not reevaluated by the independent pathologist. (MRID 43245501, 43311701)

ii. Bromoxynil Octanoate

There are no chronic toxicity studies available in which bromoxynil octanoate was the test material. There are no carcinogenicity studies available in which bromoxynil octanoate was the test material.

d. Developmental Toxicity

i. Bromoxynil Phenol

In an oral developmental toxicity study, technical grade bromoxynil phenol was administered to groups of 22 pregnant Sprague Dawley rats by gavage at doses of 0 (control), 4, 12.5 or 40 mg/kg/day on gestation days 6-15, inclusive. The developmental toxicity NOEL is 4 mg/kg/day. A dose-related increased incidence of supernumerary (14th) ribs was observed at the developmental toxicity LOEL of 12.5 mg/kg/day. Increased post-implantation loss was also observed at 12.5 mg/kg/day. At 40 mg/kg/day, the following additional effects were observed in the offspring: reduced fetal weight, increased numbers of small fetuses, and increased incidences of soft tissue and skeletal abnormalities (including anophthalmia, microphthalmia, short renal papilla, and spinal and thoracic bone abnormalities). The maternal toxicity NOEL is 12.5 mg/kg/day and the maternal toxicity LOEL is 40 mg/kg/day, based on decreased body weight gain throughout most of the treatment and post-treatment period and decreased food consumption during the treatment period. (MRID 40466802)

In an oral developmental toxicity study, groups of 28 pregnant Sprague Dawley rats received 0 (control), 5, 15 or 35 mg/kg/day of technical grade bromoxynil phenol by gavage on gestation days 5-17, inclusive. No developmental toxicity NOEL was determined in this study (below 5 mg/kg/day). At the LOEL of 5 mg/kg/day, a dose-related increased incidence of 14th ribs was observed. At the high dose of 35 mg/kg/day, additional effects included an increased incidence of late intrauterine deaths, decreased fetal body weights and an increase in the total incidence of minor anomalies. The maternal toxicity NOEL is 5 mg/kg/day and the maternal toxicity LOEL is 15 mg/kg/day, based on decreased body weight gain. At 35 mg/kg/day, 6/28 dams died between days 7 and 14 of gestation. (MRID 00116558)

Groups of 20-25 pregnant Sprague Dawley rats were given 0 (control), 1.7, 5 or 15 mg/kg/day of technical grade bromoxynil phenol by oral gavage on gestation days 6-15, inclusive. In the offspring, the litter incidences of supernumerary ribs were 30%, 60%, 50% and 90% in the control, 1.7, 5 and 15 mg/kg/day groups, respectively. The percentages of litters with supernumerary ribs were significantly increased at the 1.7 and 15 mg/kg/day dose levels. However, the increase at 1.7 mg/kg/day was not considered to be biologically significant. The developmental toxicity NOEL is 5 mg/kg/day and the developmental toxicity LOEL is 15 mg/kg/day, based on an increased incidence of supernumerary ribs. The maternal toxicity NOEL is 5 mg/kg/day and the maternal toxicity LOEL is 15 mg/kg/day, based on decreased body weight gain and increased liver weights. No consistent effects were seen on thymus, spleen or adrenal weights suggesting there was no generalized stress response in the dams. (Rogers, Francis, Barbee et al., 1991)

In a dermal developmental toxicity study, bromoxynil phenol (solubilized in water containing 50 mg/ml sodium hydroxide and 20% triethylene glycol) was applied to groups of 23 pregnant Sprague Dawley rats at dose levels of 0 (control), 5, 10, 50 or 100 mg/kg/day for 6 hours/day on gestation days 6-15, inclusive. A dose-related increased incidence of supernumerary (14th) ribs was observed in this study at 10, 50 and 100 mg/kg/day. At 10 mg/kg/day, however, the increased incidence was not statistically significant compared to the concurrent control group and was within the historical control range. The developmental toxicity NOEL is 10 mg/kg/day and the developmental toxicity LOEL is 50 mg/kg/day, based on increased 14th ribs. The maternal toxicity NOEL is 50 mg/kg/day and the maternal toxicity LOEL is 100 mg/kg/day, based on decreased body weight gain and decreased food consumption during the treatment period. No deaths or clinical signs, including skin irritation, were attributed to treatment with the test material in this study. (MRID 40881201, 40883601)

In an oral developmental toxicity study, technical grade bromoxynil phenol was administered to groups of 18 or more pregnant New Zealand white rabbits by gavage at doses of 0 (control), 15, 30 or 60 mg/kg/day on days 5-20 of gestation. A high incidence (on a litter basis) and a dose-related increased incidence (on a fetal basis) of fully formed bilateral 13th ribs and an increased incidence of all forms of supernumerary ribs were observed at 15, 30 and 60 mg/kg/day. At 60 mg/kg/day, the following additional effects were also observed: increased post-implantation loss (due primarily to 5 totally resorbed litters), decreased fetal weights, and increased numbers of litters and numbers of fetuses with major malformations (including hydrocephalus, anophthalmia, microphthalmia and defects in skull ossification). The incidence of total minor anomalies was also increased at 60 mg/kg/day. The NOEL for developmental toxicity was not determined in this study (below 15 mg/kg/day). The developmental toxicity LOEL is 15 mg/kg/day, based on the increased incidence of supernumerary ribs. The maternal toxicity NOEL is 15 mg/kg/day and the maternal toxicity LOEL is 30 mg/kg/day, based on reduced body weight gain and reduced food consumption during the treatment period. There were no deaths or clinical signs of toxicity associated with treatment. (MRID 00138149)

In an oral developmental toxicity study, groups of 22-23 pregnant New Zealand white rabbits were given 0 (control), 30, 45 or 60 mg/kg/day of technical grade bromoxynil phenol by gavage on gestation days 6-18, inclusive. The number of fetuses with decreased body weights (30% below control mean weight) was significantly increased at all dose levels. At 45 and 60 mg/kg/day, a dose-related increase in extra or rudimentary 14th ribs also was observed. At 60 mg/kg/day, several vertebral and thoracic bone abnormalities, including fused ribs, scoliosis, extra ribs, thoracic centrum misshapen and incomplete ossification of sternebrae, were observed. A NOEL for developmental toxicity was not determined in this study (below 30 mg/kg/day). The developmental toxicity LOEL is 30 mg/kg/day, based on decreased fetal weights. The maternal toxicity NOEL is 45 mg/kg/day and the maternal toxicity LOEL is 60 mg/kg/day, based on increased mortality (7/23 dams died at this dose level) and other clinical signs of toxicity, including anorexia and discharge of blood. (MRID 00142779)

In a dermal developmental toxicity study, bromoxynil phenol (solubilized in water containing 50 mg/ml sodium hydroxide and 20% triethylene glycol) was applied to groups of 20 pregnant New Zealand white rabbits at dose levels of 0 (control), 10, 50 or 150 mg/kg/day for 6 hours/day on gestation days 6-18, inclusive. The results in this study were compromised by 25 rabbits possibly being improperly dosed on days 6 and/or 7 of gestation. The developmental toxicity NOEL is 10 mg/kg/day and the developmental toxicity LOEL is 50 mg/kg/day, based on an apparent increase in agenesis of the intermediate lobe of the lung and on an increase in holes in the parietal portion of the skull. Lung agenesis has not been observed in other studies with bromoxynil and its incidence in historical controls is highly variable. The incidence of supernumerary ribs was not affected in this study. The maternal toxicity NOEL is 50 mg/kg/day and the maternal toxicity LOEL is 150 mg/kg/day, based on decreased body weight gain. Because of flaws in the execution of this study, the results have been interpreted with considerable caution and the NOELs and LOELs are considered to be tentative. (MRID 40935101, 41307801)

Groups of 16-35 pregnant Swiss Webster (CD-1) mice were given 0 (control), 11, 32 or 96 mg/kg/day of technical grade bromoxynil phenol by oral gavage on gestation days 6-15, inclusive. In the offspring, the litter incidences of 14th ribs were 50%, 28%, 56% and 81% in the control, 11, 32 and 96 mg/kg/day groups, respectively. The increased incidence was statistically significant at the high dose. Also at 96 mg/kg/day, decreased fetal weights and decreased numbers of fetuses with ossified caudal vertebrae were observed. The developmental toxicity NOEL is 32 mg/kg/day and the developmental toxicity LOEL is 96 mg/kg/day, based on increased incidence of 14th ribs, decreased fetal weights and decreased numbers of fetuses with ossified vertebrae. The maternal toxicity NOEL is 11 mg/kg/day and the maternal toxicity LOEL is 32 mg/kg/day, based on increased

mortality and increased liver weights. No consistent effects were seen on thymus, spleen or adrenal weights suggesting there was no generalized stress response in the dams. (Rogers, Francis, Barbee et al., 1991)

ii. Bromoxynil Octanoate

In an oral developmental toxicity study, technical grade bromoxynil octanoate was administered to groups of 17-20 pregnant Sprague Dawley rats by gavage at doses of 0 (control), 2.4, 7.3 or 21.8 mg/kg/day on gestation days 6-15, inclusive. In the offspring, the litter incidences of 14th ribs were 29%, 40%, 37% and 65% in the control, low, mid and high dose groups, respectively. The increased incidence was statistically significant at the high dose. Reduced fetal weights were also observed in the high dose group. The developmental toxicity NOEL is 7.3 mg/kg/day and the developmental toxicity LOEL is 21.8 mg/kg/day, based on an increased incidence of 14th ribs and on reduced fetal weights. The maternal toxicity NOEL is 7.3 mg/kg/day and the maternal toxicity LOEL is 21.8 mg/kg/day, based on decreased body weight gain and increased liver weights. No consistent effects were seen on thymus, spleen or adrenal weights suggesting there was no generalized stress response in the dams. (Rogers, Francis, Barbee et al., 1991)

In a dermal developmental toxicity study, bromoxynil octanoate (Buctril formulation diluted in water) was applied to groups of 25 pregnant Sprague Dawley rats at dose levels of 0 (Buctril formulation inerts and water controls), 2, 5, 10, 15, 20 or 75 mg a.i./kg/day for 6 hours/day on gestation days 6-15, inclusive. The developmental toxicity NOEL is 10 mg a.i./kg/day. A dose-related increased incidence of supernumerary (14th) ribs was observed at the developmental toxicity LOEL of 15 mg a.i./kg/day. At 20 and 75 mg a.i./kg/day, the incidences of supernumerary ribs were increased still further. Skin irritation was observed in the Buctril formulation inerts control and 75 mg a.i./kg/day treatment groups. The maternal toxicity NOEL is 15 mg a.i./kg/day and the maternal toxicity LOEL is 20 mg a.i./kg/day, based on decreased body weight gain and decreased food consumption during the treatment period. (MRID 41163301)

In a dermal developmental toxicity study, groups of 20 pregnant New Zealand white rabbits were treated with bromoxynil octanoate (Buctril formulation diluted in water) at dose levels of 0 (Buctril formulation inerts and water controls), 5, 10, 15, 20, 40 or 80 mg a.i./kg/day for 6 hours/day on gestation days 6-18, inclusive. Incidences of 13th ribs were high in control and all treatment groups. A dose-response relationship, however, was not evident and it was concluded that no adverse effects on offspring development were observed. The developmental toxicity NOEL is 80 mg a.i./kg/day. A developmental toxicity LOEL was not determined in this study (above 80 mg a.i./kg/day). Significant skin irritation was observed in the Buctril formulation inerts control and all treatment groups. At 15 mg a.i./kg/day and higher, the majority of rabbits displayed erythema, fissuring and desquamation. The frequency and severity of skin irritation increased with increasing concentration of Buctril. Desquamation persisted for most of the post-treatment period. Skin irritation, however, did not appear to adversely affect maternal well-being. No systemic toxicity was observed in the dams at any dose level. The NOEL for systemic maternal toxicity is 80 mg a.i./kg/day. A LOEL for systemic maternal toxicity was not determined in this study (above 80 mg a.i./kg/day). (MRID 41471901, 42183901)

e. Reproductive Toxicity

i. Bromoxynil Phenol

In a 2-generation reproduction study, technical grade bromoxynil phenol was administered in the diet to groups of 24 male and 24 female Sprague Dawley rats at dose levels of 0 (control), 10, 50 or 250 ppm (approximately 0, 0.8, 4 or 21 mg/kg/day during 14 weeks prior to mating). No reproductive toxicity was observed in this study at any dose level. The NOEL for developmental toxicity in offspring is 50 ppm (4 mg/kg/day) and the LOEL is 250 ppm (21 mg/kg/day), based on decreased body weight gain during lactation and delayed eye opening. The NOEL for systemic toxicity in adult rats is 50 ppm (4 mg/kg/day) and the LOEL is 250 ppm (21 mg/kg/day), based on decreased body weight gain in F0 and F1 females before mating, during gestation and lactation and at study termination. In addition, possibly increased liver weights were observed in both male and female adults. (MRID 41149301)

In a 3-generation reproduction study, technical grade bromoxynil phenol was administered in the diet to groups of 10 male and 20 female Wistar rats at dose levels of 0 (control), 30, 100 or 300 ppm (equivalent to 0, 1.5, 5 or 15 mg/kg/day). Definitive NOELs and LOELs were not determined in this study due to numerous deficiencies in data reporting. The following NOELs and LOELs are therefore tentative. No reproductive toxicity was observed in this study at any dose level. The NOEL for developmental toxicity in offspring is 100 ppm (5 mg/kg/day) and the LOEL is 300 ppm (15 mg/kg/day), based on decreased body weight gain, particularly in the F2 generation. The NOEL for systemic toxicity in adult rats is 30 ppm (1.5 mg/kg/day) and the LOEL is 100 ppm (5 mg/kg/day), based on decreased body weight gain in F1 and F2 parents. (MRID 00064815)

ii. Bromoxynil Octanoate

In a specially designed dermal reproduction study, groups of 20 male Crl:CRBR VAF/Plus rats were treated for 6 hours each day for 21 days with bromoxynil octanoate (Buctril formulation diluted in water) at dose levels of 0 (Buctril formulation inerts and water controls), 25, 50 or 100 mg a.i./kg/day. After 21 days of treatment, the male rats were mated with untreated female rats on days 1, 7, 14, 21, 35, 56 or 113 post-exposure. No effects on mating or fertility were observed in the male rats at any dose level. Possibly reduced prostate gland weight on day 1 post-exposure, however, was observed at 100 mg a.i./kg/day. The NOEL for male reproductive toxicity is 50 mg a.i./kg/day (tentative) and the LOEL is 100 mg a.i./kg/day (tentative), based on possibly decreased prostate gland weight. No effects on offspring development were observed. The NOEL for reproductive toxicity in offspring is 100 mg a.i./kg/day (HDT) and the LOEL is greater than 100 mg a.i./kg/day. The NOEL for systemic toxicity in the adult male rats is 25 mg a.i./kg/day and the LOEL is 50 mg a.i./kg/day, based on decreased body weight gain. At 100 mg a.i./kg/day, possibly increased liver weights were also observed. Significant skin irritation was observed in the control group (Buctril formulation inerts only) and Buctril treated groups, particularly at 100 mg a.i./kg/day. This study is a specially designed study and does not satisfy the requirement for a multigeneration reproduction study in rats (Guideline 83-4). (MRID 41667401)

f. Mutagenicity

i. Bromoxynil Phenol

In an unscheduled DNA synthesis (UDS) assay, cultures of primary rat hepatocytes were exposed to technical grade bromoxynil phenol at concentrations ranging from 0.1 to 50 ug/ml. At 50 ug/ml, all cells died. At 25 ug/ml, the next highest concentration, cell survival was 31%. Cell survival increased with decreasing concentrations of test material. The positive control (2-

acetylaminofluorene) was adequate. Bromoxynil phenol did not cause an appreciable increase in mean net nuclear grain counts compared to the negative solvent control at any of the evaluated concentrations. Bromoxynil phenol did not induce a genotoxic effect in this assay system. (MRID 00115646)

In an in vitro transformation assay, cultures of mouse C3H/10T ½ C18 cells were exposed to technical grade bromoxynil phenol at concentrations ranging from 32.5 to 390 ug/ml. Based on results in a preliminary cytotoxicity study, cell survival at these concentrations was expected to be between 20% and 100%. The positive control, benz(a)pyrene, was satisfactory. After incubation of cell cultures for approximately 6 weeks, a pooled average of Type II and Type III foci/culture was scored as the frequency of transformation. The frequency of transformed foci in bromoxynil phenol treated cultures was equal to or less than in the negative solvent control. Bromoxynil phenol did not induce a genotoxic effect in this assay system. (MRID 00115647)

In a sister chromatid exchange (SCE) assay, cultures of Chinese hamster ovary (CHO) cells were exposed to technical grade bromoxynil phenol without metabolic activation at concentrations ranging from 4.67 to 18.7 ug/ml and with metabolic activation (rat S9 mixture) at concentrations ranging from 500 to 900 ug/ml. The solvent used was DMSO. The positive controls (mitomycin c for non-activated system and cyclophosphamide for activated system) were adequate. After incubation, chromosome preparations were stained and examined. Bromoxynil phenol, without and with metabolic activation, did not induce any significant increases in sister chromatid exchanges. Bromoxynil phenol did not induce a genotoxic effect in this assay system. (MRID 00115648)

In a mouse lymphoma forward mutation assay, cultures of L5178Y TK +/- cells were exposed to technical grade bromoxynil phenol without metabolic activation at concentrations ranging from 15.6 to 250 ug/ml and with metabolic activation (rat S9 mixture) at concentrations of 3.9, 7.8, 15.6, 31.3 or 62.5 ug/ml. The solvent used was DMSO. The positive controls (ethylmethane sulfonate for non-activated system and dimethylnitrosamine for activated system) were satisfactory. After incubation, the mutant frequency was calculated as the ratio of mutant colonies to viable colonies. In the non-activated system, there were no significant increases in mutant frequency at any concentration when compared to that of the untreated and negative solvent controls--even at the highly toxic concentration of 250 ug/ml (9.5% relative growth). Significant increases in the mutant frequency, however, did occur in the activated system at the two highest, most toxic concentrations of test material. At the moderately toxic concentration of 31.3 ug/ml (39.6% relative growth), there was a 2 fold increase in mutant frequency above background levels and at the highly toxic concentration of 62.5 ug/ml (7.9% relative growth), there was a 4.1 fold increase in mutant frequency above background levels. Mutant frequencies in the positive control were greatly in excess of background levels. Bromoxynil phenol did not induce a genotoxic effect in the non-activated portion of this assay, but the dose-related increase in mutant colonies in the activated portion of this assay was considered to be a positive genotoxic response. (MRID 00115649)

In a bacterial DNA repair test using Escherichia coli indicator strains pol A+ (W3110) and pol A- (p3478), cultures of both indicator strains on agar plates were exposed to technical grade bromoxynil phenol without and with metabolic activation (rat S9 mixture) at concentrations ranging from 1.0 to 10000 ug/plate. The test material was placed in wells of uniform diameter in the center of each agar plate. The solvent used was DMSO. The positive controls (ethylmethane sulfonate and methylmethane sulfonate for non-activated system and dimethylnitrosamine for activated system) were adequate. The preferential inhibition of the pol A- strain, relative to the pol A+ strain, was determined by measuring the differential zones of inhibition produced by the test material around each well. Differential zones of inhibition, indicating a mutagenic event (involving DNA polymerase I enzyme), were observed in both the non-activated and activated systems at

concentrations from 1000 ug/plate to 10000 ug/plate. A dose-response effect was evident at concentrations from 500 ug/plate (NOEL) to 5000 ug/plate in both systems. At 10000 ug/plate, a dose-response effect may have been obscured by the high level of background cytotoxicity. Bromoxynil phenol induced a positive genotoxic response in both the non-activated and activated portions of this assay. (MRID 00115650)

In an in vitro chromosome aberration assay, cultures of Chinese hamster ovary (CHO) cells were exposed to technical grade bromoxynil phenol without metabolic activation at concentrations ranging from 100 to 1500 ug/ml (8 hour exposure) and from 50 to 500 ug/ml (20 hour exposure). CHO cells were also exposed to test material with metabolic activation (rat S9 mixture) for 2 hours at concentrations ranging from 300 to 1500 ug/ml (trial 1) and at concentration ranging from 1200 to 1600 ug/ml (trial 2). The solvent used was DMSO. The positive controls (mitomycin C for non-activated system and cyclophosphamide for activated system) were adequate. After incubation, chromosome preparations were stained and examined. In the non-activated system, there was no significant increase in chromosome aberrations when compared to the untreated and negative solvent controls. In the activated system, however, significant increases in chromosome aberrations above background levels were observed. In trial 1 at 1500 ug/ml, but not at lower concentrations, a statistically significant increase in chromosome aberrations was observed. These aberrations included numerous simple chromosome breaks and chromatid breaks and also complex aberrations such as chromatid interchanges. In trial 2 at all concentrations (1200 to 1600 ug/ml), significant increases in chromosome aberrations, including simple breaks and complex chromatid aberrations, were again observed. Bromoxynil phenol did not induce a genotoxic effect in the non-activated portion of this assay, but the significant increase in chromosome damage in the activated portion of this assay at concentrations equal to and above 1200 ug/ml was considered to be a positive genotoxic response. (MRID 00115651)

In an in vivo micronucleus assay, two doses of bromoxynil phenol were administered orally by gavage on two consecutive days to groups of 5 male and 5 female CD-1 mice at dose levels of 0 (control), 21.6, 69.0 or 215 mg/kg/day. Dose levels were based on a previously determined LD50 of 431 $\pm$ 177 mg/kg/day under similar conditions. Bone marrow was taken 6 hours after the second dose and examined for micronuclei in polychromatic erythrocytes (PCE). Normochromatic erythrocytes (NCE) were also counted and the NCE/PCE ratio was recorded for each animal. The positive control (cyclophosphamide) was satisfactory. At 215.5 mg/kg/day, 5 mice died shortly after dosing. At 215.5 (in survivors) and 69.0 mg/kg/day, depressed hematopoiesis, evidenced by shifts in the NCE/PCE ratio, indicated target cell cytotoxicity. No increased frequencies of micronuclei were observed at any dose level in the bone marrow cells of treated mice. Bromoxynil phenol did not induce a clastogenic effect in this assay system. (MRID 00124803)

In a forward mutation assay, cultures of Chinese hamster ovary (CHO)/HGPRT locus cells were exposed to technical grade bromoxynil phenol without and with metabolic activation (rat S9 mixture) at concentrations ranging from 100 to 1000 ug/ml. The solvent used was DMSO. The positive controls (5-bromo-2'-deoxyuridine for non-activated system and 3-methylcholanthrene for activated system) were adequate. After incubation, mutation frequencies were determined and compared to the negative solvent control. In the non-activated system, the concentration of 1000 ug/ml was severely toxic (4.5% relative growth). In the activated system, concentrations of 800 ug/ml and higher were also severely toxic ($\leq$ 2.7% relative growth). Cell survival increased with decreasing concentrations of test material. In the non-activated system, the test material did not significantly increase the mutation frequency at the HGPRT locus. In the activated system, increases in the mutation frequency were observed at several concentrations of test material, but were not dose-related, did not exceed the testing laboratory's acceptable background frequency, and therefore were not considered to be mutagenic events. Bromoxynil phenol, without and with metabolic activation, did not induce a genotoxic effect in this assay system. (MRID 41995702)

In a Salmonella/mammalian microsome reverse mutation assay (Ames study), strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to technical grade bromoxynil phenol without metabolic activation at concentrations ranging from 3.33 to 1000 ug/plate and with metabolic activation (rat S9 mixture) at concentrations ranging from 10.0 to 3330 ug/plate. Cytotoxicity was observed in the majority of strains exposed to 1000 ug/plate in the non-activated system and in most strains exposed to 1000 ug/plate and higher in the activated system. The solvent used was DMSO. The several positive controls (sodium azide, 2-nitrofluorene and ICR 191 for non-activated system and 2-aminoanthracene for activated system) were satisfactory. After incubation, mean numbers of revertant mutant colonies per plate were determined for each strain. Noncytotoxic concentrations of bromoxynil phenol did not significantly increase the number of revertant mutant colonies per plate over background levels in any of the 5 strains tested, without or with metabolic activation, at any of the evaluated concentrations. Bromoxynil phenol, without and with metabolic activation, did not induce a genotoxic effect in this assay system. (MRID 41995701)

In an in vivo micronucleus assay, single doses of technical grade bromoxynil phenol were administered orally by gavage to groups of 5 male and 5 female CD-1 mice at dose levels of 0 (control), 35, 70 or 105 mg/kg. Dose levels were based on the results in a previously conducted toxicity study in which dose-related mortalities of up to 80% were observed between 125 and 275 mg/kg under similar conditions. Bone marrow cells, harvested at 24, 48 and 72 hours postexposure in the high dose group and at 24 hours postexposure in the mid and low dose groups, were examined for the frequency of micronuclei in polychromatic erythrocytes (PCE). Normochromatic erythrocytes (NCE) were also counted and the PCE/NCE ratio was recorded for each animal. The positive control (cyclophosphamide) was adequate. At 105 mg/kg, 1 mouse died. No evidence of a cytotoxic response, as evidenced by an altered PCE/NCE ratio, was observed in the bone marrow cells of either sex at any dose level or sacrifice time, but the single mortality at the high dose level was consistent with the results in the previously conducted toxicity study and indicated that an appropriately high dose level was evaluated in the micronucleus assay. No increased frequencies of micronuclei were observed at any dose level or sacrifice time in the bone marrow cells of treated male or female mice. Bromoxynil phenol did not induce a clastogenic effect in this assay system. (MRID 42092301)

ii. Bromoxynil Octanoate

In a Salmonella/mammalian microsome reverse mutation assay (Ames study), strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to technical grade bromoxynil octanoate without and with metabolic activation (rat S9 mixture) at concentrations ranging from 33 to 10000 ug/plate. Compound precipitation was observed at 10000 ug/plate and minimal to moderate cytotoxicity was observed in the majority of strains exposed to 3333 ug/plate and higher. The solvent used was DMSO. The several positive controls (sodium azide, 2-nitrofluorene and 9-aminoacridine for non-activated system and 2-aminoanthracene for activated system) were satisfactory. After incubation, mean numbers of revertant mutant colonies per plate were determined for each strain. Noncytotoxic concentrations of bromoxynil phenol did not significantly increase the number of revertant mutant colonies per plate over background levels in any of the 5 strains tested. Bromoxynil octanoate, without and with metabolic activation, did not induce a genotoxic effect in this assay system. (MRID 43022701)

In an in vivo micronucleus assay, single doses of technical grade bromoxynil octanoate were administered orally by gavage to groups of 5 male CD-1 mice at dose levels up to 183 mg/kg and to groups of 5 female CD-1 mice at dose levels up to 267 mg/kg. Dose levels were based on the results in previously conducted toxicity studies in which the LD50 for males and females were determined to be 262 and 382 mg/kg, respectively. Bone marrow cells, harvested at 24, 48 and 72 hours postexposure in the high dose group and at 24 hours postexposure in the mid and low

dose groups, were examined for the frequency of micronuclei in polychromatic erythrocytes (PCE). Normochromatic erythrocytes (NCE) were also counted and the PCE/NCE ratio was recorded for each animal. The positive control (cyclophosphamide) was adequate. At 183 mg/kg, no male mice died, but at 267 mg/kg, 2 female mice died. No evidence of a cytotoxic response was observed in the bone marrow cells of either sex at any dose level or sacrifice time, but the mortalities at the high dose level for females was consistent with the results in the previously conducted toxicity study and indicated that an appropriately high dose level was evaluated. In males, although no deaths occurred, it was doubtful that the use of a higher lethal dose would have affected the outcome of the study. No increased frequencies of micronuclei were observed at any dose level or sacrifice time in the bone marrow cells of treated male or female mice. Bromoxynil octanoate did not induce a clastogenic effect in this assay system. (MRID 41930802)

In an unscheduled DNA synthesis (UDS) assay, cultures of primary rat hepatocytes were exposed to technical grade bromoxynil octanoate at concentrations ranging from 0.98 to 15.63 ug/ml. Higher concentrations ($\geq$ 31.25 ug/ml) were cytotoxic. The solvent used was DMSO. The positive control (2-acetylamino-fluorene) was adequate. Bromoxynil octanoate did not induce an appreciable increase in mean net nuclear grain counts compared to the negative solvent control at any of the evaluated concentrations. Bromoxynil octanoate did not induce a genotoxic effect in this assay system. (MRID 42078901)

g. Metabolism

i. Bromoxynil Phenol

No general metabolism study (Guideline 85-1) is available in which bromoxynil phenol was the test material. The requirement for a general metabolism study on bromoxynil phenol, however, has been waived since sufficient information on the pharmacokinetics and metabolism of bromoxynil phenol per se has been derived from general metabolism studies on bromoxynil octanoate and bromoxynil heptanoate. Refer to the discussion under k. Toxicity Equivalence below for additional information on the bromoxynil heptanoate metabolism study.

ii. Bromoxynil Octanoate

The absorption, distribution, excretion and metabolism of bromoxynil octanoate were studied in male and female Sprague Dawley rats given single oral doses of ^{14}C-bromoxynil octanoate by gavage at dose levels of 2 or 20 mg/kg or at a dose level of 2 mg/kg following 14 days of unlabeled bromoxynil octanoate administered by oral gavage at a dose level of 2 mg/kg/day. Results were similar regardless of dosing regimen. Rate of absorption was moderate in both males and females; peak plasma concentrations of radioactivity were not reached until 7-10 hours after dosing. Radioactivity was widely distributed in most tissues; highest concentrations were observed in blood, plasma, liver, kidneys and thyroid (especially in females). Levels of radioactivity in tissues were generally higher in females than in males. Most radioactivity was excreted in the urine (about 84-89% in males and 76-80% in females at 7 days) and considerably lesser amounts in the feces (about 6-10% in both males and females at 7 days). Excretion was more rapid in males than in females. Retention of radioactivity in tissues after 7 days was about 2-3% in males and 7-9% in females. Essentially all bromoxynil octanoate was rapidly and nearly completely converted to bromoxynil phenol via ester hydrolysis. In special studies, the only chemical species identified in tissues was bromoxynil phenol per se; no bromoxynil octanoate was identified in tissues. In urine, the only major species was free and conjugated bromoxynil phenol with no bromoxynil octanoate being present. In feces, however, some bromoxynil octanoate was identified. (MRID 00154756, 00154757, 42901001)

h. Neurotoxicity

i. Bromoxynil Phenol

No potential for neurotoxicity has been observed in any of the animal studies with bromoxynil phenol. Neither a delayed neurotoxicity study in hens (Guideline 81-7) nor a 28-day delayed neurotoxicity in hens (Guideline 82-6) is required. The requirements for an acute neurotoxicity study in rats (Guideline 81-8) and a 90-day neurotoxicity study in rats (Guideline 82-7) are reserved.

ii. Bromoxynil Octanoate

No potential for neurotoxicity has been observed in any of the animal studies with bromoxynil octanoate. Neither a delayed neurotoxicity study in hens (Guideline 81-7) nor a 28-day delayed neurotoxicity in hens (Guideline 82-6) is required. The requirements for an acute neurotoxicity study in rats (Guideline 81-8) and a 90-day neurotoxicity study in rats (Guideline 82-7) are reserved.

i. Dermal Absorption

i. Bromoxynil Phenol

^{14}C-Bromoxynil phenol, solubilized in water with sodium hydroxide, was topically applied to the skin of male Sprague Dawley rats at doses of 0.10, 1.0 or 10.0 mg/rat for durations of exposure of 0.5, 1, 2, 4, 10 or 24 hours (4 rats/dose/duration of exposure). The quantity of radioactivity absorbed increased with dose and duration of exposure. Percent dermal absorption at 10 hours was 1.92%, 1.74% and 1.24% for doses of 0.10, 1.0 and 10.0 mg/rat respectively. Following a soap and water wash (at 10 hours), 22.64%, 10.79% and 3.79% of the respective doses remained in/on the skin. Percent dermal absorption at 24 hours was 3.12%, 3.24% and 3.02% for doses of 0.10, 1.0 and 10.0 mg/rat respectively. Following a soap and water wash (at 24 hours), 18.99%, 7.84% and 2.03% of the respective doses remained in/on the skin. (MRID 40854602)

ii. Bromoxynil Octanoate

^{14}C-Bromoxynil octanoate, incorporated into the end-use product Buctril, which contained 33.4% bromoxynil octanoate as the active ingredient, was topically applied to the skin of male Sprague Dawley rats at doses of 0.08, 0.4 or 3.4 mg/rat for durations of exposure of 0.5, 1, 2, 4, 10 or 24 hours (4 rats/dose/duration of exposure). The quantity of radioactivity absorbed increased with dose and duration of exposure. Percent dermal absorption at 10 hours was 10.32%, 7.07% and 4.51% for doses of 0.08, 0.4 and 3.4 mg/rat respectively. Following a soap and water wash (at 10 hours), 6.46%, 8.06% and 6.13% of the respective doses remained in/on the skin. Percent dermal absorption at 24 hours was 17.58%, 18.43% and 10.88% for doses of 0.08, 0.4 and 3.4 mg/rat respectively. Following a soap and water wash (at 24 hours), 7.91%, 9.50% and 4.97% of the respective doses remained in/on the skin. (MRID 40854603)

j. Other toxicological Concerns

Bromoxynil has been temporarily registered for use on transgenic cotton as a contact herbicide to control broadleaf weeds. Normal cotton is sensitive to bromoxynil. The transgenic variety has been developed to resist the harmful effects of bromoxynil by hydrolyzing nitrile groups to a carboxylic acid, 3, 5 - dibromo-4-hydroxybenzoic acid (DBHA). In effect, this allows the cotton

grower to apply bromoxynil based on the size of the weed not to the size of the cotton .

The toxicity of DBHA must be considered as a result of the use on cotton. Significant residues of DBHA are present on cotton. At an *ad hoc* meeting of the HED Metabolism Committee held February 19, 1997, the structures of bromoxynil and DBHA were evaluated. Based on their examination of the known structures, there was no concern that DBHA would exhibit significant toxicity over that of the parent bromoxynil. This position was re-examined on May 27, 1997, in response to comments received by the Agency from the National Coalition of Concerned Scientists who consider DBHA possibly more toxic than the parent. The Agency concluded that bromoxynil and DBHA are extremely similar in structure, varying only in that bromoxynil has a cyano (-CN) group that has been converted to a carboxyl (-COOH) group in the DBHA metabolite. Conversion to a carboxyl group is generally considered to decrease the toxicity of a molecule. The conversion to the carboxyl group should cause the DBHA to be more polar and therefore more soluble in water and less in fats. Additionally, the presence of the carboxyl group will allow DBHA to combine (conjugate) with certain water soluble molecules (e.g. glucuronic acid) which should further increase DBHA's water solubility and further decrease its solubility in fats. This increased water solubility as well as the decreased fat solubility means that DBHA should be eliminated faster from the organism than bromoxynil, and thus DBHA is less likely than bromoxynil to remain in the cell and engage in the formation of additional, possibly toxic metabolites. However, until adequate data are reviewed and found acceptable which indicate DBHA is less toxic than the parent compound, HED assumes that DBHA has the same toxicity as the parent compound bromoxynil.

Additional data (four acute studies, two mutagenicity studies, and one subchronic study) addressing the toxicity of DBHA have been submitted to the Agency. These studies are currently undergoing review within HED. Based on the results of these reviews, if appropriate HED will revise the determination that DBHA has the same toxicity as the parent compound bromoxynil.

k. Toxicity Equivalence

According to the HED RfD Peer Review Committee that met on February 29, 1996, bromoxynil (phenol) and bromoxynil octanoate have been determined to be toxicologically equivalent. Bromoxynil occurs in the form of the phenol [bromoxynil phenol]; in the form of the octanoate acid ester of bromoxynil [bromoxynil octanoate]; and in the forms of several other organic acid esters of bromoxynil [such as bromoxynil heptanoate, bromoxynil butyrate, etc.]. Based on the results of "bridging" studies and other relevant information, bromoxynil (phenol), bromoxynil octanoate and bromoxynil heptanoate have been determined to be toxicologically equivalent on a molar bases.

A critical part of the evidence supporting these conclusions was determination that ester hydrolysis of bromoxynil octanoate to bromoxynil phenol (and octanoic acid) readily and almost completely occurs in vivo following oral administration. Later this was shown to be the case for bromoxynil heptanoate.

Since bromoxynil heptanoate and bromoxynil octanoate would be expected to have nearly identical chemical/physical properties (based on their very close chemical structures), it was hypothesized that hydrolysis of bromoxynil heptanoate to bromoxynil phenol (and heptanoic acid) also would readily and completely occur in vivo following oral administration and phenol as the test material would be the same, both qualitatively and quantitatively, as the results of oral studies using bromoxynil heptanoate as the test material.

The Agency required that a general metabolism study and special tissue distribution metabolite study in rats (MRID # 431914-01, DER # 010982 study date 12/22/93) using

bromoxynil heptanoate as the test material be submitted. These studies were received, reviewed and the overall conclusion: it is clear that both bromoxynil heptanoate and bromoxynil octanoate are rapidly and nearly completely converted to bromoxynil phenol in vivo and the pharmacokinetic behavior, metabolism, distribution and excretion of all three compounds are essentially identical in the animal body. (Details of these conclusions can be found in supporting documents; HED RfD Peer Review Committee document dated April 12, 1996; Memorandum from HED to RD dated December 12, 1994 entitled, "EPA Reg. No. 264-506, Bromoxynil Heptanoate Technical; Determination of Additional (TIER 2) Toxicology Studies Required to Support Conditional Registration".)

2. Bromoxynil Dose Response Assessment

a. Special Sensitivity to infants and Children

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Under this provision, the Agency will require an additional tenfold margin of safety if the Agency does not have complete and reliable data to assess pre- or post-natal toxicity relating to infants and children, or if the data indicate pre- or post-natal effects of concern. The data EPA will consider include data submitted in compliance with EPA testing requirements, available data published in the scientific literature, and any other data available to EPA and meeting general scientific standards. Where reproductive and developmental data have been found acceptable by EPA, and the data do not indicate potential pre- or post-natal effects of concern, the additional tenfold margin of safety currently is not applied.

Following a series of meetings conducted to review all available developmental and reproductive toxicity data on bromoxynil, the HED Developmental and Reproductive Toxicity Peer Review Committee (DPRC) concluded that the bromoxynil data submitted to the Agency for review are sufficient for the assessment of hazard to the developing organism (fifth DPRC memo, 4/21/92). A total of 12 developmental and 3 reproductive toxicity studies were available for review. These include oral prenatal developmental toxicity studies (four in rats, two in rabbits, and one in mice with the phenol; one in rats with the octanoate), dermal prenatal developmental toxicity studies (one each in rats and rabbits with both the phenol and the octanoate), and dietary two-generation reproduction studies in rats (two with the phenol; one with the octanoate). Developmental toxicity was observed, following *in utero* exposure to bromoxynil, in multiple studies, by two routes of exposure, and in three species. The induction of supernumerary ribs was shown to be the most sensitive indicator of developmental toxicity in fetal rats, mice, and (in certain studies) rabbits. Upon consideration of the data base in its entirety, the DPRC determined that the NOEL for the induction of supernumerary ribs resulting from prenatal exposure to bromoxynil (phenol) is 4 mg/kg/day via the oral route and 10 mg/kg/day via the dermal route. The developmental LOELs for bromoxynil phenol were 5 mg/kg/day by the oral route and 50 mg/kg/day

by the dermal route. Other forms of developmental toxicity, including resorptions and malformations, were routinely observed in bromoxynil studies at higher dose levels.

Recently, within HED, an *ad hoc* Developmental and Reproductive Peer Review Committee reviewed the bromoxynil database for developmental toxicity with particular regard to the requirements of FQPA. Two viewpoints emerged concerning the retention of the 10-fold factor for the protection of infants and children, with some committee members arguing for, and some against, retention. Since there was general agreement that the developmental and reproductive toxicity data base for bromoxynil is adequate, and that bromoxynil exposure induces developmental toxicity, the two viewpoints concerning an additional uncertainty factor emerged in large part from interpretive differences of the FQPA mandate. A summary of the positions both for and against removal of the 10-fold uncertainty factor for infants and children are presented below.

The following points, considered grounds for **retaining** the "FQPA 10X factor" with particular regard to acute, short term, and intermediate term exposures (S. Makris and J. Rowe memo to M. Metzger, 3/7/97), were presented at several briefings for the Office Director and Assistant Administrator.

- Increased fetal susceptibility is demonstrated unequivocally. Following prenatal exposure to bromoxynil, developmental effects (supernumerary ribs) occur in the absence of maternal toxicity and are considered irreversible.

- The same developmental finding of concern (supernumerary ribs) is observed to some degree in all species tested (rats, mice, and rabbits), indicating a lack of species specificity and suggesting that humans could also be affected. There are no data to demonstrate the effect(s) of bromoxynil exposure during gestation in humans, nor are there data that correlate treatment-related supernumerary ribs in animals to the same effect in humans. Lacking such data, it must be assumed that the statistically significant, treatment-related incidences of supernumerary ribs which were observed following prenatal bromoxynil exposure in animals, could be a biomarker for similar or even more severe effects that could occur in humans. This assumption is consistent with Agency 1991 Guidelines for Developmental Toxicity Risk Assessment.

- The dose-response curve for developmental effects caused by bromoxynil is steep. The oral developmental NOEL (4 mg/kg/day) for supernumerary ribs was only 1.25X lower than the LOEL for that same effect (5 mg/kg/day). By dermal administration, the NOEL of 10 mg/kg/day was only 5X lower than the developmental LOEL of 50 mg/kg/day. The fact that the dose response curve is very steep by both the oral and dermal routes of exposure were considered strongly in the weight-of-the evidence approach to determining whether an additional UF is required. This approach was agreed to by the Scientific Advisory Panel (SAP) (10/96).

- At doses only slightly higher than those that produced supernumerary ribs, more marked developmental effects (fetal death or malformations of the skeleton or eye) and the first evidence of some limited maternal toxicity were observed.

- The mechanism of action for bromoxynil has not been identified in relation to the developmental effects observed. A genotoxic basis for the

developmental effects cannot be ruled out.

The following arguments for **removing** the FQPA 10X factor were also presented at the briefings for the Office Director and Assistant Administrator.

- The NOELs are very consistent among studies and across species and routes of exposure. Because of the large magnitude of the data base and consistency of the NOEL values, the dose response relationship has been firmly established, and the increased susceptibility of a fetus exposed *in utero* has been clearly defined.

- There was scientific consensus that additional studies would not result in a lower NOEL value than that used in the risk assessment for various population groups, including infants and children, or alter any uncertainties regarding the dose response assessment.

- The data base contains no evidence that early postnatal exposure to bromoxynil, at doses equivalent to those that result in developmental effects (supernumerary ribs resulting from prenatal exposure), will result in adverse effects on growth, survival, or reproductive capacity.

- For chronic exposure to bromoxynil, the reference dose (0.015 mg/kg/day) is based upon a NOEL/LOEL of 1.5 mg/kg/day, from a 1-year canine study, with additional uncertainty factors applied for intra- (10X) and interspecies (10X) variability. This 100X uncertainty factor incorporated into the RfD calculation could be considered adequate for the protection of infants and children, an interspecies subpopulation.

Following extensive discussion within HED and with OPP management, it was determined that an additional 10X safety factor for the protection of infants and children, as required by FQPA would be appropriate for risk assessments utilizing developmental endpoints. This decision was based upon concerns emanating from the toxicological profile, including evidence of increased susceptibility of fetuses to bromoxynil exposure, although it is recognized that there are extensive and reliable data available and there are no outstanding uncertainties regarding the effects on developing animals following pre- and/or postnatal exposure to bromoxynil.

The population of concern is the developing fetus and the endpoint of concern is supernumerary ribs. This endpoint, a developmental anomaly, results from *in utero* exposure; therefore the population subgroup of concern is females 13+ years old. Although some systems in infants and children continue developing, it is unlikely that supernumerary ribs, even though observed across multiple species, would result from postnatal exposure. A 10-fold factor safety factor, as required by FQPA will provide additional protection for infants and children and ensure a reasonable certainty of no harm to this sensitive subpopulation.

b. Reference Dose

The HED RfD Peer Review Committee met on February 29, 1996 to determine the RfD for bromoxynil phenol. The RfD is 0.015 mg/kg/day, based on the threshold NOEL/LOEL of 1.5 mg/kg/day determined in a 12-month chronic oral toxicity study in dogs using bromoxynil phenol as the test material (MRID 40780301, 41304701) Effects observed at the threshold NOEL/LOEL of 1.5 mg/kg/day in the 12-month canine study were slightly decreased body weight gain in males. At the next higher dose level (7.5 mg/kg/day), the following effects were observed in both males and females: decreased body weight gain; increased salivation, panting, liquid feces, and pale

gums; decreased erythrocytes, hemoglobin, and packed cell volume; increased urea nitrogen; and increased liver weights. An uncertainty factor of 100 based on interspecies extrapolation (10X) and intraspecies variability (10X) was applied. The 10X safety factor as required by FQPA for the protection of infants and children was removed since the RfD is not based on a development effect.

It should be noted that this chemical has not been reviewed by the FAO/WHO Joint Committee.

c. Assessment of Developmental and Reproductive Toxicity

Both bromoxynil phenol and bromoxynil octanoate are developmental toxicants which induce structural malformations at dose levels below those which cause maternal toxicity when administered either orally or dermally to experimental animals. The induction of supernumerary ribs is the most sensitive indicator of developmental toxicity in rats, mice and in some studies in rabbits. Bromoxynil induces additional forms of developmental toxicity regularly observed at higher dose levels. These include resorptions; reduced fetal weights; increased overall incidences of minor anomalies; major soft tissue abnormalities (such as anophthalmia and microphthalmia); defects in ossification of vertebrae, sternebrae and skull; and major skeletal abnormalities (particularly vertebral and thoracic bone malformations). Reproductive toxicity, as manifested in multigeneration reproduction studies, is not observed at dose levels below those which induce systemic toxicity. The HED Peer Review Committee for Developmental and Reproductive Toxicity (DPRC), met in 1991 to consider all available developmental toxicity and reproduction studies and related information on both compounds, determined that the following NOELs and LOELs are applicable for the purpose of assessing developmental risk to humans. The MRID number(s) of the particular developmental toxicity study(ies) from which the NOEL or LOEL was derived is shown in parenthesis.

Bromoxynil Phenol

Oral Exposure

Developmental NOEL = 4 mg/kg/day (MRID 40466802)
Developmental LOEL = 5 mg/kg/day (MRID 00116558)
based on increased incidence of supernumerary ribs in rats
Maternal NOEL = 5 mg/kg/day (MRID 00116558, Rogers et al., 1991)
Maternal LOEL = 15 mg/kg/day (MRID 00116558, Rogers et al.. 1991)
based on decreased body weight gain in rats

Dermal Exposure

Developmental NOEL = 10 mg/kg/day (MRID 40881201, 40883601)
Developmental LOEL = 50 mg/kg/day (MRID 40881201, 40883601)
based on increased incidence of supernumerary ribs in rats
Maternal NOEL = 50 mg/kg/day (MRID 40881201, 40883601)
Maternal LOEL = 100 mg/kg/day (MRID 40881201, 40883601)
based on decreased body weight gain and reduced food consumption in rats

Bromoxynil Octanoate

Oral Exposure

Developmental NOEL = 7.3 mg/kg/day (Rogers et al., 1991)
Developmental LOEL = 21.8 mg/kg/day (Rogers et al., 1991)
based on increased incidence of supernumerary ribs and reduced fetal weights in rats
Maternal NOEL = 7.3 mg/kg/day (Rogers et al., 1991)
Maternal LOEL = 21.8 mg/kg/day (Rogers et al., 1991)
based on decreased body weight gain and increased liver weights in rats

Dermal Exposure

Developmental NOEL = 10 mg a.i./kg/day (MRID 41163301)
Developmental LOEL = 15 mg a.i./kg/day (MRID 41163301)
based on increased incidence of supernumerary ribs in rats
Maternal NOEL = 15 mg a.i./kg/day (MRID 41163301)
Maternal LOEL = 20 mg a.i./kg/day (MRID 41163301)
based on decreased body weight gain and reduced food consumption in rats

Following the meeting of the HED Peer Review Committee for Developmental and Reproductive Toxicity in 1991, a comprehensive risk assessment for occupational exposures to bromoxynil octanoate was prepared in 1992 (fifth DPRC memo 4/21/92). Subsequently, a more restrictive labeling on certain end-use products containing bromoxynil octanoate and other precautionary actions were required by EPA. An example of the more restrictive labeling is shown on the current label for Buctril Herbicide (EPA Reg. No. 264-437) which is appended to this document.

d. Carcinogenicity Classification and Risk Quantification

Bromoxynil phenol has been classified by the HED Carcinogenicity Peer Review Committee (2/14/96 memo dated 3/12/97) as a Group C, possible human carcinogen. The committee also recommended that a low dose extrapolation model (Q_1^*) be applied to the experimental animal tumor data for quantification of human risk. This weight-of-the-evidence determination was based primarily on results in two mouse carcinogenicity studies. In the first study (MRID 00068077) in Swiss albino mice, a dose-related increased incidence of liver adenomas/carcinomas combined was observed in the male mice. The increase was statistically significant at 100 ppm. The liver tumor response in male mice included both benign and malignant tumors with the carcinomas contributing to almost one-half of the total adenomas/carcinomas at the mid- and high-dose levels. An increase in the incidence of hyperplastic nodules, some of which may have been adenomas, was also observed in the livers of male mice at the mid- and high-dose levels. An increased incidence of neoplasms was not observed in female mice, but dose levels for the female mice in this study were determined to be too low to assess carcinogenic potential. In the second study (MRID 43245501, 43311701) in CD-1 mice, treatment-related increased incidences of liver adenomas, carcinomas and adenomas/carcinomas combined were observed in male mice at all dose levels. For female mice given 300 ppm, slightly increased incidences of liver carcinomas and of adenomas/carcinomas combined also were considered to be related to treatment with bromoxynil phenol. Dose levels in this study were adequate. Information from genotoxicity studies, which included three positive studies, and structure activity relationship (SAR) data provided additional support for the classification.

An increased incidence of neoplasms was not observed in carcinogenicity studies in Fischer 344 rats (MRID 00096521) or in Sprague Dawley rats (MRID 40612501, 41374801). Dose levels in the Fischer 344 rat study, however, were determined to be too low to assess carcinogenic potential.

For the purpose of estimating carcinogenic risk to humans, the estimated unit risk or Q_1^* of bromoxynil phenol, based upon male hepatocellular tumors is 1.03×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents (converted from animals to humans by use of the 3/4's scaling factor-1994,Tox_Risk, 3.5-K.Crump).

e. Other Toxicological Endpoints for Use in Human Health Risk Assessment

ia. Acute dietary (for females 13+)

The Toxicology Endpoint Selection Committee (TESC) (3/5/97, updated 5/5/97) determined that a risk assessment for acute dietary exposure for females 13+ years old is required. The NOEL to be used for risk assessment is the developmental toxicity NOEL of 4 mg/kg/day from a developmental toxicity study (MRID 40466802) where bromoxynil phenol was administered to groups of pregnant Sprague-Dawley rats orally by gavage at daily doses on gestation days 6-15, inclusive. The developmental LOEL is 5 mg/kg/day, based on an increased incidence of supernumerary ribs in rats from a developmental toxicity study (MRID 00116558).

Comments about study and/or endpoint:

1. For dietary exposure, it is anticipated that the exposure will be to Bromoxynil phenol, rather than to Bromoxynil octanoate, since Bromoxynil octanoate is converted to Bromoxynil phenol in the environment. Therefore, the endpoint selected for acute dietary risk assessment for females 13+ years old was derived from an oral developmental toxicity study on bromoxynil phenol.

2. Regarding the overall (most sensitive) LOEL for developmental toxicity in oral studies, the DPRC (May and Baker, 1981) concluded that the LOEL should be derived from a different oral developmental study (MRID 00116558) in rats than the study (MRID 40466802) used to establish the NOEL. The LOEL was 5 mg/kg/day, also based on a dose-related increased incidence of supernumerary ribs.

3. For maternal toxicity the DPRC (May and Baker, 1981) concluded that the overall (most sensitive) NOEL and LOEL should also be derived from different oral developmental studies (MRID 00116558, Rogers et al., 1991) in which the NOEL was 5 mg/kg/day and the LOEL was 15 mg/kg/day based on decreased body weight gain in rats.

4. Another oral (gavage) developmental toxicity study (Rogers et al., 1991) in rats is available in which the test material was Bromoxynil octanoate. Results of this study support the results of the Bromoxynil phenol studies above. In the Bromoxynil octanoate study, the results were as follows (doses in molar equivalent units of Bromoxynil phenol):

developmental toxicity NOEL = 5 mg/kg/day
developmental toxicity LOEL = 15 mg/kg/day, based on increased supernumerary ribs and decreased fetal weights

maternal toxicity NOEL = 5 mg/kg/day
maternal toxicity LOEL = 15 mg/kg/day, based on decreased body weight gains and increased liver weights

An uncertainty factor of 1000, based on interspecies extrapolation (10X), intraspecies variability (10X) as well as a safety factor of 10X for the protection of infants and children, as discussed earlier in the Special Sensitivity to Infants and Children section, is recommended. Therefore, the appropriate Margin of Exposure (MOE) for acute dietary risk for females 13+ is 1000.

ib. Acute Dietary (All populations except females 13+)

The TESC selected the NOEL of 8 mg/kg/day from the 13-week range-finding study (MRID 43166701) in which bromoxynil phenol was administered orally in capsules to male and female beagle dogs as the endpoint to be used for acute dietary risk assessment for all populations except females 13+. The LOEL of 12 mg/kg/day was based on increased incidence of panting on day 1, suggestive of a compensatory reaction to the effects of the test material, which at higher doses is expressed as elevated body temperature.

Comments about study and/or endpoint:

There is a particular concern for events occurring during the first day of the study (following a single oral dose of the test material) since this time frame was directly applicable to the acute dietary exposure scenario. During the first day of the study, the predominant events were mortality, elevated rectal temperatures and panting. These three events were considered to be directly related to one another. The TESC determined 8 mg/kg/day to be the NOEL for toxic effects for the first day of the study (i.e. following a single oral dose of the test material). At this dose level (8 mg/kg/day), no deaths and no elevated temperatures were observed. Although some panting was observed during the first week of treatment, it could not be established that panting occurred after a single dose of the test material on day one. The TESC also determined that the LOEL for toxic effects for the first day of the study was 12 mg/kg/day. At this dose level, no deaths and no elevated rectal temperatures were observed. It was established, however, that panting most likely did occur at this dose level after 1 (or 2) doses of test material. At the higher dose levels of 16 and 20 mg/kg/day, both panting and elevated rectal temperatures were observed early in the study at 1 (or 2) days.

The TESC considered the clinical signs noted in the treated animals (particularly panting at 8 and 12 mg/kg/day and higher) to be suggestive of a compensatory reaction to the toxic effects of the of the test material. At higher dose levels (16 mg/kg/day and higher) effects were expressed as elevated body temperatures, and at still higher dose levels (30 mg/kg/day and higher) as deaths in the first few days of the study.

A NOEL of 8 mg/kg/day was determined since panting could not be established as occurring at that dose level on day 1 and a LOEL of 12 mg/kg/day was determined since panting could be established as occurring at that dose level on day 1. **It is noted that at the dose level of 5 mg/kg/day, neither elevated rectal temperatures nor panting were observed in the first week of the study.**

The determination of a NOEL of 8 mg/kg/day and a LOEL of 12 mg/kg/day, based on effects occurring in the first day of the 13-week dose-range finding dog study, was supported by results in a 1-year chronic oral dog study (MRID 40780301, 41304701) that was conducted shortly after the range-finding study. In the 1-year study, which used dose levels up to 7.5 mg/kg/day (capsule, 6 dogs/sex/dose), the incidence of panting was observed in nearly all dogs at the highest dose level tested (7.5 mg/kg/day) during the first week of the study. Like the dose level of 8 mg/kg/day in the 13-week study, however, it could not be established that the panting occurred on the first day of the study.

An uncertainty factor of 100 based on interspecies extrapolation (10X) and intraspecies variability (10X) is recommended. A safety factor of 10X for the protection of infants and children is not required since the acute dietary endpoint for use in risk assessment for all populations except females 13+ is not based upon a developmental effect, nor was the endpoint of concern supernumerary ribs. Therefore, the appropriate MOE for acute dietary risk for all population except females 13+ is 100.

ii. Short term (1 to 7 days) & Intermediate term (1 week to several months) Occupational Exposure

The TESC selected the NOEL of 10 mg a.i./kg/day from the developmental toxicity study (MRID 41163301) in which Bromoxynil octanoate (incorporated into Buctril formulation blank) was applied dermally to groups of pregnant Sprague-Dawley rats. A dose-related increased litter incidence of supernumerary ribs was observed at the developmental toxicity LOEL of 15 mg a.i./kg/day. At 20 and 75 mg a.i./kg/day, the litter incidences of supernumerary ribs were increased still further. The maternal toxicity NOEL is 15 mg a.i./kg/day and the maternal toxicity LOEL is 20 mg a.i./kg/day, based on decreased body weight gain and decreased food consumption. (Extracted from "Fifth Developmental and Reproductive Toxicity Peer Review of Bromoxynil", Gary Burin and Ann Clevenger, April 21, 1992). This endpoint is appropriate for all occupational subpopulations because, in this case, it happens to be the MOST sensitive endpoint overall for estimating occupational risks. ,

An uncertainty factor of 100, based on interspecies extrapolation (10X) and intraspecies variability (10X) is recommended. An additional 10x is not required because the FQPA safety factor is not applied for occupational exposure scenarios. Therefore, a MOE of 100 is considered appropriate for short term and intermediate term exposure to occupational workers. Since this endpoint is derived from a dermal study the percent dermal absorption should not be used for these risk assessments.

iii. Inhalation Exposure

Inhalation exposures are expected to be negligible compared to the dermal route. The acute inhalation LC_{50} for bromoxynil octanoate is 0.81 mg/L (M) and 0.79 mg/L (F) (toxicity category III) and the acute inhalation LC_{50} for Buctril formulation is 1.1 mg/liter (toxicity category III). The active ingredient for all registered end-use products is either bromoxynil octanoate or bromoxynil heptanoate. On this basis the TESC determined a risk assessment for exposure by the inhalation route is not required.

There are no repeated dose inhalation studies on either bromoxynil octanoate or bromoxynil phenol.

iv. Chronic (noncancer) Exposure (dermal route)

The TESC selected the developmental NOEL of 10 mg a.i./kg/day from a developmental toxicity study (MRID 41163301) in which bromoxynil octanoate (incorporated into Buctril formulation blank) was applied **dermally** to groups of pregnant Sprague-Dawley rats on gestation days 6-15, inclusive. A dose-related increased incidence of supernumerary ribs was observed at the developmental toxicity LOEL of 15 mg a.i./kg/day. At 20 and 75 mg a.i./kg/day, the incidences of supernumerary ribs were increased still further. The maternal toxicity NOEL is 15 mg a.i./kg/day and the maternal toxicity LOEL is 20 mg a.i./kg/day, based on decreased body weight gain and decreased food consumption. (Extracted from "Fifth Developmental Toxicity Peer Review of Bromoxynil", Gary Burin and Ann Clevenger, April 21, 1992)

An uncertainty factor of 100, based on interspecies extrapolation (10X) and intraspecies variability (10X) is recommended. An additional 10x is not required because the FQPA safety factor is not applied for occupational exposure scenarios. Therefore, a MOE of 100 is considered appropriate for chronic (non-cancer) term exposure to occupational workers. Since this endpoint is derived from a dermal study the percent dermal absorption should not be used for these risk assessments.

v. Dermal Absorption

^{14}C-Bromoxynil octanoate, incorporated into the end-use product Buctril, which contained 33.4% Bromoxynil octanoate as the active ingredient, was topically applied to the skin of male Sprague-Dawley rats at doses of 0.08, 0.4 or 3.4 mg/rat for durations of exposure of 0.5, 1, 2, 4, 10 or 24 hours (4 rats/dose/duration of exposure). The quantity of radioactivity absorbed increased with dose and duration of exposure. Percent dermal absorption at 10 hours was 10.32%, 7.07% and 4.51% for doses of 0.08, 0.4 and 3.4 mg/rat respectively. Following a soap and water wash (at 10 hours), 6.46%, 8.06% and 6.13% of the respective doses remained in/on the skin. Percent dermal absorption at 24 hours was 17.58%, 18.43% and 10.88% for doses of 0.08, 0.4 and 3.4 mg/rat respectively. Following a soap and water wash (at 24 hours), 7.91%, 9.50% and 4.97% of the respective doses remained in/on the skin. (MRID 40854603)

Based on the results of this study the TESC recommended for the purposes of risk assessment, 10.32% absorbed should be assumed.

Comments about study and/or endpoint:
For dermal exposure, it is anticipated that the exposure will be to the end-use product Buctril, which contains 33.8% Bromoxynil octanoate as the active ingredient.

Table 3: Summary of toxicological Endpoints for Bromoxynil

Exposure Duration	Exposure Route	Endpoint
Acute females 13+	Dietary	Developmental NOEL of 4 mg/kg/day (oral) MRID 40466802 & 00116558 MOE = 1000
Acute general population (except females 13+)	Dietary	Systemic NOEL of 8 mg/kg/day (oral) MRID 43166701 MOE = 100
Chronic (non-cancer)	Dietary	NOEL/LOEL 1.5 mg/kg/day (oral) MRID 40780301 & 41304701 UF = 100 RfD = 0.015 mg/kg/day
Chronic (cancer)	Dietary	Q_1^* = 0.103 (mg/kg/day)$^{-1}$
Short-Term Occupational	Dermal	Developmental NOEL of 10 mg/kg/day (dermal) MRID 41163301 MOE = 100
Intermediate-Term Occupational	Dermal	Developmental NOEL of 10 mg/kg/day (dermal) MRID 41163301 MOE = 100
Inhalation (any time period)	Inhalation	Risk assessment not required.
Chronic Occupational (noncancer)	Dermal	Developmental NOEL of 10 mg/kg/day (dermal) MRID 41163301 MOE = 100
Carcinogenic Potential Occupational	Dermal	Q_1^* = 0.103 (mg/kg/day)$^{-1}$

3. Dietary Exposure and Risk Characterization

a. Dietary Exposure - Food Sources

i. Directions for Use

A search of the Agency's Reference Files System (REFS) on 10/19/95 indicates that there are five bromoxynil end-use products (EPs) with food/feed uses registered to Rhône-Poulenc Corporation. These EPs are presented below.

Active Ingredient (code)/ EPA Reg No.	Label Acceptance Date	Formulation Class [a]	Product Name
Bromoxynil octanoate (035302)			
264-437	6/95	2 lb/gal EC	Buctril® Herbicide
264-438 [b]	3/95	2 lb/gal EC	Bronate® Herbicide
264-477 [c]	3/95	1 lb/gal EC	Buctril® + atrazine Herbicide
264-531 [d]	11/95	4 lb/gal WP[e]	Buctril® Gel
264-540 [d]	5/95	4 lb/gal EC	Buctril® 4EC Herbicide
Bromoxynil heptanoate (128920)			
264-531	11/95	4 lb/gal WP[e]	Buctril® Gel
264-540	5/95	4 lb/gal EC	Buctril® 4EC Herbicide

[a] The active ingredients for the formulated products are expressed in terms of bromoxynil equivalents.
[b] EPA Reg. No. 264-438 is a MAI formulation that also contains 34.0% isooctyl ester of MCPA (2 lb/gal MCPA equivalents).
[c] EPA Reg. No. 264-477 is a MAI formulation that also contains 21.6% atrazine (2 lb/gal).
[d] *EPA Reg. Nos. 264-531 and 264-540 are MAI formulations containing both the octanoic and* heptanoic acid esters of bromoxynil for a total of 4 lb bromoxynil equivalent/gal.
[e] This is a gel formulation, designated as a WP.

Based on available data, registered labels should specify the following for rotational crops:

"After applying up to 2 pints/A/season of [Buctril® or Buctril ® 4EC], wait a minimum of 30 days from the date of the application, and then plant any rotational crop."

"After applying more than 2 pints/A/season of [Buctril® or Buctril ® 4EC], only transgenic BXN cotton may be planted as a rotational crop."

Required limited field rotational crop studies reflecting a maximum application rate of 1.5 lb ai/A are on going.

The registrant's use directions for corn (field and pop), sorghum, onions, and sudangrass are inconsistent and should be amended:

- *Corn (field and pop)*: Use directions on labels 264-437 and 264-531 specify a maximum seasonal rate of 0.5 lb ai/A, while labels 264-477 and 264-540 specify a maximum seasonal rate of 0.75 lb ai/A. In addition, on labels 264-531 and 264-540, maximum seasonal rates listed under "Special Use Directions" (0.75-1.25 lb ai/A) are higher than the maximum seasonal rates listed under "Use Restrictions" (0.5-0.75 lb ai/A). Use directions for corn should be amended so that all labels specify the maximum seasonal use rate of 0.5 lb ai/A, which is supported by available residue data.

- *Sorghum*: Labels 264-437 and 264-531 specify a maximum seasonal rate of 0.5 lb ai/A, while labels 264-477 and 264-540 specify a maximum seasonal rate of 0.75 lb ai/A. In addition, the maximum seasonal rate listed on label 264-540 under "Special Use Directions" (1.25 lb ai/A) is higher than the maximum seasonal rate listed under "Use Restrictions" (0.75 lb ai/A). Labels 264-437 and 264-540 also list maximum single application rates of 0.5-0.75 lb ai/A, but state "do not apply at 0.5 lb ai/A rate to sorghum". Use directions for sorghum should be amended so that all labels specify the maximum single and seasonal use rate of 0.5 lb ai/A, which is supported by available residue data.

- *Onions*: Use directions on labels 264-437 and 264-531 restrict preemergence application to onions grown east of the Mississippi River on muck soils with >10% organic matter. Label 264-540 should be amended to include this restriction. In addition, label 264-437 specifies that postemergence applications should not be made using aerial equipment. This restriction should be deleted from the label since it implies that preemergence applications using aerial equipment are acceptable [under "Application Procedures," the only type of equipment listed for applications on onions is ground equipment].

- *Sudangrass*: Labels 264-437 and 264-531 specify a pre-grazing interval (PGI) of 30 days. The Agency does not currently permit PGIs for grasses grown only for forage. However, since products containing bromoxynil are applied prior to the pre-boot stage, and since the first cutting for forage would occur in approximately 30 days, HED will allow the PGI to remain on registered labels. Residues in sudangrass (forage) are covered under both grass and sorghum forage tolerances.

The conclusions listed in *Tolerance Reassessment Summary* (found at the end of the chapter) regarding the reregistration eligibility of bromoxynil food uses are based on the use patterns registered by the basic producer, Rhône-Poulenc Corporation. When end-use product DCIs are developed (e.g., at issuance of the RED), RD should require that all end-use product labels (e.g., MAI labels, SLNs, and products subject to the generic data exemption) be amended to be consistent with the basic producer labels.

Refer to Appendix I for a summary of the "Food/Feed Use Patterns Subject to Reregistration for Bromoxynil".

ii. Plant and Livestock Metabolism

For the purpose of reregistration, the qualitative nature of the residue in plants is adequately understood based on acceptable alfalfa, sweet corn, and transgenic (BXN) cotton metabolism studies conducted using bromoxynil octanoate. The residue of concern in plants other than cotton is bromoxynil *per se*. The residues of concern in transgenic BXN cotton and cotton commodities (i.e. hulls, meal and cotton gin byproducts) are bromoxynil and its metabolite 3,5-dibromo-4-hydroxybenzoic acid (DBHA). The DBHA metabolite is only found in transgenic cotton, and not in other commodities.

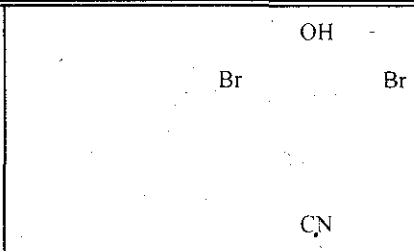
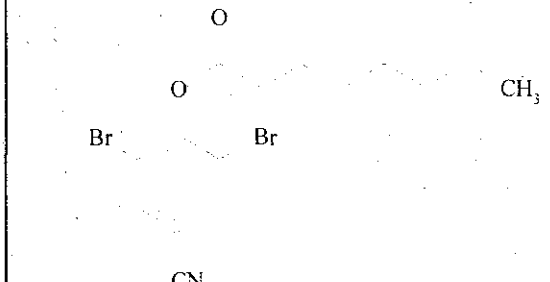
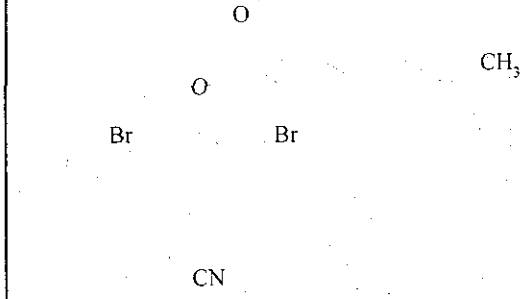
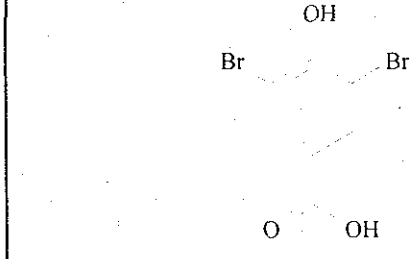
The qualitative nature of the residue in livestock is adequately understood for bromoxynil octanoate, based on acceptable ruminant and poultry metabolism studies. Since the metabolite DBHA is found in commodities considered to be livestock feed items, the potential for transfer of secondary residues to livestock exists. The nature of the residue in livestock following oral dosing with DBHA is not adequately understood. The HED Metabolism Committee has concluded that DBHA is of potentially equal toxicity to the parent, bromoxynil, and could transfer to livestock tissues in proportion to the parent. Therefore, pending receipt of additional metabolism data for DBHA, HED has concluded that the residues of concern in livestock are bromoxynil and its metabolite DBHA.

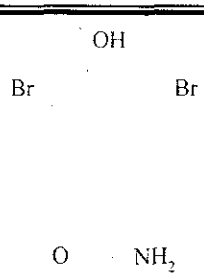
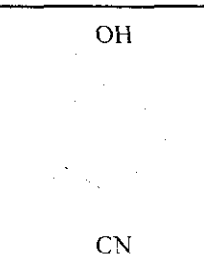
The registrant must conduct livestock metabolism studies in which ruminants and poultry are dosed with radiolabeled DBHA, and the nature of the residue determined in the meat, meat by-products, milk, and fat of ruminants and in the meat, skin/fat, liver and eggs of poultry. Based on the results of livestock metabolism studies, the need for feeding studies and concomitant analytical methods will be determined.

The structures of bromoxynil, its octanoic and heptanoic acid esters, and its major metabolites are

presented in Figure A.

Figure A. Bromoxynil, its octanoic and heptanoic acid esters, and metabolites.

Common Name/Chemical Name	
Bromoxynil 3,5-dibromo-4-hydroxybenzonitrile	
Bromoxynil octanoate	
Bromoxynil heptanoate	
3,5-dibromo-4-hydroxybenzoic acid (DBHA)	

Common Name/Chemical Name	
3,5-dibromo-4-hydroxybenzamide	
4-hydroxybenzonitrile	

iii. Residue Analytical Method - Plants and Livestock

Adequate analytical methodology is available for data collection and tolerance enforcement for bromoxynil *per se* in plants. Method I in PAM, Vol. II, is a GLC/MCD that has undergone a successful EPA method validation on wheat grain. This method involves alkaline hydrolysis in methanolic KOH to convert residues to bromoxynil, cleanup by liquid-liquid partitioning, methylation using diazomethane, further cleanup on a Florisil column, and determination by GLC/MCD. Method Ia is the same method, but uses GC/ECD for determination of methylated bromoxynil.

Method A is a GC/MCD or ECD method for the analysis of bromoxynil residues in livestock tissues and is essentially the same as Method I. Method B is a GC/ECD method that is also similar to Method I, with modifications to the cleanup procedures.

Rhône-Poulenc methods SOP 90018 and SOP 90020 and McKenzie Laboratories Method PRM-029 were used in determining residues of bromoxynil for data collection in plants and livestock. These are all GC/ECD methods that are similar to Method I and use modified cleanup procedures following extraction. The limits of quantitation (LOQs) for bromoxynil using these methods are 0.02 ppm for plant commodities and 0.05 ppm for livestock commodities.

The FDA PESTDATA database dated 1/94 (Pam Vol. I, Appendix I) indicates that recovery of bromoxynil octanoate and bromoxynil butyrate using FDA Multiresidue Protocol E (PAM I Section 211.1) is variable. Bromoxynil has recently been tested through Multiresidue Protocols B and C; since bromoxynil was not detected through Protocol C, further testing under Protocol E was not required. Testing under Protocols A and D was not required. This information has been forwarded to FDA for inclusion in the PESTDATA database. No data are reported for the methyl ether of bromoxynil.

For data collection purposes, cottonseed and gin trash samples were analyzed using the analytical method "Bromoxynil: Method of Analysis for Bromoxynil and its Metabolite, 3,5-Dibromo-4-hydroxybenzoic Acid in Cottonseed, Gin Trash, and Seed Processed Fractions using GC-MSD." The method (Method RES9603) has been the subject of an Independent Laboratory Validation (ILV) and an Agency Petition Method Validation (PMV); although there were problems with the LOQ for DBHA in gin trash during the PMV, HED concludes the method is adequate for data collection. Additional method validation data submitted to the Agency 1/7/98 address problems encountered with the PMV, and are under review in HED; approval of the method for enforcement purposes is anticipated.

There is currently no method available for data collection or tolerance enforcement for the DBHA metabolite in livestock commodities. Although the use of measurement of parent bromoxynil residues as a marker for the DBHA metabolite has been discussed, the HED Chemistry Science Advisory Council (ChemSAC) concluded the use of the parent bromoxynil as a "marker" for the DBHA metabolite in meat, milk, poultry and eggs cannot be supported, based on available residue data for bromoxynil and the DBHA metabolite in cotton gin trash and cottonseed.

iv. Storage Stability

No additional storage stability data are required to support currently registered uses. Bromoxynil octanoate residues are stable in plant commodities stored at -10 C for up to 12 months. Adequate storage stability data have been submitted on the following commodities: alfalfa (forage and hay), barley (grain, forage, hay, and straw), field corn (grain, forage, silage, and fodder), sweet corn (kernels, K+CWHR, cannery waste, and forage), flax (seed and straw), grass (forage, hay, and seed screenings), garlic, onion, sorghum (grain, forage, fodder, silage, and hay), and wheat (grain, forage, hay, and straw). Supporting storage stability data for livestock matrices are not required since the majority of samples in both the ruminant and poultry feeding studies were analyzed within 21 days of sacrifice.

Adequate data demonstrate stability of bromoxynil phenol in frozen storage in frozen cotton substrates (cottonseed, meal, hulls, gin trash and cottonseed oil) for an interval of at least 9 months. The DBHA metabolite is stable in frozen cottonseed, gin trash, meal, and oil for at least 9 months; in cotton hulls, DBHA residues declined 50% after 1 month of storage.

v. Magnitude of the Residue/Potable Water- not applicable

vi. Magnitude of the Residue/Fish - not applicable

vii. Magnitude of the Residue/Irrigated Crops- not applicable

viii. Magnitude of the Residue - Food Handling - not applicable

ix. Magnitude of the Residue - Meat, Milk, Poultry & Eggs

Tolerances are currently established for bromoxynil residues in the fat, meat, and meat by-products of cattle, goats, hogs, horses, and sheep [40 CFR §180.324(a)(1)]. Although required based on available data, tolerances are not yet established for residues in milk, eggs, or poultry. Acceptable ruminant and poultry feeding studies have been submitted for bromoxynil. No feeding studies conducted using the DBHA metabolite have been submitted; therefore, the results of the bromoxynil feeding studies have been used as the basis for setting tolerances which include the DBHA metabolite. HED has recommended inclusion of tolerances for secondary residues in livestock commodities under 40 CFR §180.324(a)(2), i.e. including bromoxynil and DBHA.

Although HED previously concluded that residues in poultry commodities could be classified under Category 3 of 40 CFR §180.6(a), i.e., no reasonable expectation of detectable residues, clarification of HEDs policy with respect to Category 3 changes this conclusion for bromoxynil/poultry. HED now concludes that tolerances are required for secondary residues of bromoxynil and DBHA in poultry commodities. Tolerances in livestock commodities have been reassessed based on available field trial data and label revisions for livestock feed items, including cotton commodities. The following tolerances for bromoxynil and DBHA residues have been recommended for meat-by-products, fat, and meat of cattle, goats, hogs, horses and sheep and in milk, eggs and the meat, fat, and meat by-products of poultry [refer to the "Tolerance Reassessment Summary"]:

Ruminants/Swine
meat 0.5 ppm
mbyp 3.5 ppm
fat 1.0 ppm
milk 0.1 ppm

Poultry
meat 0.05 ppm
fat 0.05 ppm
mbyp 0.3 ppm
eggs 0.05 ppm

A new poultry feeding study had been required, pending submission of additional cotton field trial data; based on the new field trial data and resultant theoretical maximum dietary burden for poultry, the requirement for a new poultry feeding study is waived.

x. Magnitude of the Residue - Crop Field Trials/ Processed Food/Feed

The reregistration data requirements for magnitude of the residue in plants are fulfilled for the following crops: barley, corn (field and pop), flax, garlic, onions, sorghum, wheat, aspirated grain fractions, alfalfa, grasses (including Sudangrass) and mint. Adequate field trial data depicting residues of bromoxynil following applications made according to the maximum or proposed use patterns (provided that changes stipulated under "Directions for Use" are made on registered labels) have been submitted for these commodities. Geographic representation is adequate and a sufficient number of trials reflecting representative formulation classes were conducted. Barley and wheat data can be translated to oats and rye. Residue data are adequate to support the currently registered uses.

The reregistration requirements for magnitude of the residue in processed food/feed commodities are fulfilled for barley, corn, cottonseed, flaxseed, oats, rye, sorghum, wheat and mint. Data from the barley and wheat processing studies can be translated to oats and rye. Bromoxynil residues do not concentrate in processed plant commodities. Residues of the metabolite DBHA concentrate in cottonseed hulls. No additional data are required.

xi. Magnitude of the Residue-Cotton Petition (PP#3F4233)

Reduced rate cotton field trials required by the Agency as a condition of extension of the time-limited tolerances were submitted to the Agency and found to be adequate for the purpose of tolerance assessment and for dietary risk assessment. Transgenic (BXN) cotton was treated with two broadcast applications of bromoxynil, once at 1 lb ai/A when cotton was 12-14 inches tall, and

again at 0.5 lb ai/A at first bloom. The resulting (maximum) seasonal application rate was 1.5 lb ai/A. The Agency has accepted labels specifying: 1 or 2 applications of 0.5 lbs ai/A/application timed prior to planting, just prior to cotton emergence but after weed emergence, or until cotton reaches a height of 12 inches; and a third application at 0.5 lb ai/A after cotton is 12 inches tall during bloom but no later than 75 days prior to harvest. Therefore, when application instructions to transgenic BXN cotton are discussed in Agency documents, the following should apply:

> "Apply from just prior to planting cotton until 75 days prior to harvest. Do not exceed 2 applications before cotton is 12 inches tall and 1 application after cotton exceeds 12 inches in height. Make the last application during bloom, but not later than 75 days before harvest."

Based on the new field trial data, revised recommended tolerances for bromoxynil and DBHA residues in cottonseed, cotton gin by-products and cotton hulls are 1.5, 7.0 and 5.0 ppm, respectively [refer to the Tolerance Reassessment Summary].

xii. Reduction of the Residues - not applicable

xiii. Confined Rotational Crops

Adequate data are available to determine the nature of the residue in rotational crops; the residue of concern in rotational crops is bromoxynil, *per se*.

xiv. Field Rotational Crops

Submitted field rotational crop data indicate that registered labels should specify the following:

> "After applying up to 2 pints/A/season of [Buctril® or Buctril ® 4EC], wait a minimum of 30 days from the date of the application, and then plant any rotational crop."

> "After applying more than 2 pints/A/season of [Buctril® or Buctril ® 4EC], only transgenic BXN cotton may be planted as a rotational crop."

Required additional limited field rotational crop studies reflecting a maximum seasonal application rate of 1.5 lb ai/A are ongoing.

a 30-day plantback interval (PBI) for all crops except cotton. HED notes that required additional limited field rotational crop studies have not been submitted to the Agency; acceptable studies previously submitted in support of reregistration reflect a maximum seasonal and single application rate of 0.5 lb ai/A, but the use on cotton constitutes a maximum seasonal application rate of 1.5 lb ai/A. Pending receipt of these studies registered labels must restrict rotation of treated cotton fields to cotton.

xv. Anticipated Residues for Dietary Risk Assessment

During preparation of previous drafts of the HED RED chapter for bromoxynil, and in conjunction with the petition for permanent tolerances in cotton commodities, several anticipated residue assessments were prepared. Each iteration of anticipated residues incorporated either new residue data or the registrant's proposed refinements to the anticipated residues (based on revised labels, changes in ruminant diets, etc.).

In spite of a lack of monitoring data for bromoxynil, the anticipated residues summarized below are considered to be highly refined. First, field trial residues in racs consumed by people were nondetectable; anticipated residues were based on ½ the limit of quantitation (LOQ), and were further refined by percent crop treated data provided by BEAD. Field trial residues from all forages (i.e. sorghum, wheat, oat, corn, alfalfa) and all hays were averaged, and the additional refinement for percent crop treated was applied. Although forages and hays contained detectable bromoxynil residues, the averages used were significantly lower than tolerance-level residues.

Based on the registrant's proposal, HED reduced the contribution of cotton gin products (gin trash) to the dietary burden for ruminants by assuming 5% of the diet for beef cattle and 1% for dairy cattle. The refinement for the proposed cotton percent crop treated was also included. The only commodities which contribute significantly to exposure to bromoxynil and/or DBHA in the diet for the general US population (or any subpopulation) are meat, milk, poultry and eggs, based on secondary residues resulting from consumption of livestock feed items.

Note that the anticipated residues calculated and summarized below were all significantly lower than residues which can be reliably measured using available analytical methods.

Tables 4 and 5 summarize anticipated residues (ARs) that were used in the chronic/cancer dietary risk assessment for bromoxynil. The first table includes ARs for commodities other than cotton and livestock, while the second table includes cotton/livestock ARs for a cotton percent crop treated of 0, 3 and 10%. The values for percent crop treated for all commodities (provided by BEAD or proposed by the registrant) were incorporated into the anticipated residues, and were therefore not applied in conducting the DRES analyses.

Table 4. Summary of Bromoxynil Anticipated Residues (Except Cotton/Livestock) for Chronic/Cancer Dietary Risk Assessment.

Commodity	Recommended Tolerance (ppm)	Anticipated Residue in RAC (ppm)[1]	% Crop Treated[2]	Anticipated Residue for DRES Run (ppm)
Cereal Grains [wheat, corn, oats, barley, rye, sorghum][3] **Includes processed commodities**	0.05	0.01	10	0.001
Onions	0.1	0.01	62	0.0062
Garlic	0.1	0.01	100	0.01
Peppermint oil/Spearmint oil	--	0.03	71	0.02[4]

1 Anticipated residues of 0.01 ppm represent ½ the limit of quantitation (LOQ), since there were no detectable residues.

2 Data forwarded to HED from BEAD indicate a maximum percent crop treated of 13% for barley, 10% for corn, 13% for durum wheat, and 10% for spring and other wheats; the likely maximum percent crop treated for remaining cereal grains (i.e. rye, oats, and sorghum) was much lower. For the current dietary risk assessment, 10% crop treated was assumed for all cereal grains as well as for forages/hays.

3 Since residues do not concentrate in processed commodities of cereal grains, the anticipated residue of 0.001 ppm was used for such commodities in the DRES analysis (i.e. corn oil, flour, etc.).

4 There is no tolerance for residues in mint oil, since residues are reduced during processing of hay to produce mint oil [tolerances are no longer established for residues in mint hay, and therefore, and tolerances for residues in oil are only established when concentration is observed].

Table 5. Summary of Bromoxynil Anticipated Residues in Cotton/Livestock for Chronic/Cancer Dietary Risk Assessment.

RAC	Tolerance (ppm)	Anticipated Residue, Relative to %CT for Transgenic Cotton (ppm)		
		0%	3%	10%
Cottonseed	7.0[1]	n/a	0.01	0.03
Cottonseed meal	--		0.003	0.01
Cottonseed oil	--[2]		0.01	0.03
Meat[3]	0.5	0.0015	0.0020	0.0030
MBYP[3]	3.0	0.0088	0.0114	0.0175
Fat[3]	1.0	0.0032	0.0042	0.0064
Milk[3]	0.1	0.00037	0.00030	0.00040
Swine meat	0.5	0.00007	0.00009	0.00016
Swine MBYP	3.0	0.00039	0.00053	0.00094
Swine fat	1.0	0.00014	0.00020	0.00034
Poultry meat	n/a[4]	0.00009	0.00013	0.00025
Poultry MBYP		0.00053	0.00074	0.0014
Poultry Skin/Fat		0.00012	0.00017	0.00031
Eggs		n/a[4]	0.000056	0.00010

[1] Refer to the 6/18/98 FR notice for details regarding time-limited tolerances in cotton commodities. Based on new residue data, the recommended revised tolerances for bromoxynil and DBHA residues are 1.5 ppm in cottonseed, 7 ppm in cotton gin by-products, and 5 ppm in cottonseed hulls.

[2] The residue level in cottonseed was also be used for cottonseed oil in the DRES analysis.

[3] These anticipated residues were also be used for meat, fat and meat by-products of horses, goats and sheep in the DRES runs.

[4] Tolerances are not currently established for bromoxynil residues in poultry commodities, but will be required based on revised dosing levels in the poultry feeding study, and on the ChemSAC decision dated 10/30/97. Tolerances for poultry commodities are included in the tolerance reassessment.

b. Dietary Risk Characterization - Food Sources

The toxicity endpoints identified in the Dose Response Section and the Dietary Exposure Section of this document indicate a chronic, cancer and two acute dietary risk assessments are appropriate for bromoxynil.

i. Acute Dietary Risk (Food Sources)

In the previous HED RED chapter (9/24/97) a detailed acute dietary exposure analysis was conducted using anticipated residues on blended commodities as applicable and tolerances. Anticipated residues were used for grains, milk and mint oils, without the adjustment for percent crop treated. Tolerance level residues were used for onions; garlic; fat, meat by-products and meat of cattle, goats, hogs, horses and sheep. For bromoxynil, the acute dietary risk from food sources for the general population and all population subgroups, except females 13+ years old did not exceed HED's level of concern. The MOE for females 13+ was less than 1000 and therefore exceeded HED's level of concern.

The registrant has since submitted an acute (probabilistic) dietary analysis including the proposed cotton use incorporating the residue data submitted to support the lower use rates discussed above. The assessment was performed by Novigen Sciences, Inc. for Rhone Poulenc. The assessment used the consumption data from the 1989-1992 Continuing Survey of Food Intakes by Individuals (CSFII). The consumption database used in this probabilistic assessment has been provided to HED as requested in previous correspondence.

The acute dietary risk assessment was conducted as a probabilistic risk assessment, assuming single day exposure. In the assessment, each person-day of food consumption was matched with randomly selected residue values for this assessment from field trails submitted in support of the chemical. Percent crop treated data were included in the assessment as zeroes to account for portions of the crop to which bromoxynil was not applied. This process was repeated one thousand times for each person-day in consumption database. The assessment assumed that the treated commodities were evenly distributed in the food supply. Secondary residues in meat and milk from consumption of treated feed items were included in the form of a probabilistic assessment, varying residues in the diet in accordance with the data from the field trials. The assumptions for the dietary exposure were reviewed and found to be acceptable. The assessments assumed that 10% of the cotton crop would be treated.

The acute assessment used a NOEL of 4 mg/kg BW/day based on developmental effects for females 13+ years old and a NOEL of 8 mg/kg BW/day based on systemic effects for all populations except females 13+ years old. For the acute assessment, all of the subgroups evaluated has MOEs far in excess of the required value of 1000 for females 13+ and 100 for all populations except females 13+ years old indicating that the potential for an adverse effect from a single day dietary (food only) exposure in unlikely. The MOEs and the exposure values for the population subgroups are listed in Table 6 below.

Table 6. Acute Dietary Assessment for Bromoxynil		
Population Subgroup	**Exposure (mg/kg BW/day)**	**MOE**
US population	0.000137	>58,000
Non-Nursing Infants	0.000244	>32,000
Nursing Infants	0.000097	> 82,000
All Infants	0.000219	> 36,000
Children (1-6 years)	0.000288	>35,000
Children (7-12 years)	0.000144	>55,000
Females 13+	0.000082	>24,000

ii. Chronic Dietary Risk (Food Sources)

In the previous HED RED chapter (9/24/97) the chronic and carcinogenic dietary exposure analysis from food sources (including cotton) was conducted using refined residue levels based on anticipated residues and percent crop treated information. A revised chronic and carcinogenic dietary exposure analysis from food sources (including cotton) has been conducted for bromoxynil in conjunction with Rhône-Poulenc's 9/24/97 petition to increase the acreage for application to transgenic BXN cotton. The current assessment has been prepared using new cotton residue data submitted by Rhône-Poulenc along with other data supporting re-instatement of the time-limited tolerances for bromoxynil and its metabolite DBHA (3,5-dibromo-4-hydroxybenzoic acid) in cotton commodities, which expired 1/1/98.

Table 7 below lists the results of the chronic dietary risk analysis conducted based on the new residue data (C. Swartz memo dated 3/2/98), and on revised anticipated residues which incorporate all uses of bromoxynil (refer to Tables 4&5 above).

Table 7. Chronic Dietary Risk for Bromoxynil - % of RfD

Population Subgroup	**Registered Uses (i.e., Excluding Cotton)**	**Cotton @ 3 %CT + Registered Uses**	**Cotton @ 10 %CT + Registered Uses**
U.S. Population	<1	<1	<1
Non-Nursing Infants[1] (<1 Year Old)	<1	<1	<1

[1]Non-Nursing Infants is the population subgroup with the highest exposure to bromoxynil.

For chronic effects other than cancer, for all population subgroups, less than 1% of the reference dose was consumed regardless of the cotton % crop treated.

Table 8 below shows the results of the carcinogenic dietary risk analyses conducted based on the new residue data (C. Swartz memo dated 3/2/98), and on revised anticipated residues which incorporate all uses of bromoxynil (refer to Tables 4 & 5 above).

Table 8. Carcinogenic Dietary Risk for Bromoxynil

Commodity	Registered Uses (i.e., Excluding Cotton)	Cotton @ 3 %CT + Registered Uses	Cotton @ 10 %CT + Registered Uses
Grain/cottonseed	2.0×10^{-7}	2.2×10^{-7}	2.6×10^{-7}
Bulb vegetables	0.7×10^{-7}	0.7×10^{-7}	0.7×10^{-7}
Meat	3.5×10^{-7}	4.7×10^{-7}	7.0×10^{-7}
Milk	4.0×10^{-7}	3.3×10^{-7}	4.4×10^{-7}
Poultry	$<0.1 \times 10^{-7}$	$<0.1 \times 10^{-7}$	0.2×10^{-7}
Total Dietary Risk	**1.0×10^{-6}**	**1.1×10^{-6}**	**1.5×10^{-6}**

The cancer risk from food sources range from 1 in a million without cotton and up to 1.5 in a million if 10% of the cotton is treated. These risk estimates are based on anticipated residues and percent crop treated information which represents the most refined estimate HED can currently conduct. The additional (0.5 in 1 million) risk resulting from the cotton use is due to high residue levels of the metabolite, DBHA. DBHA is formed by the transgenic BXN cotton which has been developed to hydrolyze the nitrile group of bromoxynil to a carboxylic acid, DBHA. DBHA is currently considered toxicologically equal to bromoxynil.

c. Dietary Exposure - Drinking Water

The Office of Pesticide Programs is in the process of developing procedures and methods for determining the likelihood of a pesticide occurring in drinking water and, if so, the exposure levels and associated risk. Previous exposure and risk assessments have been conducted for bromoxynil as a possible contaminant in drinking water. The following estimation of exposure and risk from drinking water reflects yet the latest information and method for estimating drinking water exposure.

i. Ground Water

Bromoxynil octanoate does not exhibit the mobility or persistence characteristics of pesticides that are normally found in ground water. Bromoxynil phenol (which bromoxynil octanoate readily degrades to) has the potential to leach to ground water under certain conditions **except** it rapidly degrades under aerobic and anaerobic conditions reducing the likelihood of ground water contamination. Limited monitoring information for bromoxynil in ground water is available. The "Pesticides in Ground Water Database" (EPA 1992) reports sampling for bromoxynil in 107 wells in four counties in Oregon between 1985 and 1987. The well samples in each area (public water supply and domestic) were selected based on suspected vulnerability, susceptibility to contamination, and availability of information on well construction and depth. No additional information on the details of the monitoring was available. No detections of bromoxynil were reported.

Additional monitoring data from the United States Geological Survey (USGS) National Water Quality Program (NAQWA) represent the highest quality data and most recent data available (1993-1994). The program was carefully designed to obtain monitoring data for surface and ground waters from diffuse (non-point) sources and included locations that correlated with the use of bromoxynil. For ground water, one detection of bromoxynil (concentration not specified) was reported from a total of 2, 245 samples. Clearly, these compounds (bromoxynil phenol and octanoate) are not considered candidates for restricted use due to ground water concerns and the potential for ground water contamination (and exposure) from bromoxynil is extremely low.

DBHA is not expected to be found in ground water.

ii. Surface Water

Environmental fate studies indicate that bromoxynil (phenol and octanoate) should not persist in surface waters. However, to satisfy the requirements of FQPA and in the interim until drinking water exposure and risk policies are established, all possible routes of exposure are being considered. Estimated environmental concentrations (EECs) were based on the cotton use and not the small grains, corn or other uses bromoxynil because, it has been EFED's experience, that cotton compared to these crops results in a higher possible surface water exposure. Cotton represents the most conservative use for surface water exposure (i.e. the highest possible exposure scenario).

A Tier II analysis based on the PRZM - EXAMS model (Pesticide Root Zone Model Version 2.3 plus Exposure Analysis Modeling System Version 2.94) was conducted for the cotton use. PRZM-EXAMS uses data on the physical-chemical properties of the pesticide plus soil and topographic characteristics, weather data, and water quality parameters for the modeled site. This model uses this information to estimate runoff from a 10 hectare agricultural field into an immediately adjacent 1 hectare by 2 meter deep pond. PRZM-EXAMS considers reduction in dissolved pesticide concentrations due to adsorption of pesticide to soil or sediment, incorporation, degradation in soil before wash off to a water body, direct deposition of spray drift into the water body, and degradation of the pesticide within the water body.

Water monitoring data from the U.S. Geological Survey (USGS) NAWQA Program were reported during the 1993-1995 period from 7 of 20 river basins throughout the U.S. The NAWQA Program examined drainage basins that were primarily agricultural use. The percentage of detections was 1.1% from a total of 1,925 surface water samples. Analysis of the 20 detections $\geq$0.03 ppb yielded a median value of 0.105 ppb with a mean of 0.53 ppb. The maximum concentration was one data point at 6.1 ppb (12.2 ppb when accounting for 50% recovery) measured in the South Platte River Study Unit, CO. For urban land use, bromoxynil was not detected in surface waters. It is important to note the laboratory recoveries were approximately 50%. Apparently the laboratory recoveries did not vary considerably from the 50% level. Comparison of the Models (above) estimating environmental concentrations (EECs 12.4 ppb) with the USGS NAWQA monitoring data suggests reasonable agreement among the various data sources for an upper bound, 90th percentile, exposure estimate. Additionally, the monitoring data does not represent "drinking water".

The maximum or peak estimated concentration for bromoxynil was 12.3 parts per billion (ppb) and the maximum estimated long-term mean was 0.24 ppb (based on modeling using 36 years of weather data). These values represent what might be expected in a small water body near a cotton field highly prone to runoff. The maximum peak estimated concentration for bromoxynil from the model correlates with the highest value detected in the USGS monitoring data, 12.2 ppb, which has been corrected for an analytical recovery rate of 50%. EPA reviewed USGS national monitoring data and determined which of these sites were likely to have bromoxynil use. To

estimate a reasonable high end exposure, EPA focused on the calculated time weighted annual mean concentrations of bromoxynil at each of 11 USGS monitoring sites, which the EPA views as located in watersheds likely to have bromoxynil use. (These values were not corrected for the analytical recovery rate of 50%.) These time weighted annual mean concentrations ranged from 0.011 ppb to 0.18 ppb, with 10 out of the 11 sites with time weighted annual mean concentrations below 0.05 ppb. Six of the 10 sites had time weighted annual mean concentrations at or below 0.014 ppb. The highest annual time-weighted mean (0.18 ppb) was located in a relatively small watershed (approximately 100 square miles) and a relatively small water body, and the calculated annual mean value at this site was significantly influenced by the presence of a single high value (the highest value found in all of the available monitoring data). Based on this information, EPA believes that 0.05 ppb is a reasonable high end estimate for purposes of estimating drinking water exposure. However, EPA imposed surface water monitoring requirements as a condition of registration to allow use of more precise estimates in the future.

Table 9: Bromoxynil Exposure Values Estimated for Surface Water Sources of Drinking Water

Subpopulation by weight, water consumption per day	Acute (mg/kg/day)[1]	Chronic (mg/kg/day)[1]
Male 70 kg, 2 Liters	3.5×10^{-4}	1.4×10^{-6}
Female 60 kg, 2 Liters	3.5×10^{-4}	1.6×10^{-6}
Child 10 kg, 1 Liter	12×10^{-4}	5×10^{-6}

[1] Exposure (mg/kg/day) = (concentration in water ug/L) (0.001 mg/ug) (water consumption L/day) / (body weight kg).

Where the 4-day (acute) exposure concentration is 12.3 ppb and the reasonable high end estimate for purposes of estimating drinking water exposure is 0.05 ppb.

DBHA is not expected to be found in surface water.

d. Dietary Risk Characterization - Drinking Water

The potential for ground water contamination (and exposure) from bromoxynil is extremely low. Environmental fate studies indicate that bromoxynil (phenol and octanoate) should not persist in surface waters. In fact, it decomposes due to aquatic aerobic metabolism in approximately 6 days. These estimates of exposure were based on cotton use which, considering all of the uses of bromoxynil, the cotton use represents the most conservative scenario for surface water exposure. The exposure and risk are summarized in Table 10 below.

Table 10: Bromoxynil Exposure and Risk from Drinking Water

Subpopulation by weight, water consumption/ day	Drinking water Exposure (mg/kg/day)[1]		Risk from Drinking Water		
	Acute	Chronic	Acute[1] MOE	Chronic[2]	Cancer[3]
Male 70 kg, 2 Liters	3.5×10^{-4}	1.4×10^{-6}	>10,000	< 1%	0.2×10^{-6}*
Female 60 kg, 2 Liters	3.5×10^{-4}	1.6×10^{-6}	>10,000	<1 %	
Child 10 kg, 1 Liter	12×10^{-4}	5×10^{-6}	>10,000	<1 %	N/A*

[1] Acute Risk = MOE = NOEL (mg/kg/day) / Exposure (mg/kg/day). The NOEL for females ages 13+ is 4 mg/kg/day and the other subpopulation groups is 8 mg/kg/day (for details see Dose Response Section of document). A MOE of greater than 1000 is recommended for females 13+ and 100 for all other populations except females. The EEC used to estimate the acute exposure was derived from monitoring data (12.2 ppb) or modeling (12.3 ppb). The drinking water chronic exposure (0.05 ppb) was estimated using a reasonable high end estimate.

[2] %RfD = Chronic Dietary Risk = Exposure as a percentage of the RfD (0.015 mg/kg/day). The %RfD is considered a risk concern when it exceeds 100%.

[3] The upper bound Carcinogenic Risk = risk quotient Q_1^* (0.103 [mg/kg/day]$^{-1}$) X Exposure (mg/kg/day).

* N/A = Not Applicable. Cancer Risk has only been estimated for the general population (in this case the average exposure between males and females) and is based on a 70 year lifetime.

There appears to be no chronic or acute risk of concern for the subpopulations from surface water source drinking water (only) when using monitoring data or modeling data for the acute exposure and risk and when using modeling data for the chronic and cancer exposure and risk. We believe this cancer risk is over estimated for many reasons. The PRZM-EXAMS model was designed to estimate exposure for ecological risk assessments and substantially overestimate pesticide residues in drinking water for several reasons. Surface water source drinking water generally comes from bodies of water that are substantially larger than a 1 hectare (2.5 acres) pond. The model also assumes that essentially the whole basin receives an application of the pesticide. Yet, in virtually all cases, basins large enough to support a drinking water facility will contain a substantial fraction of the area which does not receive the pesticide. Additionally, there is often at least some flow (in a river) or turn over (in a reservoir or lake) of the water so the persistence of the pesticide near the drinking water facility is usually overestimated. Second, even assuming a reservoir is directly adjacent to an agricultural field, the agricultural field may not be used to grow a crop on which the pesticide in question is registered for use. Further, the PRZM-EXAMS model does not take into account reductions in residue-loading due to applications of less than the maximum application rate or no treatment of the crop at all (percent crop treated data). Also, since this model was designed to estimate ecological exposure, this estimate does not take into account drinking water facility treatment which generally reduces contaminants.

Further, the exposure, should it occur, will be seasonal corresponding to the time of application which is NOT daily or even monthly. The USGS monitoring data indicates that exposure is possible on a seasonal basis, but rare considering there was one significant concentration out of 1,925 samples (and only 20 detects total). These data showed that approximately one percent of the samples were positive for bromoxynil. Most importantly, the sampling was conducted predominantly in locations not representative of drinking water intakes, and NONE of the samples were from "the tap".

Lastly, water consumption is defined as all water throughout the household tap that is consumed either directly as a beverage or is used to prepare foods (e.g. mixing water with a can of soup) and beverages (e.g. diluting frozen orange juice from concentrate). Two generally accepted default values for water consumption are 2 liters a day for adults and 1 liter a day for children. These defaults are consistent with those currently used in the EPA/Office of Drinking Water. (It should be noted, however, that the Agency is in the process of evaluating the water consumption values and associated policy to assure consistency within the Agency.) Additional assumptions include the "average" weight of the subpopulations and that water from the same source containing the same contaminant level is consumed throughout a 70 year lifetime for chronic or cancer risks. The second of these assumptions is extremely conservative, since most of the U.S. population moves at some time during their life and does not live in the same area, drinking from the same water source for a 70 year lifetime. On the other hand, these default values for water consumption are considered averages.

In conclusion, the quantified cancer risk is based on an a reasonable high end estimate of exposure. Although there are data points from the USGS monitoring study that seems to confirm that this level may possibly occur in surface water, it is not necessarily reflective of concentrations of bromoxynil in drinking water, much less on a long-term basis. It is possible for bromoxynil to occur in surface water, but if it does, it will be on an occasional basis correlating with the use during the growing season for the crops. Further, bromoxynil degrades rapidly in water, and should a measurable concentration occur in drinking water it would not be on a long-term basis resulting in a chronic exposure. Realistically the drinking water risk is much lower than that which the PRZM/EXAMS model or USGS monitoring data estimates.

4. Occupational Exposure and Risk Characterization

An occupational and/or residential exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete.

The toxicological endpoints of concern for occupational exposure are summarized in the Dose Response Section. It should be noted for short term and intermediate term exposure the toxicological endpoint is from a dermal developmental study so a separate dermal absorption factor was not applied. The cancer risk was determined using an oral toxicity endpoint which, for occupational risk necessitates the use of a dermal absorption factor. The dermal absorption for the bromoxynil octanoate is 10.32% and the bromoxynil phenol is 1.92% based on studies (MRIDs 40854602 & 40854603) summarized in the Hazard Assessment Section of this document. For the sake of simplicity and to remain consistent, the occupational cancer risk was determined using the conservative absorption factor of 10% (rounded from 10.32%). Lastly, although a chronic (noncancer) endpoint was identified for bromoxynil, a chronic-term exposure/risk assessment was not conducted. It is unlikely that there will be chronic exposures to bromoxynil, thus the chronic risk assessment is not warranted. Inhalation exposures were considered negligible compared to the dermal route and no inhalation endpoint was identified for use in risk assessment.

a. Handler Exposures and Risk

i. Handler Exposures and Assumptions

EPA has determined that there are potential exposures to mixers, loaders, applicators, or other handlers during usual use-patterns associated with bromoxynil. Based on the use patterns, seven major exposure scenarios were identified for bromoxynil:

(1) mixing/loading liquids for groundboom applications;
(2) mixing/loading liquids for aerial and sprinkler irrigation applications;
(3) groundboom applications;
(4) aerial applications;
(5) flaggers;
(6) mixing/loading/applying liquid formulations by groundboom; and
(7) mixing/loading/applying liquid formulations by aircraft.

Bromoxynil is also packaged in water soluble gel packets. No exposure data are available for the water soluble gel packets, but the exposure potential is expected to be less than open pouring liquids.

A chemical-specific study (MRID 41730001) was reviewed and accepted by EPA in 1991. However, there are concerns regarding the low field recoveries reported in the study. For example, the field recoveries fortified with the formulated product and analytical grade for the handwash averaged 56 percent with a coefficient of variation (c.v.) of 48 percent; facial wipes averaged 56 percent with a c.v. of 64 percent; and the whole-body dosimeters averaged 53 percent with a c.v. of 55 percent. The Agency's concern is that the low field recoveries (especially at low fortification levels) may have produced exposure values that are "false negatives". Therefore, and in order to provide a criterion for comparison with the Pesticide Handlers Exposure Database (PHED) data, HED characterizes the data as "low to medium grade" quality data. The PHED based data are considered "medium to high grade" quality data. Because of the quality of the chemical-specific study (MRID 41730001), the risk assessment in this document is based on PHED V1.1 data.

HED notes that a rebuttal to this decision has been received however a cursory examination of the rebuttal package indicates that there are no new data that would cause HED to change our decision to use PHED data.

PHED V1.1 surrogate data were used to estimate exposures for handlers wearing "baseline," "PPE," and "engineering controls." The baseline work clothing represent: long sleeved shirts, long pants and no gloves, and using open mixing/loading and open cab tractors. PPE is based on handlers wearing coveralls over long sleeved shirts, long pants and chemical resistant gloves while using open mixing/loading and open cab tractors. The engineering controls are based on long sleeved shirts, long pants, and no gloves (except where noted) while using closed loading systems and enclosed cockpits/tractors.

When evaluating the exposure and risk estimates presented in this document the following should be taken into consideration:

- The PHED estimates do not account for the potential exposure reduction from the "wide-mouth" containers designed to reduce splashing during pouring (2.5 gallon containers) used in the chemical specific study, and therefore, potentially overestimate risks to bromoxynil.

- Data indicate that most private applicators do their own mixing and loading for groundboom applications. The registrant indicated that approximately 95% of bromoxynil is mixed and loaded by the same person who applies the pesticide.

- It is reasonable to assume that for aerial and commercial groundboom applications the mixer/loader and the applicator are separate handlers. Aerial and commercial applications are limited. Apparently aerial applications to range land, sod and turfgrass seed farms seldom occur, if ever.

The exposure assessments using both chemical-specific data and PHED V1.1 surrogate data are presented in Table 11. Table 12 summarizes the caveats and parameters specific to each exposure scenario and corresponding risk assessments.

The daily dose was calculated using the following formula:

$$Daily\ Dose\left(\frac{mg}{Kg\ Day}\right) = Daily\ Exposure\left(\frac{mg}{Day}\right) \cdot \left(\frac{1}{Body\ Weight\ (Kg)}\right) \cdot \%\ dermal\ absorption$$

Table 11: Short-term and Intermediate-term Exposure to Bromoxynil

Exposure Scenario	Dermal Unit Exposure (mg/lb ai)			Crop Type[d]	Acres Treated/Day[e]	Maximum Application Rate (lb ai/acre)f	Daily Dermal Dose (mg/kg/day)[g]		
	Baseline[a]	PPE[b]	Engineering Controls[c]				Baseline	PPE	Engineering Controls
MIXER/LOADER									
Mixing/Loading Liquids for Groundboom Applicators	2.9	0.017	0.0086 (gloves)	Wheat	240	0.5	5.8	0.034	0.017
				Corn	150		3.6	0.021	0.011
				Cotton	200		4.8	0.028	0.014
				Garlic	69		1.7	0.010	NA
				Onions	77		1.9	0.011	0.0055
				Seedling Alfalfa-East	50		1.2	0.0071	NA
				Seedling Alfalfa-West	133		3.2	0.019	0.0095
				Canary Grass	50		1.2	0.0071	NA
				Oats and Rye	50		1.2	0.0071	NA
				Barley	133		3.2	0.019	0.0095
				Mint	48		1.2	0.0068	NA
				Sorghum	200		4.8	0.028	0.014
				Flax	70		1.7	0.0099	NA
				Turfgrass Seed Farm	111		2.7	0.016	0.0080
				Sod Farm	100		2.4	0.014	0.0072
				Range Land	250		6.0	0.035	0.018
Mixing Liquids for Sprinkler Irrigation and Aerial Applications				All	350		8.5	0.050	0.025

Table 11: Short-term and Intermediate-term Exposure to Bromoxynil

Exposure Scenario	Dermal Unit Exposure (mg/lb ai)			Crop Type[d]	Acres Treated/Day[e]	Maximum Application Rate (lb ai/acre)f	Daily Dermal Dose (mg/kg/day)[g]		
	Baseline[a]	PPE[b]	Engineering Controls[c]				Baseline	PPE	Engineering Controls
APPLICATOR									
Groundboom Applicator	0.015	0.011	0.0050	Wheat	240	0.5	0.03	0.022	0.010
				Corn	150		0.019	0.014	0.0063
				Cotton	200		0.025	0.018	0.0083
				Garlic	69		0.0086	0.0063	NA
				Onions	77		0.0096	0.0071	NA
				Seedling Alfalfa-East	50		0.0063	0.0046	NA
				Seedling Alfalfa-West	133		0.017	0.012	0.0055
				Canary Grass	50		0.0063	0.0046	NA
				Oats and Rye	50		0.0063	0.0046	NA
				Barley	133		0.017	0.012	0.0055
				Mint	48		0.006	0.0044	NA
				Sorghum	200		0.025	0.018	0.0083
				Flax	70		0.0088	0.0064	NA
				Turfgrass Seed Farm	111		0.014	0.010	NA
				Sod Farm	100		0.013	0.0092	NA
				Range Land	250		0.031	0.023	0.010
Aerial Application - Enclosed Cockpit	No Data	No Data	0.005	All	350		No Data	No Data	0.032

Table 11: Short-term and Intermediate-term Exposure to Bromoxynil

Exposure Scenario	Dermal Unit Exposure (mg/lb ai)			Crop Type[d]	Acres Treated/Day[e]	Maximum Application Rate (lb ai/acre)f	Daily Dermal Dose (mg/kg/day)[g]		
	Baseline[a]	PPE[b]	Engineering Controls[c]				Baseline	PPE	Engineering Controls
FLAGGERS									
Flagging Liquids	0.011	0.01	0.00022	All	350	0.5	0.032	0.029	0.00064
MIXER/LOADER/APPLICATOR[h]									
Mixing/Loading Liquids and Applying with Groundboom Equipment	2.9	0.028	0.014	Wheat	240	0.5	5.8	0.056	0.028
				Corn	150		3.6	0.035	0.018
				Cotton	200		4.8	0.047	0.023
				Garlic	69		1.7	0.016	0.0081
				Onions	77		1.9	0.018	0.0090
				Seedling Alfalfa-East	50		1.2	0.012	0.0058
				Seedling Alfalfa-West	133		3.2	0.031	0.016
				Canary Grass	50		1.2	0.012	0.0058
				Oats and Rye	50		1.2	0.012	0.0058
				Barley	133		3.2	0.031	0.016
				Mint	48		1.2	0.011	0.0056
				Sorghum	200		4.8	0.047	0.023
				Flax	70		1.7	0.016	0.0082
				Turfgrass Seed Farm	111		2.7	0.026	0.013
				Sod Farm	100		2.4	0.023	0.012
				Range Land	250		6.0	0.038	0.029

a PHED V1.1; Baseline: handlers wearing long sleeved shirts, long pants and no gloves while using open mixing/loading and open cab tractors.

b PHED V1.1; PPE: handlers wearing coveralls over long sleeved shirts, long pants and chemical resistant gloves while using open mixing/loading and open cab tractors; flaggers wearing coveralls over long pants, long sleeved shirts, and no gloves; aerial applicators wearing long pants, long sleeved shirts, and no gloves while using enclosed cockpit fixed wing airplanes

(open cockpit data are not available).

c PHED V1.1; Engineering Controls: long pants, long sleeved shirt, chemical resistant gloves for closed mixing/loading; long pants, long sleeved shirt, no gloves for enclosed cab tractor (groundboom) and inside truck (flagger); and aerial applicators wearing long pants, long sleeved shirts, and no gloves while using enclosed cockpit fixed wing airplanes (open cockpit data are not available).

d,e Crop and acres. Sources: (1) Evaluation of Bromoxynil Worker Exposure Study; Memorandum from C. Lunchick to P. Parsons dated April 29, 1991. (2) Bromoxynil Heptanoate and Bromoxynil Octanoate, May 1996. Use data for Bromoxynil Exposure Analysis; Memorandum from G.W. Keitt, PhD to S.Bachus dated 7/15/92.

f Application rates are from maximum values found in the following bromoxynil labels: 264-477, 264-438, 264-531, 264-540, and 51036-256.

g Daily Dermal Dose (mg/kg/day) = [Exposure (mg/lb ai) * Appl. Rate (lb ai/A) * Acres Treated]/60 kg body weight. Short-term and intermediate-term toxicological endpoint is from a dermal study; therefore, adjustment for dermal absorption is not necessary.

h Mixer/Loader estimates + Applicator estimates.

Table 12: Exposure Scenario Descriptions for Uses of Bromoxynil

Exposure Scenario	Data Source	Standard Assumptions	Comments[a]
		Mixer/Loader Exposure	
Mixing/Loading Liquids	PHED V1.1	**Baseline:** PHED V1.1, handlers wearing long sleeved shirts and long pants; open mixing/loading **PPE:** MOE Assessment: PHED V1.1; handlers wearing coveralls over long sleeved shirts, long pants, and chemical resistant gloves; open mixing/loading. Cancer Assessment: PHED V1.1; handlers wearing long sleeved shirts, long pants and chemical resistant gloves; open mixing/loading **Engineering Controls:** PHED V1.1; handlers wearing long sleeved shirts and chemical resistant gloves; closed mixing/ loading	**Baseline:** "Best Available" grades: Dermal and hands acceptable grades. Dermal = 25 to 122 replicates; Hands = 53 replicates. High confidence in dermal data. No protection factors (PFs) were necessary. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates; Dermal = 72 to 122 replicates. High confidence in dermal data. No PFs were necessary for the cancer assessment, 50 percent PF used to simulate coveralls for MOE assessment. **Engineering Controls:** "Best Available" grades: Dermal and hands acceptable grades. Dermal = 16 to 22 replicates; Hands = 31 replicates. High confidence in dermal data. No PFs were necessary.
		Applicator Exposure	
Groundboom Tractor	PHED V1.1	**Baseline:** PHED V1.1; handlers wearing long sleeved shirts and long pants **PPE:** Cancer Assessment: PHED V1.1; handlers wearing long sleeved shirts, long pants and chemical resistant gloves; open cab tractors **Engineering Controls:** PHED V1.1; handlers wearing long pants, long sleeved shirts, and no gloves; enclosed tractor cab	**Baseline:** "Best Available" grades: Dermal and hands acceptable grades. Dermal = 23 to 42 replicates; Hands = 29 replicates. High confidence in dermal data. **PPE:** "Best Available" grades: Hands grades A,B,C; dermal acceptable grades. Hands = 21 replicates; Dermal = 23 to 42 replicates. Medium confidence in dermal data. No PFs were necessary for the cancer assessment, 50 percent PF used to simulate coveralls for MOE assessments. **Engineering Controls:** "Best Available" grades: Dermal and Hands = grades A,B,C,. Dermal = 20 to 31 replicates; Hands = 16 replicates. Medium confidence in data. No PFs were necessary.
Aerial Application - Enclosed Cab	PHED V1.1	**Engineering Controls:** PHED V1.1; applicators wearing long pants, long sleeved shirts and no gloves while using enclosed cockpit fixed wing airplanes (open cockpit data are not available)	**Engineering Controls:** "Best Available" grades: Dermal = grades A,B,C; hands = acceptable grades. Dermal = 24 to 48 replicates; hands = 34 replicates. Medium confidence in dermal data. No PFs were necessary.

Table 12: Exposure Scenario Descriptions for Uses of Bromoxynil

Exposure Scenario	Data Source	Standard Assumptions	Comments[a]
		Flagger Exposure	
Flagging Liquids	PHED V1.1	**Baseline:** PHED V1.1; flaggers wearing long pants, long sleeved shirts, and no gloves **PPE:** PHED V1.1; flaggers wearing coveralls over long pants, long sleeved shirts, and no gloves **Engineering Controls:** PHED V1.1; flaggers wearing long pants, long sleeved shirts, and no gloves; inside truck	**Baseline:** "Best Available" grades: hands and dermal = acceptable grades. Dermal = 16 to 18 replicates; hands = 16 replicates. High confidence in dermal data. PHED data were used for baseline, no PFs were necessary. **PPE:** The PPE scenario was calculated by using a 50 percent PF for the addition of coveralls. **Engineering Controls:** Calculated by applying a 98 percent PF to the baseline assessment.

[a] "Best Available" grades are defined by OREB SOP for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B, and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D, and E or any combination of grades with less than 15 replicates

ii. Handler Risks

The short-term and intermediate-term MOEs were calculated using the following formula:

$$MOE = \frac{NOEL\left(\frac{mg}{kg\ day}\right)}{Daily\ Dose\left(\frac{mg}{kg\ day}\right)}$$

For the short-term and intermediate-term risk assessment, a NOEL of 10 mg/kg/day from a dermal study was used along with a 60 kg body weight since the toxicological endpoint is for developmental effects.

The lifetime average daily dose (LADD), used to calculate the cancer risk, was calculated using the following formula:

$$\text{LADD (mg/kg/day)} = \left[\frac{\text{Daily Dose (mg/kg/day)} \cdot \text{Treatments Per Year}}{\text{365 Days Per Year}}\right] \cdot \left[\frac{\text{40 Work Years}}{\text{75 Lifetime Years}}\right]$$

The cancer risks were calculated using the following formula:

$$\text{Cancer Risk} = \text{LADD (mg/kg/day)} * Q_1^* \text{ (mg/kg/day)}^{-1}$$

Table 13 presents the corresponding MOE estimates for the short-term and intermediate-term exposures. Table 14 presents the cancer risk assessment for private handlers (growers) based on PHED data. Table 15 presents the cancer risk assessments for commercial handlers.

Table 13: Short-term and Intermediate-term Risks of Bromoxynil

Exposure Scenario	Crop Type	Dermal MOE[a]		
		Baseline[b]	PPE[c]	Engineering Controls[d]
MIXER/LOADER				
Mixing/Loading Liquids for Groundboom Applicators	Wheat	2	290	590
	Corn	3	480	910
	Cotton	2	360	710
	Garlic	6	1,000	NA
	Onions	5	910	1,800
	Seeding Alfalfa - East	8	1,400	NA
	Seeding Alfalfa - West	3	530	1,100
	Canary Grass	8	1,400	NA
	Oats and Rye	8	1,400	NA
	Barley	3	530	1,100
	Mint	8	1,500	NA
	Sorghum	2	360	710
	Flax	6	1,000	NA
	Turfgrass Seed Farm	4	630	1,300
	Sod Farm	4	710	1,400
	Range Land	2	290	560
Mixing/Loading Liquids for Sprinkler Irrigation and Aerial Applications	All	1	200	400

Table 13: Short-term and Intermediate-term Risks of Bromoxynil

Exposure Scenario	Crop Type	Dermal MOE[a]		
		Baseline[b]	PPE[c]	Engineering Controls[d]
APPLICATOR				
Groundboom Applicators	Wheat	333	450	1,000
	Corn	526	710	1,600
	Cotton	400	560	1,200
	Garlic	1,163	1,600	NA
	Onions	1,042	1,400	NA
	Seeding Alfalfa - East	1,587	2,200	NA
	Seeding Alfalfa - West	588	830	1,800
	Canary Grass	1,587	2,200	NA
	Oats and Rye	1,587	2,200	NA
	Barley	588	830	1,800
	Mint	1,667	2,300	NA
	Sorghum	400	560	1,200
	Flax	1,136	1,600	NA
	Turfgrass Seed Farm	714	1,000	NA
	Sod Farm	769	1,100	NA
	Range Land	323	430	1,000
Aerial Application - Enclosed Cockpit	All	No Data	No Data	310
FLAGGER				
Flagging Liquids	All	313	340	16,000

Table 13. Short-term and Intermediate-term Risks of Bromoxynil

Exposure Scenario	Crop Type	Dermal MOE[a]		
		Baseline[b]	PPE[c]	Engineering Controls[d]
MIXER/LOADER/APPLICATOR[e]				
Mixing/Loading Liquids and Applying with Groundboom Equipment	Wheat	2	180	360
	Corn	3	290	560
	Cotton	2	210	430
	Garlic	6	630	1,200
	Onions	5	560	1,100
	Seeding Alfalfa - East	8	830	1,700
	Seeding Alfalfa - West	3	320	630
	Canary Grass	8	830	1,700
	Oats and Rye	8	830	1,700
	Barley	3	320	630
	Mint	8	910	1,800
	Sorghum	2	210	430
	Flax	6	630	1,200
	Turfgrass Seed Farm	4	380	770
	Sod Farm	4	430	830
	Range Land	2	170	340

a Dermal MOE = NOEL (10 mg/kg/day)/Daily Dermal Dose (mg/kg/day); refer to Table 16
b PHED V1.1 based data. Baseline: handlers wearing long sleeved shirts, long pants and no gloves while using open mixing/loading and open cab tractors.
c PHED V1.1; PPE: handlers wearing coveralls over long sleeved shirts, long pants and chemical resistant gloves while using open mixing/loading and open cab tractors; flaggers wearing coveralls over long pants, long sleeved shirts, and no gloves; aerial applicators wearing long pants, long sleeved shirts, and no gloves while using enclosed cockpit fixed wing airplanes (open cockpit data are not available).
d PHED V1.1; Engineering Controls: long pants, long sleeved shirt, chemical resistant gloves for closed mixing/loading; long pants, long sleeved shirt, no gloves for enclosed cab tractor (groundboom) and inside truck (flagger); and aerial applicators wearing long pants, long sleeved shirts, and no gloves while using enclosed cockpit fixed wing airplanes (open cockpit data are not available).
e Mixer/Loader estimates + Applicator estimates; refer to Table 16

Table 14: Private Handler (grower) Cancer Risks for Bromoxynil using PHED Data

Exposure Scenario	Crop Type	Typical Rate (lb ai/A)[a]	Acres Treated/Day	Treatments per Year[a]	LADD (mg/kg/day)[b]		Cancer Risk[c]	
					Baseline[d]	PPE[d]	Baseline[d]	PPE[d]
MIXER/LOADER								
Mixing/Loading liquids for Groundboom Applications	Wheat	0.2	240	1	3.5E-04	5.1-06	**3.6E-05**	5.3E-07
	Corn	0.3	150	1	3.3E-04	4.8E-06	**3.4E-05**	4.9E-07
	Cotton	0.3	200	2	8.7E-04	1.3E-05	**9.0E-05**	1.3E-06
	Garlic	0.4	69	2	4.0E-04	5.9E-06	**4.1E-05**	6.1E-07
	Onions	0.2	77	2	2.2E-04	3.3E-06	**2.3E-05**	3.4E-07
	Seedling Alfalfa-East	0.4	50	1	1.4E-04	2.1E-06	**1.4E-05**	2.2E-07
	Seedling Alfalfa-West	0.4	133	1	3.9E-04	5.7E-06	**4.0E-05**	5.9E-07
	Canary Grass	0.5	50	1	1.8E-04	2.7E-06	**1.9E-05**	2.8E-07
	Oats and Rye	0.4	50	1	1.4E-04	2.1E-06	**1.4E-05**	2.2E-07
	Barley	0.3	133	1	2.9E-04	4.3E-06	**3.0E-05**	4.4E-07
	Mint	0.3	48	2	2.1E-04	3.1E-06	**2.2E-05**	3.2E-07
	Sorghum	0.3	200	2	8.7E-04	1.3E-05	**9.0E-05**	1.3E-06
	Flax	0.3	70	1	1.5E-04	2.2E-06	**1.5E-05**	2.3E-07
	Turfgrass Seed Farm	0.5	111	1	4.0E-04	5.9E-06	**4.1E-05**	6.1E-07
	Sod Farm	0.5	100	2	7.2E-04	1.1E-05	**7.4E-05**	1.1E-06
	Range Land	0.5	250	1	9.0E-04	1.3E-05	**9.3E-05**	1.3E-06
Sprinkler Irrigation and Aerial Applications	All	0.5	350	1	1.2E-03	1.8E-05	**1.2E-04**	1.9E-06

Table 14: Private Handler (grower) Cancer Risks for Bromoxynil using PHED Data

Exposure Scenario	Crop Type	Typical Rate (lb ai/A)[a]	Acres Treated/Day	Treatments per Year[a]	LADD (mg/kg/day)[b]		Cancer Risk[c]	
					Baseline[d]	PPE[d]	Baseline[d]	PPE[d]
APPLICATOR								
Groundboom	Wheat	0.2	240	1	1.8E-06	1.6E-06	1.9E-07	1.6E-07
	Corn	0.3	150	1	1.6E-06	1.5E-06	1.6E-07	1.5E-07
	Cotton	0.3	200	2	4.5E-06	4.2E-06	4.6E-07	4.3E-07
	Garlic	0.4	69	2	2.1E-06	1.9E-06	2.2E-07	2.0E-07
	Onions	0.2	77	2	1.1E-06	1.1E-06	1.1E-07	1.1E-07
	Seedling Alfalfa-East	0.4	50	1	7.4E-07	6.9E-07	7.6E-08	7.1E-08
	Seedling Alfalfa-West	0.4	133	1	1.9E-06	1.8E-06	2.0E-07	1.9E-07
	Canary Grass	0.5	50	1	9.3E-07	8.7E-07	9.6E-08	9.0E-08
	Oats and Rye	0.4	50	1	7.4E-07	6.9E-07	7.6E-08	7.1E-08
	Barley	0.3	133	1	1.5E-06	1.4E-06	1.5E-07	1.4E-07
	Mint	0.3	48	2	1.1E-06	1.0E-06	1.1E-07	1.0E-07
	Sorghum	0.3	200	2	4.5E-06	4.2E-06	4.6E-07	4.3E-07
	Flax	0.3	70	1	7.9E-07	7.3E-07	8.1E-08	7.5E-08
	Turfgrass Seed Farm	0.5	111	1	2.1E-06	1.9E-06	2.2E-07	2.0E-07
	Sod Farm	0.5	100	2	3.8E-06	3.5E-06	3.9E-07	3.65E-07
	Range Land	0.5	250	1	4.7E-06	4.4E-06	4.8E-07	4.5E-07
Aerial Application - Enclosed Cockpit	All	0.5	350	1	6.5E-06	6.0E-06	6.7E-07	6.2E-07
FLAGGERS								
Flagging liquids	All	0.5	350	1	4.3E-06	3.0E-06	4.4E-07	3.1E-07

Table 14: Private Handler (grower) Cancer Risks for Bromoxynil using PHED Data

Exposure Scenario	Crop Type	Typical Rate (lb ai/A)[a]	Acres Treated/Day	Treatments per Year[a]	LADD (mg/kg/day)[b]		Cancer Risk[c]	
					Baseline[d]	PPE[d]	Baseline[d]	PPE[d]
MIXER/LOADER/APPLICATOR[e]								
Mixing/Loading Liquids and Applying with Groundboom Equipment	Wheat	0.2	240	1	3.5E-04	6.8E-06	**3.6E-05**	7.0E-07
	Corn	0.3	150	1	3.3E-04	6.4E-06	**3.4E-05**	6.6E-07
	Cotton	0.3	200	2	8.7E-04	1.7E-05	**9.0E-05**	1.8E-06
	Garlic	0.4	69	2	4.0E-04	7.9E-06	**4.1E-05**	8.1E-07
	Onions	0.2	77	2	2.2E-04	4.4E-06	**2.3E-05**	4.5E-07
	Seedling Alfalfa-East	0.4	50	1	1.4E-04	2.9E-06	**1.4E-05**	3.0E-07
	Seedling Alfalfa-West	0.4	133	1	3.9E-04	7.5E-06	**4.0E-05**	7.7E-07
	Canary Grass	0.5	50	1	1.8E-04	3.6E-06	**1.9E-05**	3.7E-07
	Oats and Rye	0.4	50	1	1.4E-04	2.9E-06	**1.4E-05**	3.0E-07
	Barley	0.3	133	1	2.9E-04	5.7E-06	**3.0E-05**	5.9E-07
	Mint	0.3	48	2	2.0E-04	4.1E-06	**2.1E-05**	4.2E-07
	Sorghum	0.3	200	2	8.1E-04	1.7E-05	**9.0E-05**	1.8E-06
	Flax	0.3	70	1	1.5E-04	3.0E-06	**1.5E-05**	3.1E-07
	Turfgrass Seed Farm	0.5	111	1	4.0E-04	7.9E-06	**4.1E-05**	8.1E-07
	Sod Farm	0.5	100	2	7.2E-04	1.4E-05	**7.4E-05**	1.4E-06
	Range Land	0.5	250	1	9.0E-04	1.7E-05	**9.3E-05**	1.8E-06

a Typical Annual Usage for Bromoxynil; May 1996, Halvorson, A. BEAD/EPA.

b LADD (mg/kg/day) = [(Daily Dose (mg/kg/day) x (Treatments per year)/365 days per year)] x [40work-yrs/75 yrs-lifetime] x [0.103 dermal absorption factor]

c Cancer Risk = LADD (mg/kg/day) x Q_1^*(mg/kg/day)$^{-1}$; where $Q_1^* = 1.03 \times 10^{-1}$ (mg/kg/day)$^{-1}$

d PHED V 1.1 based data. Baseline: handlers wearing long sleeved shirts, long pants and no gloves while using open mixing/loading and open cab tractors. PPE: handlers wearing long sleeved shirts, long pants and chemical resistant gloves while using open mixing/loading and open cab tractors; flaggers wearing coveralls over long pants, long sleeved shirts, and no gloves; aerial applicators wearing long pants, long sleeved shirts, and no gloves while using enclosed cockpit fixed wing airplanes (open cockpit data are not available).

e Mixer/Loader estimates + Applicator estimates

Table 15. Commercial Handler Cancer Risks for Bromoxynil Using PHED Data

Exposure Scenario	Crop Type	Typical Rate (lb ai/A)[a]	Treatments per Year[a]	LADD (mg/kg/day)[b]		Cancer Risk[c]	
				Baseline	PPE	Baseline	PPE
MIXER/LOADER							
Groundboom Applications	Wheat	0.2	21	7.2E-03	1.1E-04	**7.4E-04**	**1.1E-05**
	Corn	0.3	20	6.5E-03	9.6E-05	**6.7E-04**	9.9E-06
	Canary Grass	0.5	21	3.8E-03	5.6E-05	**3.9E-04**	5.8E-06
	Oats and Rye	0.4	21	3.0E-03	4.4E-05	**3.1E-04**	4.5E-06
	Barley	0.3	21	5.9E-03	9.1E-05	**6.1E-04**	9.3E-06
	Sorghum	0.3	14	6.0E-03	9.0E-05	**6.2E-04**	9.2E-06
	Flax	0.3	7	1.0E-03	1.5E-05	**1.0E-04**	1.5E-06
Sprinkler Irrigation and Aerial Applications	All	0.5	21	2.7E-02	3.9E-04	**2.8E-03**	**4.0E-05**
APPLICATOR							
				Open Cab	Open Cab	Open Cab	Open Cab
Groundboom	Wheat	0.2	21	3.8E-05	3.5E-05	3.9E-06	3.6E-06
	Corn	0.3	20	3.3E-06	3.3E-05	3.4E-07	3.4E-06
	Canary Grass	0.5	21	1.9E-05	1.9E-05	2.0E-06	2.0E-06
	Oats and Rye	0.4	21	1.5E-05	1.5E-05	1.5E-06	1.5E-06
	Barley	0.3	21	3.1E-05	2.9E-05	3.2E-06	3.0E-06
	Sorghum	0.3	14	3.1E-05	3.0E-05	3.2E-06	3.1E-06
	Flax	0.3	7	5.5E-06	5.2E-06	5.7E-07	5.4E-07
Aerial Application - Enclosed Cockpit	All	0.5	21	No Data	4.7E-05	No Data	4.8E-06
FLAGGERS							
Flagging liquids	All	0.5	21	9.1E-05	6.2E-05	9.4E-06	**6.4E-06**

a Typical Annual Usage for Bromoxynil; May 1996, Halvorson, A. BEAD/EPA.

b LADD (mg/kg/day) = [(Daily Dose (mg/kg/day) x (Treatments per year)/365 days per year)] x [40work-yrs/75 yrs-lifetime] x [0.103 dermal absorption factor]

c *Cancer Risk = LADD (mg/kg/day) x Q_1^* (mg/kg/day)$^{-1}$; where $Q_1^* = 1.03 \times 10^{-1}$ (mg/kg/day)$^{-1}$*

Based on use of the PHED V1.1 data the calculations of risk indicate that the MOEs for short-term and intermediate-term exposures are greater than 100 for all scenarios when PPE is required. The cancer risk for the Private Handler (grower) range from 2 x 10^{-6} or lower for all the scenarios when PPE is required. The cancer risk for Commercial Handlers range of 4 x 10^{-5} and lower for all scenarios when PPE is required. The highest cancer risk estimate from these particular scenarios was 4 X 10^{-5} (commercial mixer/loaders for aerial applications and sprinkler irrigation). These estimates were based on PPE currently required on the bromoxynil labels: (1) coveralls over long pants and long sleeved shirts, chemical resistant gloves. These risk estimates do not account for the potential exposure reduction from the use of "wide-mouth" containers (designed to reduce spillage) for mixer/loaders. At the present time the PHED database does not allow HED to quantify this risk mitigation measure. Therefore, the use of the "wide-mouth" containers may reduce the reported risk further.

Estimates of Risks from Short-Term Exposures Using PHED Data

The calculations of risk based on PHED V1.1 which are considered medium to high grade data indicate that the MOEs are greater than 100 for the following scenarios:

- mixers/loaders supporting groundboom, aerial and sprinkler irrigation applications using **open loading systems** and wearing chemical-resistant gloves in addition to coveralls over long-sleeve shirts and long pants;
- applicators using open-cab groundboom equipment while wearing long-sleeve shirts and long pants and no gloves;
- all flaggers supporting aerial applications while wearing long-sleeve shirts, long pants and no gloves;
- mixer/loader/applicators supporting groundboom applications using **open loading systems** and open cab tractor wearing chemical-resistant gloves in addition to coveralls over long-sleeve shirts and long pants;
- all applicators using enclosed-cockpit aircraft while wearing long-sleeve shirts, long pants, and no gloves.

Estimates of Cancer Risks Using PHED Data

The calculations of cancer risk based on PHED V1.1 which are considered medium to high grade data indicate that the cancer risks are less than or approximately equal to 1 X 10^{-6} for the following private applicator (grower) scenarios:

- all mixers/loaders supporting all applications using open loading systems and wearing chemical-resistant gloves in addition to long-sleeve shirts and long pants;
- all applicators using open-cab groundboom equipment and wearing long-sleeve shirts and long pants;
- all aerial applicators using enclosed-cockpit aircraft and wearing long-sleeve shirts and long pants (note: no open-cockpit data are available);
- all flaggers supporting aerial applications and wearing long-sleeve shirts and long pants;
- all mixer/loader/applicators supporting groundboom applications using open loading systems and open-cab equipment and wearing chemical-resistant gloves in addition to long-sleeve shirts and long pants.

The calculations of cancer risk based on PHED V1.1 data indicate that the cancer risks are less than or approximately equal to 1 X 10^{-5} for the following commercial handler scenarios:

- all mixers/loaders supporting all groundboom applications using open loading systems

and wearing chemical-resistant gloves in addition to long-sleeve shirts and long pants;
- *all applicators using open-cab groundboom equipment and wearing long-sleeve shirts* and long pants;
- all aerial applicators using enclosed-cockpit aircraft and wearing long-sleeve shirts and long pants (note: no open-cockpit data are available);
- all flaggers supporting aerial applications and wearing long-sleeve shirts and long pants;
- mixer/loader/applicators supporting groundboom applications to garlic, onions, seeding alfalfa in the East, canary grass, oats and rye, mint, and flax while using closed loading systems and enclosed cab equipment and wearing chemical-resistant gloves (mixing/loading only) in addition to long-sleeve shirts and long pants.

For commercial handlers mixing/loading to support aerial applications and mixing/applying for sprinkler-irrigation applications, the estimated cancer risk based on PHED data is 4.0×10^{-5}.

It should be noted that, based on use/usage data provided by BEAD and the registrant, for 95% of bromoxynil applications, the person who mixes and loads is the same person who applies the pesticide. It should also be noted that both aerial and commercial applications are very limited.

b. Postapplication Exposures and Risk

EPA has determined that there is potential exposure to persons entering treated sites after application is complete. Post application exposures may occur to *i*) workers following applications to agricultural crops during routine crop production practices (e.g., cultivation, scouting, hoeing), *ii*) workers entering treated commercially grown sod, *iii*) golf course maintenance workers following applications to turfgrass, *iv*) landscape and ground maintenance workers following applications to commercial/industrial areas and other no-crop areas.

There are no postapplication exposure data available at this time to determine potential risks from bromoxynil uses. In lieu of chemical-specific data, a surrogate range-finder postapplication exposure assessment was performed for occupational settings.

The range finder assessment in Table 15 is based on the application rate of 0.5 lb ai/A for all crops. The transfer coefficients (Tc) range from low exposure potentials such as hoeing in various field crops (500 cm^2/hr) and scouting early season cotton (1,000 cm^2/hr) to high exposure potentials such as harvesting sod (10,000 cm^2/hr). Assuming an acceptable MOE of 100, the restricted entry interval (REI) ranges from 0 days to 26 days.

Table 16. Bromoxynil Short-Term and Intermediate-Term Postapplication Occupational Surrogate Assessment (Range Finder)

Table 16. All Crops Except Cotton (0.5 lb ai/A)					
DAT[a]	DFR ($\mu g/cm^2$)[b]	Dermal Dose (mg/kg/day)[c]		MOE[d]	
		Low	High	Low	High
0	1.12	0.075	1.49	130	7
26	0.72	0.005	0.097	2000	100
Cotton (0.5 lb ai/A)					
DAT[a]	DFR ($\mu g/cm^2$)[b]	Dermal Dose (mg/kg/day)[c]		MOE[d]	
0	2.2	0.30	1.2	33	NA
4	0.78	0.10	0.42	100	NA

a DAT = Days after treatment.

b DFR ($\mu g/cm^2$) = Appl. rate (lb ai/A) x 11.209 (μg per cm^2/lb ai per acre conversion) x 0.2 (fraction of ai retained on foliage). A dissipation rate of 10 percent per day is assumed, however, environmental fate data were not reviewed for this surrogate assessment.

c Dermal Dose (mg/kg/day) = DFR ($\mu g/cm^2$) x T_c (cm^2/hr) x 1 mg/1,000 μg conversion) x 1 (100% dermal absorption) x 8 (hrs/day) / 60 kg BW. Where LOW potential exposure = 500 to 1,000 cm^2/hr and High potential exposure = 10,000 cm^2/hr.

d MOE = NOEL (mg/kg/day) / Dermal Dose (mg/kg/day). Where NOEL = 10 mg/kg/day.

Bromoxynil is a contact herbicide and should be applied while weeds are actively growing. The application timing for crops like corn and small grains, which comprise approximately 90% of bromoxynil usage, is early in the season (from preemergence to prior to tassel emergence/boot stage). Because of the use patterns and mode of action of bromoxynil most workers entering treated fields would likely be performing scouting tasks or low contact labor tasks such as mechanical incorporation and cultivation. One likely exception is workers entering transgenic cotton fields. The window of application for transgenic cotton is wider which increases the potential for worker contact with treated surfaces. Cotton is scouted frequently. Another likely exception is post-application exposures to workers entering commercially grown sod areas. The sod may be harvested soon after an application, which could result in relatively high post-application exposures.

Based on the surrogate assessment, HED has concerns regarding low exposure activities for cotton and high exposure activities for crops other than cotton (e.g., harvesting sod for applications less than 26 days from harvest). The interim REI established by the WPS is 24 hours. Since the toxicological endpoint for short-term and intermediate-term exposure is based on a NOEL for developmental effects, HED is concerned that the default REI of 24 hours is not protective enough, especially for cotton workers and sod harvesters where there is significant potential for postapplication exposures. **HED recommends REIs of 4 days for cotton and 26 days for sod** be established.

It is the short-term exposure driving the risk estimate for reentry concerns so HED believes any measures to reduce short term risks will be protective for cancer risks.

c. Epidemiological Information

Only a limited number of incidents involving the use of bromoxynil alone have been reported. Eye or skin illnesses were the most frequently reported in the 11 cases received by the California Pesticide Illness Surveillance Program from 1982-1993, inclusively. The number of systemic incidents per 1,000 applications for 1990 was 0 based on California use data (beginning in 1990 all agricultural uses had to be reported, prior to that only data on restricted use applications were required). The ratio of systemic poisonings to applications for all years is generally low when compared to organophosphate and carbamate insecticides. No recommendations for risk mitigation are warranted based on the limited data available on poisoning incidents.

5. Aggregate Risk

Aggregate risk is estimated by combining dietary (food and water) and residential exposures. Bromoxynil has no residential uses, therefore, the aggregate risk estimate will be based on the dietary exposure from food and water only for the most highly exposed population subgroups and the general population as appropriate. Table 17 (below) shows the aggregate risk for bromoxynil; however, for details concerning the exposure to determine these estimated aggregate risks, see Tables 6 - 10. Details concerning the assumptions and risk characterizations are in the corresponding sections of the document previously discussed.

Table 17: Estimates of Aggregate Risk from Bromoxynil from Dietary Sources (Food and Water) including the use on BXN Transgenic Cotton.

Population Subgroup[1]	Chronic %RfD[2] Cotton @ 10 %CT + Registered Uses 10	Acute MOE[3] Cotton @ 10 %CT + Registered Uses	Cancer[4] Registered Uses (i.e., Excluding Cotton)	Cancer[4] Cotton @ 3 %CT + Registered Uses	Cancer[4] Cotton @ 10 %CT + Registered Uses
whole U.S. population	<1%	>16,000	1.2×10^{-6}	1.3×10^{-6}	1.7×10^{-6}**
females 13+	<1%	> 11,000	N/A*	N/A*	N/A*
children 1-6 years	<1%	>5,000	N/A*	N/A*	N/A*

[1] The most highly exposed population subgroups.

[2] Chronic risk is a concern when more than 100% of the RfD is consumed.

[3] An MOE >1000 indicates there is NO aggregate acute dietary risk concern.

$MOE_{acute} = \frac{NOEL}{\text{Aggregate exposure (food + water)}}$

[4] As discussed in Table 10 the carcinogenic risk from drinking water is 0.2×10^{-6}.

* N/A = Not Applicable. Cancer Risk has only been estimated for the general population (in this case the average exposure between males and females) because it is based on a 70 year lifetime.

** The dietary risk based on dietary risk from food plus the drinking water risk (0.2×10^{-6}).

The chronic and acute aggregate risk estimates do not trigger a concern. The dietary (food) exposure and risk is highly refined using anticipated residues and considering percent crop treated information resulting in a more highly refined cancer risk estimate. The estimated drinking water risk (from surface water sources) was based on a reasonable high end estimate of exposure and is potentially much lower since it may only occasionally occur in water (not necessarily drinking water) and degrades in approximately 7 days. Therefore, the aggregate cancer risk estimate from food plus water is most likely the same as from food alone, roughly 1 to 1.5 in 1 million.

Because of FQPA aggregate and cumulative risk considerations, it is important to note that bromoxynil heptanoate (which is NOT part of the reregistration case) has some of the same uses as bromoxynil phenol and octanoate, but not ALL of the same uses and none different. Therefore, the exposure and risk associated with the use of the heptanoate is not greater than that described for the phenol and octanoate. Also, the heptanoate would in no way "add" to the current risk described above since these active ingredients would be used "in place" of one another rather than in an "additive" manner. Any exposure and risk associated with the bromoxynil phenol and octanoate would present the same or more conservative risk estimate for the heptanoate for the purposes of aggregate risk.

6. Cumulative Risk

Section 408(b)(2)(D)(V) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, but also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanism of toxicity with any other substances, EPA does not at this time have the methodology to fully resolve the scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical specific data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides as to which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanism of activity will be assumed).

In the case of bromoxynil, EPA has not conducted a detailed review of common mechanism to determine whether it is appropriate, or how to include this chemical in a cumulative risk assessment. After EPA develops a methodology to apply common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine these tolerance decisions.

TOLERANCE REASSESSMENT SUMMARY

The residue chemistry chapter of the HED RED was completed 7/7/96 [C. Swartz; CBRS No. 17206, DP Barcode No. D225380]. Since the completion of the chapter, time-limited tolerances have been established for residues of bromoxynil and its DBHA metabolite in cotton commodities. Based on the tolerances published in the FR Notice dated 6/18/97, and on additional data, proposed label amendments and clarification of HED policy on 40 CFR §180.6(a)(3), a revised tolerance reassessment summary is needed for the HED chapter of the RED, and is provided herein.

Prior to the 6/18/97 FR notice, all tolerances for bromoxynil residues were expressed in terms of bromoxynil *per se*; the separate tolerance expressions listed under 40 CFR §180.324(a), (b), and (c) were redundant, and therefore HED recommended for revision of the tolerance expression to delete §180.324(b) and (c), and to place reassessed and new tolerances under §180.324(a). The 6/18/97 FR Notice provides a revised §180.324(a), with the previously recommended tolerances under §180.324(a)(1), and tolerances for residues in cotton commodities under §180.324(a)(2). In addition, it is noted that §180.324(b), (c), and (d) are reserved for Section 18 emergency exemptions, tolerances with regional registrations, and indirect or inadvertent residues, respectively.

The tolerance expression for §180.324(a)(1)is as follows:

> "Tolerances are established for residues of the herbicide bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) resulting from application of its octanoic and/or heptanoic acid ester in or on the following commodities:"

The tolerance expression for §180.324(a)(2) is as follows:

> "Tolerances are established for residues of the herbicide bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) and its metabolite 3,5-dibromo-4-hydroxybenzoic acid resulting from application of its octanoic and/or heptanoic acid ester in or on the following commodities:"

No tolerance expressions are specified for the reserved categories, §180.324(b), (c) and (d). The revised tolerance reassessment table reflects the changes associated with the establishment of time-limited tolerances for residues in cotton commodities. Note that tolerances for residues in livestock commodities have been moved from 180.324(a)(1) to 180.324(a)(2) based on a determination that secondary residues of the metabolite DBHA transfer to livestock.

REVISED TOLERANCE REASSESSMENT SUMMARY

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Tolerances listed under 40 CFR §180.324 (a)(1):			
Alfalfa, seedling	0.1	Revoke	Tolerances should be proposed for alfalfa forage and hay (see below).
Barley, forage, green	0.1	Revoke	Barley forage is no longer a regulated feed item.
Barley, grain	0.1	0.05	Based upon available residue data, tolerances for residues in all cereal grains should be lowered to 0.05 ppm.
Barley, straw	0.1	4.0	The proposed tolerance is supported by the available data.
Corn, fodder, (dry)	0.1	Revoke	Tolerances are already established for residues in field corn commodities and separate tolerances should be established for residues in pop corn commodities.
Corn, forage, (green)	0.1		
Corn, grain	0.1		
Corn, fodder, field (dry)	0.1	0.2	The proposed tolerance is supported by available data; *Corn, field, fodder.*
Corn, forage, field (green)	0.1	0.3	Based upon available data, the tolerance should be increased; *Corn, field, forage.*
Corn, grain, field	0.1	0.05	See comment under barley grain; *Corn, field, grain.*
Flaxseed	0.1	0.1	*Flax, seed.*
Flax straw	0.1	Revoke	Flax straw is no longer a regulated feed item.
Garlic	0.1	0.1	
Grass, canary, annual, seed	0.1	Revoke	Concomitant with establishing tolerances in grass commodities, tolerances for residues in canary grass seed and straw should be revoked.
Grass, canary, annual, straw	0.1		
Mint hay	0.1	Revoke	Mint hay is no longer a regulated feed item.
Oats, forage, green	0.1	0.3	Based on residue data translated from barley forage, the tolerance should be increased; *Oats, forage.*
Oats, grain	0.1	0.05	See comment under barley grain.
Oats, straw	0.1	4.0	Based on residue data translated from barley straw, the tolerance should be increased.
Onions (dry bulb)	0.1	0.1	*Onion, bulb*

REVISED TOLERANCE REASSESSMENT SUMMARY

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Rye, forage, green	0.1	1.0	Based on residue data translated from wheat forage, the tolerance should be increased; *Rye, forage*.
Rye, grain	0.1	0.05	See comment under barley grain.
Rye, straw	0.1	2.0	See comment under wheat, straw.
Sorghum, fodder	0.1	0.2	Based on available residue data, the tolerance should be increased.
Sorghum, forage	0.1	0.5	
Sorghum, grain	0.1	0.05	See comment under barley grain.
Wheat, forage, green	0.1	1.0	Based on available data, the tolerance should be increased; *Wheat, forage*.
Wheat, grain	0.1	0.05	See comment under barley grain.
Wheat, straw	0.1	2.0	Based on available data, the tolerance should be increased.
Tolerances to be Listed under 40 CFR §180.324(a)(2):			
Cotton gin by-products	50	7.0	Originally established as stated in the FR Notice dated 6/18/97
Cotton hulls	21	5.0	
Cotton, undelinted seed	7	1.5	
Cattle, fat	0.1	1.0	Based upon the available feeding study data, tolerances should be increased.
Cattle, mbyp	0.1	3.5	
Cattle, meat	0.1	0.5	
Milk	None	0.1	The registrant should propose the tolerance for residues in milk, based on data from the ruminant feeding study.
Hogs, fat	0.1	1.0	Based upon the available feeding study data, tolerances should be increased [tolerances translated from cattle].
Hogs, mbyp	0.1	3.5	
Hogs, meat	0.1	0.5	
Horses, fat	0.1	1.0	Based upon the available feeding study data, tolerances should be increased [tolerances translated from cattle].
Horses, mbyp	0.1	3.5	
Horses, meat	0.1	0.5	
Poultry, meat	None	0.05	Residues in poultry can no longer be classified under Category 3 of 40 CFR §180.6(a).
Poultry, fat	None	0.05	
Poultry, eggs	None	0.05	
Poultry, mbyp	None	0.3	

REVISED TOLERANCE REASSESSMENT SUMMARY

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Goats, fat	0.1	1.0	Based upon the available feeding study data, tolerances should be increased.
Goats, mbyp	0.1	3.5	
Goats, meat	0.1	0.5	
Sheep, fat	0.1	1.0	Based upon the available feeding study data, tolerances should be increased [tolerances translated from cattle].
Sheep, mbyp	0.1	3.5	
Sheep, meat	0.1	0.5	
New Tolerances Required under 40 CFR §180.324(a)(1):			
Alfalfa, hay	None	0.5	The registrant should propose the tolerance, based on available data.
Alfalfa, forage	None	0.1	The registrant should propose the tolerance, based on available data.
Aspirated grain fractions	None	0.3	The registrant should propose the tolerance, based on available data.
Barley, hay	None	9.0	The registrant should propose the tolerance, based on available data.
Corn, pop, fodder	None	0.2	The registrant should propose the tolerance, based on available data; *Corn, field, fodder.*
Corn, pop, grain	None	0.05	See comment under barley grain.
Grass, forage	None	3.0	A crop group tolerance should be proposed for residues in forage and hay of grasses. Note that grass forages/hay have not been included in ruminant diets, since bromoxynil is only used on grass grown for seed and on grass grown under the CRP. Changes in the use on grass may require revision of livestock tolerances.
Grass, hay	None	3.0	
Oats, hay	None	9.0	The registrant should propose the tolerance, based on available barley hay data.
Wheat, hay	None	4.0	The registrant should propose the tolerance, based on available wheat hay data.
§180.324(b) Section 18 emergency exemptions [Reserved]			
§180.324(c) Tolerances with regional registrations [Reserved]			
§180.324(d) Indirect or inadvertent [Reserved]			

CODEX HARMONIZATION

Since there are no established or proposed Codex MRLs for bromoxynil residues, no compatibility questions exist with respect to U.S. tolerances and Codex.

Appendix I

Food/Feed Use Patterns Subject to Reregistration for Bromoxynil (Case 2070)

Site Application Type Application Timing Application Equipment [a]	Formulation [EPA Reg. No.]	Max. Single Application Rate [b]	Max. # Apps.	Minimum Retreatment Interval (Days)	Use Limitations [c]
Alfalfa					
Postemergence to seedling alfalfa Ground, aerial, or sprinkler [d] irrigation equipment	2 lb/gal EC [264-437] 4 lb/gal WP [264-531] 4 lb/gal EC [264-540]	0.38 lb/A 0.5 lb/A chemigation only	1 [e]	Not applicable (NA)	Do not cut for feed or graze spring treated alfalfa within 30 days of treatment. Do not cut for feed or graze fall or winter treated alfalfa until spring, at least 60 days after treatment. Do not exceed 0.5 lb/A/season.
Corn (field and pop)					
Preemergence and postemergence prior to tassel emergence. Ground, aerial, or sprinkler irrigation equipment	2 lb/gal EC [264-437]	0.38 lb/A - preemergence 0.5 lb/A - postemergence	2 [f]	7	Do not cut crop for feed or graze within 30 days after application. Do not plant rotational crops until the following season. Do not exceed 0.5 lb ai/A/season.
Preemergence and postemergence before crop is 12 inches in height. Ground and aerial equipment	1 lb/gal EC [264-477]	0.38 lb/A	Not specified (NS)	NA	Do not cut crop for feed or graze within 30 days after application. Do not exceed 0.75 lb ai/A/season.
Preemergence and postemergence prior to tassel emergence. Ground or aerial equipment	4 lb/gal WP [264-531]	0.5 lb/A	2 [f]	7	Do not cut crop for feed or graze within 30 days after application. Do not plant rotational crops until the following season. Under "Use Restrictions", the label lists a maximum seasonal rate of 0.5 lb ai/A, but a maximum season rate of 0.75 lb ai/A is also listed under "Special Use Directions" for corn and sorghum.

Site Application Type Application Timing Application Equipment [a]	Formulation [EPA Reg. No.]	Max. Single Application Rate [b]	Max. # Apps.	Minimum Retreatment Interval (Days)	Use Limitations [c]
Corn (field and pop) - continued					
Preemergence and postemergence prior to tassel emergence. Ground, aerial, or sprinkler irrigation equipment	4 lb/gal EC [264-540]	0.38 lb/A - preemergence 0.75 lb/A - postemergence	2 [f]	7	Do not cut crop for feed or graze within 30 days after application. Do not plant rotational crops until the following season. Under "Use Restrictions", the label lists a maximum seasonal rate of 0.75 lb ai/A, but maximum seasonal rates of 1.0-1.25 lb/A are implied under "Special Use Directions" for corn and sorghum.
Cotton (transgenic BXN™ cotton only)					
Broadcast or banded (over-the-row) preemergence and *postemergence* Ground equipment	2 lb/gal EC [264-437] 4 lb/gal WP [264-540]	broadcast/banded 0.5 lb/A	3	NS	Do not exceed 1.5 lb ai/planted acre/season. Do not graze any portion of crop or cut crop for feed or fodder. Do not apply within 75 days of harvest. After applying up to 2 pints/A/season of [Buctril® or Buctril ® 4EC], wait a minimum of 30 days from the date of the application, and then plant any rotational crop. After applying more than 2 pints/A/season of [Buctril® or Buctril ® 4EC], only transgenic BXN cotton may be planted as a rotational crop.
Flax (*Linium usitatissium* only)					
Postemergence to plants 2 to 8 inches in height Ground or aerial equipment	2 lb/gal EC [264-437] 4 lb/gal WP [264-531] 4 lb/gal EC [264-540]	0.25 lb/A	NS	NA	Do not apply to flax during or after the bud stage. Do not use on ornamental flax.

Site Application Type Application Timing Application Equipment [a]	Formulation [EPA Reg. No.]	Max. Single Application Rate [b]	Max. # Apps.	Minimum Retreatment Interval (Days)	Use Limitations [c]
Garlic					
Postemergence before plant is 12 inches in height Ground, aerial, or sprinkler irrigation equipment	2 lb/gal EC [264-437] 4 lb/gal EC [264-531] 4 lb/gal EC [264-540]	0.5 lb/A	NS	NA	Do not harvest within 112 days of treatment. Label 264-531 states that garlic grown in muck soils in the Northeastern U.S. may be harvested 60 days after treatment. Use a minimum of 20 gal/A for ground applications.
Grass (sundangrass)					
Postemergence, after 3-leaf stage and prior to preboot stage Ground, aerial, or sprinkler irrigation equipment	2 lb/gal EC [264-437] 4 lb/gal WP [264-531]	0.38 lb/A	NS	NA	Do not cut crop for feed or graze within 30 days after application. Do not exceed 0.5 lb ai/A/season Do not plant rotational crops until the following season.
Grasses (in conservation reserve program areas/ or grown for seed or sod)					
Postemergence after 3-leaf stage Ground or aerial equipment	2 lb/gal EC [264-437] [264-438] 4 lb/gal WP [264-531] 4 lb/gal EC [264-540]	0.5 lb/A	NS	NA	Do not allow livestock to graze in treated areas or feed treated grass to livestock.
Mints (established peppermint and spearmint only)					
Postemergence to dormant or actively growing fields harvested at least one year prior to treatment Ground or sprinkler irrigation equipment [g]	2 lb/gal EC [264-437] 4 lb/gal WP [264-531] 4 lb/gal EC [264-540]	0.38 lb/A	NS	NA	Do not use in spring on newly established fields. Do not harvest within 70 days of treatment. Do not apply more than 1.5 lb ai/A/season.

Site Application Type Application Timing Application Equipment [a]	Formulation [EPA Reg. No.]	Max. Single Application Rate [b]	Max. # Apps.	Minimum Retreatment Interval (Days)	Use Limitations [c]
Onion, dry bulb					
Preemergence (at least 3 to 4 days prior to emergence) and postemergence to plants with 2-5 true leaves Ground or sprinkler irrigation equipment	2 lb/gal EC [264-437] 4 lb/gal EC [264-540]	0.38 lb/A	NS	NA	For postemergence applications, use at least 50-70 gal/A. Label 264-540: Do not apply with aerial equipment. Label 264-437: Preemergence application is restricted to onions grown east of the Mississippi River on muck soils with >10% organic matter. Do not apply preemergence to onions grown west of the Mississippi River. Do not apply postemergence applications using aerial equipment.
Preemergence (at least 3 days prior to emergence) and postemergence to plants with 2-5 true leaves Ground or aerial equipment	4 lb/gal WP [264-531]		NS	NA	Preemergence application using ground or aerial equipment is restricted to onions grown east of the Mississippi River on muck soils with >10% organic matter. Do not apply preemergence to onions grown west of the Mississippi River. For postemergence applications, use at least 50-70 gal/A. Do not apply postemergence applications using aerial equipment.

Site Application Type Application Timing Application Equipment [a]	Formulation [EPA Reg. No.]	Max. Single Application Rate [b]	Max. # Apps.	Minimum Retreatment Interval (Days)	Use Limitations [c]
Small Grains (wheat, barley, oats, rye and triticale)					
Postemergence prior to boot stage Ground, aerial, or sprinkler irrigation equipment	2 lb/gal EC [264-437] [264-438] 4 lb/gal WP [264-531] 4 lb/gal EC [264-540]	0.5 lb/A	NS	NA	Do not graze treated field within 30 days of application. Labels 264-437 and 264-531 also list a maximum seasonal use rate of 0.5 lb ai/A and state "Do not plant rotational crops until the following season."
Sorghum (grain and forage)					
Preemergence and postemergence prior to preboot stage Ground or aerial equipment	1 lb gal EC [264-477]	0.38 lb/A	NS	NA	Do not cut crop for feed or graze within 30 days after application. Do not apply more than 0.75 lb ai/A/season.
Preemergence and postemergence prior to preboot stage Ground, aerial, or sprinkler irrigation equipment	2 lb/gal EC [264-437]	0.38 lb/A - preemergence 0.5 lb/A - postemergence/ chemigation	2 [f]	7	Do not cut crop for feed or graze within 30 days after application. Do not plant rotational crops until the following season. Label directions allow applications at 0.5 lb ai/A, but also state "do not apply 0.5 lb/A rate to sorghum." Do not apply more than 0.5 lb ai/A/season.
Preemergence and postemergence prior to preboot stage Ground or aerial equipment	4 lb/gal WP [264-531]	0.38 lb/A	2 [f]	7	Do not cut crop for feed or graze within 30 days after application. Do not plant rotational crops until the following season. Do not apply to sorghum at 0.5 lb ai/A, and do not use more than 0.5 lb ai/A/season.

Site Application Type Application Timing Application Equipment [a]	Formulation [EPA Reg. No.]	Max. Single Application Rate [b]	Max. # Apps.	Minimum Retreatment Interval (Days)	Use Limitations [c]
Sorghum (continued)					
Preemergence and postemergence prior to preboot stage Ground, aerial, or sprinkler irrigation equipment	4 lb/gal EC [264-540]	0.38 lb/A - preemergence 0.75 lb/A - postemergence	2 [f]	7	Do not cut crop for feed or graze within 30 days after application. Do not plant rotational crops until the following season. Label directions allow an application at up to 0.75 lb ai/A, but also state "do not apply 0.5 lb/A rate to sorghum." Under "Use Restrictions", the label lists a maximum seasonal rate of 0.75 lb ai/A, but a seasonal maximum of 1.25 lb/A is also listed under "Special Use Directions" for control of Large Velvet Leaf.

[a] Unless otherwise specified, all labels specify minimum application volumes of 5 and 3 gal/A for ground and aerial applications, respectively. The label for one of the 2 lb/gal ECs [EPA Reg. No. 264-437] states that minimum application volumes are 10 and 5 gal/A in CA for ground and aerial applications, respectively. The label for the 1 lb/gal EC [EPA Reg. No. 264-477] prohibits applications through any type of irrigation system, and the label for the 4 lb/gal gel formulation [EPA Reg. No. 531], which is designated as a WP, does not include applications using irrigation systems.

[b] Rates are expressed in terms of bromoxynil equivalents.

[c] All labels specify a 12-hour restricted entry interval (REI); the 4 lb/gal gel formulation [264-531] is not registered for use in CA.

[d] Apply only through the following sprinkler irrigation systems: center pivot, lateral move, side (wheel) roll, solid set, and hand move.

[e] One seasonal application is implied.

[f] Under "Special Use Directions for Corn and Sorghum", several labels specified a repeat application at 7 to 10 days.

[g] For use on mint, label 264-437 allows applications through sprinkler equipment; whereas, labels 264-531 and 264-540 allow applications only through ground equipment.

Table B. Residue Chemistry Science Assessments for Reregistration of Bromoxynil.

GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References[1]
860.1200: Directions for use	N/A	Yes[2]	See Table A.
860.1300: Plant Metabolism	N/A	No	**00115594**, **00165547** 42436901[3], 42677703[4,5] 43151701[6], 43307701[7] 43307702[7], 42677703[8] 43151701[9]
860.1300: Livestock Metabolism	N/A	Yes[10]	42346401[11], 42346402[8]
860.1340: Residue Analytical Methods	N/A	No[12]	**00075671**, **00084589**
860.1360: Multiresidue Methods Plants and Livestock			**00139591**, 42283201[13] 42283202[10], 42331001[14] 42331002[11], 42350701[15] 42433401[16], 42460501[17] 42460502[18], 42465401[15] 42501601[19], 42571401[15] 42677701[4], 42718702[20] 42950101[21], 42950102[18] 42950103[18], 43108801[22] 43307001[23], 43389001[24] 43922301[25], 439809-03 and -04[26], 44168801[27] 44168802[28]
860.1380: Storage Stability	N/A	No	43108801[19], 44248501/44352201[29]
860.1500: Crop Field Trials			
Bulb Vegetables Group			
Garlic	0.1	No	42331002[11], 42540602[15]
Onion, bulb	0.1	No	42350701[12], 42747601[30]
Cereal Grains Group			
Barley	0.1	No	42331001[11], 42540601[15]
Corn (field and pop)	0.1	No	42501601[16], 42757601[31]
Oats	0.1	No	

Table B *(continued)*.

GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References[1]
Rye	0.1	No	
Sorghum	0.1	No	42718702[17], 43506901[32]
Wheat	0.1	No	42460501[14], 42747701[22]
Forage, Fodder, and Straw of Cereal Grains Group			
Barley forage and straw	0.1	No	42331001[11], 42540601[15]
Corn forage and fodder (field and pop)	0.1	No	42501601[16], 42757601[23]
Oats forage and straw	0.1	No	
Rye forage and straw	0.1	No	
Sorghum forage and fodder	0.1	No	42718702[17], 43506901[24]
Wheat forage and straw	0.1	No	42460501[14], 42747701[22]
Grass Forage, Fodder, and Hay Group			
Grasses	0.1	No	42950102[18], 43648102[33]
Nongrass Animal Feeds Group			
Alfalfa	0.1	No	**00150382**, 42950101[18]
Miscellaneous Commodities			
Aspirated grain fractions	None	No	42460502[15], 42465401[15] 42571401[15], 42950103[18]
Flax (seed and straw)	0.1	No	42283201[10], 42759601[34]
Peppermint	0.1	No	**00118506**, 43648101[25]
Spearmint	0.1	No	**00118506**, 43648101[25]
Cotton, Undelinted seed	1.5	No	42677701[35], 439809-01 and -02[36], 44183301[37], 44458901[38]
860.1520: Processed Food/Feed			
Barley	None	No	42331001[11], 42460502[15]
Corn	None	No	42571401[15]

Table B *(continued)*.

GLN: Data Requirements	Current Tolerances, ppm [40 CFR]	Must Additional Data Be Submitted?	References[1]
Flaxseed	None	No	42283202[10], 42759602[26]
Mints (peppermint and spearmint)	None	No	43648101[25]
Oats	None	No	
Rye	None	No	
Sorghum	None	No	42465401[15]
Wheat	None	No	42950103[18]
Cotton gin by-products	7.0	No	42677702[39], 4389809-01 and -02[36], 44458901[38]
Cotton hulls	5.0	No	42677702[39], 4389809-01 and -02[36]
860.1480: Meat, Milk, Poultry, and Eggs			
Eggs	0.05	No	43389001[21]
Cattle, goats, hogs, horses, and sheep		No[40]	43307001[20]
Fat	1.0		
Meat	0.5		
MBYP	3.5		
Poultry		No	43389001[21]
Fat/meat	0.05		
MBYP	0.3		
Milk	0.1	No[38]	43307001[20]
860.1400: Water, Fish and Irrigated Crops	N/A		
860.1460: Food Handling Establishments	N/A		
860.1850: Confined Rotational Crops	None	No	
860.1900: Field Rotational Crops	None	Yes[41]	43279401[42]

1. **Bolded** references were cited in the Bromoxynil Phase 4 Review (L. Cheng, 1/30/91). Unbolded references were reviewed as noted.

2. Use directions for corn and sorghum, should be amended such that all labels with corn and sorghum uses specify the same maximum single application rates and maximum seasonal use rates.

Use directions for onions on the label of the 4 lb/gal EC (EPA Reg. No. 264-540) should be amended to include the following restriction, "preemergence application is restricted to onions grown east of the Mississippi River on muck soils with >10% organic matter." In addition, the prohibition against postemergence aerial applications to onions should be deleted from EPA Reg. No. 264-437, as this label already does not allow any type of aerial application to onions.

Use directions for Sudangrass on labels 264-437 and 264-531 specify a pre-grazing interval (PGI) of 30 days. The Agency does not currently allow PGIs for grasses grown only for forage; however, CBRS will allow the 30-day PGI to remain on registered labels, since bromoxynil is applied to Sudangrass prior to the preboot stage, and the first cutting of forage would occur approximately 30 days later.

3. CBRS No. 10421, DP Barcode D181694, C. Swartz, 4/23/93.

4. PP#3G4197, CBTS No. 11636, DP Barcode D189368, G. Kramer, 9/20/93, and CBTS No. 12757, DP Barcode D196421, G. Kramer, 3/25/94.

5. PP#3F4233, CBTS Nos. 13402 and 13404, DP Barcodes D200496 and D200471, G. Kramer, 4/19/94.

6. CBTS Nos. 13402 and 13404, DP Barcodes D200496 and D200471, G. Kramer, 4/19/94.

7. CBRS No. 14097, DP Barcode D205873, C. Swartz, 6/7/95.

8. DP Barcode D196421, G. Kramer, 3/28/94.

9. DP Barcodes D200496 and D200471, G. Kramer, 4/25/94.

10. The nature of the residue following dosing with the DBHA metabolite is not adequately understood. Poultry and ruminant metabolism studies for DBHA are required. DP Barcode D224250, C. Swartz, 3/19/98.

11. CBRS No. 10091, DP Barcode D179470, S. Funk, 9/2/92.

12. The requirement for analysis of representative samples from the animal metabolism studies using the enforcement method remains outstanding. However, since greater than 90% of the TRR was identified as bromoxynil and bromoxynil octanoate, the requirement is waived.

13. CBRS No. 9855, DP Barcode D178167, S. Knizner, 10/15/92.

14. CBRS Nos. 9987 and 10003, DP Barcodes D179251 and D179257, C. Swartz, 7/21/92.

15. CBRS No. 10032, DP Barcode D179571, S. Knizner, 10/15/92.

16. Multiresidue method testing data have been forwarded to the FDA (F. Griffith, 11/4/92).

17. CBRS No. 10633, DP Barcode 182873, C. Swartz, 10/27/92.

18. CBRS Nos. 10872, 11039, 10615; DP Barcodes D184641, D185636, D182875; S. Funk; 6/28/94.

19. CBRS No. 10748, DP Barcode D183667, S. Knizner, 11/16/92.

20. CBRS No. 11754, DP Barcode D190384, S. Knizner, 8/27/03.

21. CBRS No. 12701, DP Barcode D195998, C. Swartz, 3/6/96.

22. CBRS Nos. 13215 and 13877, DP Barcodes D199274 and D204403, S. Knizner, 7/14/94.

23. CBRS No. 14101, DP Barcode D205851, C. Swartz, 9/11/95.

24. CBRS No. 14533, DP Barcode 208235, C. Swartz, 9/11/95.

25. Letter to FDA dated 4/11/96.

26. DP Barcode D227990, G. Kramer, 10/4/96.

27. DP Barcode D233875, G. Kramer, 3/25/97.

28. DP Barcode D232104, G. Kramer, 1/14/97.

29. DP Barcode D238372, W. Donovan, 11/20/97.

30. CBRS No. 11847, DP Barcode 191062, C. Swartz, 5/10/94.

31. CBRS No. 11900, DP Barcode D191340, C. Swartz, 10/18/94.

32. CBRS No. 14978, DP Barcode D210923, C. Swartz, 6/23/95.

33. CBRS No. 15604, DP Barcode No. D215853, C. Swartz, 2/22/96.

34. CBRS No. 12154, DP Barcode D191341, C. Swartz, 9/13/93.

35. DP Barcode D189368, G. Kramer, 9/17/93.

36. DP Barcode D227990, G. Kramer, 10/4/96.

37. DP Barcode D232957, G. Kramer, 3/11/97.

38. DP Barcode D243651, C. Swartz, 3/2/98.

39. DP Barcode D196421, G. Kramer, 3/28/94.

40. No additional data are required, provided livestock metabolism studies conducted with DBHA do not show significant transfer of DBHA residues to livestock.

41. The registrant has agreed to conduct limited rotational crop field trials using the higher seasonal application rate for cotton.

42. CBRS No. 13950, DP Barcode No. D204985, C. Swartz, 2/20/96.

BIBLIOGRAPHY

00004620 Velsicol Chemical Corporation (1972) Wheat: Project No. 404000. (Unpublished study including report nos. 23, 32 and 116, received Jan 3, 1973 under 876-25; CDL:005050-D)

00025394 Rydrich, D.; Wallace, K.; Beck, B.; et al. (1976) Residue Results: Banvel plus Bromoxynil plus MCPA Tank Mix: Summary. (Unpublished study received Feb 18, 1976 under 876-25; prepared in cooperation with Oregon State Univ., submitted by Velsicol Chemical Corp., Chicago, Ill.; CDL:225197-C)

00037225 Ames, G.D.; Stewart, V.; Betz, J.; et al. (1965) Analysis of Wheat or Barley by Diablo for Possible Residues of Bromoxynil or Ioxynil. (Unpublished study received Aug 26, 1965 under 264-204; prepared in cooperation with Univ. of Idaho and others, submitted by Union Carbide Agricultural Products Co., Ambler, Pa.; CDL:002166-F)

00053029 Union Carbide Agricultural Products Company, Incorporated (1965) Summary Section III. Includes undated methods entitled: Analysis of wheat grain for possible residues of Ioxynil (3,5-Diiodo-4-hydroxybenzonitrile); Analysis of wheat and barley samples for possible residues of Bromoxynil (3,5-Dibromo-4-hydroxybenzonitrile). (Reports by various sources; unpublished study received Aug 26, 1965 under unknown admin. no.; CDL:107620-A)

00061772 American Cyanamid Company (1975) Avenge® Residue--Wheat. (Unpublished study received Apr 26, 1977 under 241-250; CDL: 229617-B)

00075671 Guardigli, A. (1972) Determination of Total Bromoxynil as Bromoxynil Methyl Ether Derivative in Plant Substrates, Soil, and Water by Electron Capture Gas Liquid Chromatography. Method no. 117 dated Aug, 1972. (Unpublished study received Aug 10, 1981 under 359-564; submitted by Rhone-Poulenc Chemical Co., Monmouth Junction, N.J.; CDL:245674-B)

00075673 Guyton, C.L.; Chow, W.; Burr, R.; et al. (1980) Bromoxynil and MCPA Residue Results in/on Wheat, Barley and Soil following a Single Tank Mix Application: PPD Report No. 80/006. (Unpublished study received Aug 10, 1981 under 359-564; prepared in cooperation with Univ. of Idaho, submitted by Rhone-Poulenc Chemical Co.,Monmouth Junction, N.J.; CDL:245673-A)

00075674 Guyton, C.L.; Chow, W.; Zick, M. (1981) Bromoxynil and MCPA Residue Results in/on Wheat and Soil following a Single Tank Mix Application: PPD Report No. 81/005. (Unpublished study received Aug 10, 1981 under 359-564; submitted by Rhone-Poulenc Chemical Co.,Monmouth Junction, N.J.; CDL:245672-A)

00075675 Guyton, C.L.; Chow, W.; Foresman, C.; et al. (1980) Bromoxynil and MCPA Residues in Wheat and Soil Samples: PPD Report No. 80/001. (Unpublished study receivequid Chromatography. Method no. 117 (Unpublished study received Aug 10, 1981 under 359-564; prepared in cooperation with J.G. Boswell Co., submitted by Rhone-Poulenc Chemical Co., Monmouth Junction, N.J.; CDL:245671-A)

00084292 Interregional Research Project Number 4 (1980) Summary of Residue Chemistry Data. (Compilation; unpublished study received Sep 10, 1981 under 1E2577; CDL:070361-A)

00084293 Interregional Research Project Number 4 (1980) Summary of Residue Chemistry Data. (Compilation; unpublished study received Sep 10, 1981 under 1E2578; CDL:070362-A)

00084589 Cubbedge, S.D. (1981) Analysis for Residues of Bromoxynil Octanoate as the Bromoxynil Methyl Ether in Soil, Wheat Grain, Wheat Straw and Wheat Plants: Tolerance Study SS/80 H-1. (Unpublished study received Sep 15, 1981 under 359-564; prepared by Biospherics, Inc., submitted by Rhone-Poulenc Chemical Co., Monmouth Junction, N.J.; CDL:245923-D)

00103103 Rhone-Poulenc, Inc. (1982) Summary. Summary of studies 070895-B and 070895-C. (Unpublished study received May 28, 1982 under 359-564; CDL:070895-A)

00108987 Chipman Chemical Co. (1966) [Residue Studies with Bromoxynil Octanoate, M & B 10,731 on Various Crops]. (Compilation; unpublished study received Jun 18, 1966 under 7F0536; CDL:090654-A)

00111184 Rhone-Poulenc, Inc. (1964) [Bromoxynil Octanoate: Residues in Wheat and Other Crops]. (Compilation; unpublished study received Feb 25, 1965 under unknown admin. no.; CDL:003111-B)

00111199 Collins, R.; Pullin, E. (1965) Bromoxynil Octanoate (M & B 1073). Direct Comparison of Methods of Residue Analysis (Gas Liquid Chromoatography and Infra-red): Report No. C.240. (Unpublished study received Dec 6, 1965 under 359-564; prepared by May &Baker Ltd., Eng. submitted by Rhone-Poulenc, Inc., Monmouth Junction, NJ; CDL:003161-A)

00111201 Rhone-Poulenc, Inc. (1966) [Residues Studies with Buctril: Immature and Harvest Cereals and Flax]. (Compilation; unpublished study received Apr 22, 1966 under 359-564; CDL:003162-B)

00111202 Muggleton, D. (1965) Bromoxynil Octanoate: Estimation by Infra Red Method: Ref CRC/BJH/DW/2712. (Unpublished

study received Dec 6, 1965 under 359-564; prepared by May & Baker Ltd., Eng., submitted by Rhone-Poulenc, Inc., Monmouth Junction, NJ; CDL:050036-B)

00111209 May and Baker, Ltd. (1970) Conclusions for Bromoxynil Metabolism Studies. (Unpublished study received Apr 5, 1970 under 0F0994; Report No. C.240. (Unpublished submitted by Amchem Products, Inc., Ambler, PA; CDL:091709-A)

00111210 Davis, M.; Muggleton, D. (1970) Herbicides--Bromoxynil Octanoate ...: Summary of Metabolism and Residue Studies on Wheat: PRG 691. Summary of studies 091709-C through 091709-H. (Unpublished study received Apr 5, 1970 under 0F0994; prepared by May &Baker, Ltd., Eng., submitted by Amchem Products, Inc., Ambler,PA; CDL:091709-B)

00111211 Mulcock, P.; Threlfall, C. (1970) Herbicides--Bromoxynil Octanoate ...: Qualitative Radiochemical Studies on Growing Wheat in an Enclosed System: Report No. PRG/642. (Unpublished study received Apr 5, 1970 under 0F0994; prepared by May & Baker, Ltd., Eng., submitted by Amchem Products, Inc., Ambler, PA; CDL: 091709-C)

00111212 Threlfall, C. (1969) Herbicides--Bromoxynil Octanoate ...: Quantitative Radiochemical Balance Studies on Growing Wheat in an Enclosed System: Report No. PRG.497. (Unpublished study received Apr 5, 1970 under 0F0994; prepared by May & Baker, Ltd., Eng.,submitted by Amchem Products, Inc., Ambler, PA; CDL:091709-D)

00111213 Buckland, J.; Collins, R.; Henderson, M.; et al. (1970) Herbicides--Bromoxynil Octanoate ...: Distribution and Decline Studies in Growing Wheat Plants Using 14C-tracers: Report No. PRG/ 560. (Unpublished study received Apr 5, 1970 under 0F0994; prepared by May & Baker, Ltd., Eng., submitted by Amchem Products, Inc., Ambler, PA; CDL:091709-E)

00111214 Buckland, J.; Collins, R. (1970) Herbicides--Bromoxynil Octanoate ...: Distribution Studies in Harvested Wheat using 14C-tracers: Report No. PRG/626. (Unpublished study received Apr 5, 1970 under 0F0994; prepared by May & Baker, Ltd., Eng., submitted by Amchem Products, Inc., Ambler, PA; CDL:091709-F)

00111215 Buckland, J.; Collins, R.; Pullin, E. (1970) Herbicides--Bromoxynil Octanoate ...: Metabolism Studies in Growing Wheat Plants Using 14C-tracers: Report No. PRPRG.497. (Unpublished study received Apr 5, 1970 under 0F0994; prepared by May & Baker, Ltd., Eng., submitted by Amchem Products, Inc., Ambler, PA; CDL:091709-G)

00111222 Rhone-Poulenc, Inc. (1965) [Bromoxynil Octanoate: Residual Bromine Levels in Cereals and Comparison of Methods of Residue Analysis]. (Compilation; unpublished study received Dec 6, 1975 under 359-564; CDL:101367-A)

00111232 Union Carbide Agricultural Products Co., Inc. (1965) Analysis of Wheat and Barley for Possible Residues of Ioxynil or Bromoxynil. (Compilation; unpublished study received Aug 26, 1965 under unknown admin. no.; CDL:119304-B)

00111235 Rhone-Poulenc, Inc. (1965) [Determination of Bromoxynil Octanoate Residues in Various Crops]. (Compilation; unpublished study received Mar 16, 1965 under unknown admin. no.; CDL:121321-B)

00114137 Union Carbide Agricultural Products Co., Inc. (1982) Residue and Metabolism: [Bromoxynil]. (Compilation; unpublished study received Sep 10, 1982 under G/633. (Unpublished study received Sep 10, 1982 under 264-340; CDL:071084-B)

00115594 Huhtanen, K.; Heintzelman, R. (1982) Distribution of Residues and Metabolism of 14C-Bromoxynil Octanoate in Foliar-treated Corn: File No. 30773. (Unpublished study received Oct 13, 1982 under 2F2753; submitted by Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC; CDL:071179-A)

00115657 Gemma, A.; Wargo, J.; Heinzelmann, G. (1982) 14C Bromoxynil Field Rotational Crop Study: The Potential Uptake of 14C Bromoxynil and/or Its Metabolites in Various Crops from Soil Treated with 14C Bromoxynil Octanoate: ASD Report No. 82/055. (Unpublishedstudy received Oct 13, 1982 under 359-564; submitted by Rhone-Poulenc, Inc., Monmouth Junction, NJ; CDL:248550-A)

00118506 Interregional Research Project No. 4 (1982) The Results of Tests on the Amount of Bromoxynil Residues Remaining in or on Mint, Including a Description of the Analytical Method Used. (Compilation; unpublished study received Dec 3, 1982 under 3E2804; CDL:071278-A)

00124227 Gemma, A.; Wargo, J.; Heinzelmann, G. (1982) 14C Bromoxynil Field Rotational Crop Study: The Potential Uptake of 14C Bromoxynil and/or Its Metabolites in 264-340; CDL:071084-B) and/or Its Metabolites in Various Crops from Soil Treated with 14C Bromoxynil Octanoate: ASD Report No. 82/055. (Unpublishedstudy received Jan 19, 1983 under 359-564; submitted by Rhone-Poulenc, Inc., Monmouth Junction, NJ; CDL:249297-A)

00137602 Guyton, C.; Chow, W.; Thomson, C.; et al. (1983) Bromoxynil Residue Data on Sweet Corn, Forage and Processed Cannery Fractions--1983 Field Program A-28: Ref. No. 83/BHL/912/AG; ASD No. 83/062. (Unpublished study received Feb 8, 1984 under 359-564; submitted by Rhone-Poulenc, Inc., Monmouth Junction, NJ; CDL:252434-A)

00137603 Guyton, C.; Merrick, J.; Ourisson, P.; et al. (1983) Bromoxynil Residue Data on Corn Silage, Fodder and Grain Treated

with Buctril--1983 Field Program K-3: Ref. No. 83/BHL/882/AG; ASD No. 83/058. (Unpublished study received Feb 8, 1984 under 359- 564; submitted by Rhone-Poulenc, Inc., Monmouth Junction, NJ; CDL:252435-A)

00139591 Guyton, C.; Heinzelmann, G.; Guardigli, A. (1983) Bromoxynil Residue Data on Sorghum Plants, Fodder and Grain: Ref. No. 83/644/ BHL/AG; ASD No. 83/038. (Various Crops from Soil Treated with BHL/AG; ASD No. 83/038. (Unpublished study received Nov 17, 1983 under 359-564; submitted by Rhone-Poulenc, Inc., Monmouth Junction, NJ; CDL:252171-A)

00146106 Guyton, C. (1984) Residue Data on Corn, Barley, Oats and Wheat Treated with Bromoxynil HB . Unpublished compilation. 196 p.

00148129 Union Carbide Agricultural Products Co., Inc. (1984) Metabolism and Residue Data of Bromoxynil in Sweet Corn . Unpublished compilation. 75 p.

42283201 Nygren, R. (1992) Buctril/Flax/Magnitude of Residue Pregram for Reregistration: Lab Project Number: USA90B25: 41182. Unpublished study prepared by Rhone-Poulenc Ag Co., McKenzie Laboratories, Inc. 159 p.

42283202 Nygren. R. (1992) Buctril/Flax/Magnitude of Residue Processing Study for Reregistration: Lab Project Number: USA90B26: 41168. Unpublished study prepared by Rhone-Poulenc Ag Co., Ag Soil Science; et al. 149 p.

42346401 Downs, J.; Marsh, J.; Krautter, G. (1992) Nature of the Residue Study with [carbon14]-Bromoxynil Octanoate in Dairy Goats: Lab Project Number: 610: 1432: EC91-160. Unpublished study prepared by PTRL East, Inc. 180 p.

42346402 Downs, J.; Marsh, D.; Krautter, G. (1992) Nature of the Residue Study with [carbon 14]-Bromoxynil Octanoate in Laying Hens: Lab Project Number: 611: 1437: EC91-161. Unpublished study prepared by PTRL East, Inc. 185 p.

42350701 Kowite, W. (1992) Buctril/Onions/Magnitude of the Residue: Lab Project Number: USA91BO9: 41209. Unpublished study prepared by Rhone-Poulenc Ag. Co in coop with CYAL, Inc.; Agsearch Co.; Cal. Ag Research, Inc., et al. 218 p.

42436901 Wootton, M.; Johnson, T. (1992) Metabolic Fate and Distribution of [carbon 14]-Bromoxynil Octanoate in Sweet Corn: Lab Project Number: 571: 1410. Unpublished study prepared by PTRL East, Inc. 102 p.

42460501 Cappy, J. (1992) Buctril/Wheat/Magnitude of Residue (USA91B05): Lab Project Number: 41240. Unpublished study

prepared by CYAL, Inc. in cooperation with other field cooperator laboratories. 410 p.

42460502 Cappy, J. (1992) Buctril/Barley/Magnitude of Residue in Processing Fractions (USA 91B07): Lab Project Number: 41263. Unpublished study prepared by Rhone-Poulenc Ag Co. in cooperation with The Texas A&M University System and CYAL, Inc. 156 p.

42465401 Cappy, J. (1992) Buctril/Sorghum/Magnitude of Residue in Processing Fractions (USA91B04): Lab Project Number: 41283: USA91B04. Unpublished study prepared by Stewart Agricultural Research Services, Inc. in cooperation with The Texas A&M University System and CYAL, Inc. 223 p.

42501601 Cappy, J. (1992) Buctril/Corn/Magnitude of Residue (USA91B01): Lab Project Number: USA91B01: 41290. Unpublished study prepared by CYAL Inc. 423 p. Unpublished study prepared by prepared by CYAL Inc. 423 p.

42571401 Cappy, J. (1992) Buctril/Corn/Magnitude of Residue in Processing Fractions (USA91B02): Lab Project Number: USA91B02: 41323. Unpublished study prepared by Rhone-Poulenc. 228 p.

42677701 Cappy, J. (1993) Buctril/Cotton/Magnitude of Residue: Lab Project Number: USA91B10: 41342. Unpublished study prepared by Rhone-Poulenc Ag Co. 419 p.

42677702 Cappy, J. (1993) Buctril/Cotton/Magnitude of Residue in Processing Fractions: Lab Project Number: USA91B11: 41345. Unpublished study prepared by Rhone-Poulenc Ag Co. 217 p.

42677703 Yenne, S.; Macy, L. (1993) Metabolic Fate and Distribution of (carbon 14)-Bromoxynil Octanoate in Cotton and Genetically Modified Cotton: Final Report: Lab Project Number: EC90-122: 41370. Unpublished study prepared by Rhone-Poulenc Ag Co.108 p.

42718702 Cappy, J. (1993) BUCTRIL /Sorghum/ Magnitude of Residue: Lab Project Number: USA91B03: 44109. Unpublished study prepared by McKenzie Lab., Inc. 360 p.

42747601 Kowite, W. (1993) Additional Data to Support MRID 423507-01: Bromoxynil: Buctril/Onions/Magnitude of Residue: Lab Project Number: USA91B09. Unpublished study prepared by Cyal, Inc. 42 p.

42747701 Cappy, J. (1993) Additional Data to Support MRID 424605-01: Buctril/Wheat/Magnitude of Residue (USA91B05): (Bromoxynil octanoate): Lab Project No. USA91B05. Unpublished study prepared by CYAL, Inc. 113 p.

42757601 Cappy, J. (1993) Additional Data to Support MRID 425061-01: Buctril/Corn/Magnitude of Residue: Lab Project Number: USA91B01. Unpublished study prepared by Cyal, Inc. 178 p.

42759601 Nygren, R. (1993) Additional Data to Support MRID 422832-01: BUCTRIL/Flax/Magnitude of Residue Program for Reregistration: Lab Project Number: USA90B25. Unpublished study prepared by McKenzie Labs., Inc. 9 p.

42759602 Nygren, R. (1993) Additional Data to Support MRID 422832-02: BUCTRIL/Flax/Magnitude of Residue: Processing Study for Reregistration: Lab Project Number: USA90B26. Unpublished study prepared by McKenzie Labs., Inc. 13 p.

42950101 Rhone-Poulenc Ag Co. (1993) BUCTRIL/Seedling Alfalfa/Magnitude of Residue: Lab Project Number: USA92B01: 44208. Unpublished study prepared by McKenzie Labs; Crop Management Strategies, Inc.; French Agricultural Research, Inc. 216 p.

42950102 Rhone-Poulenc Ag Co. (1993) BUCTRIL/Grass Grown for Seed/Magnitude of Residue: Lab Project Number: USA92B02: 44209. Unpublished study prepared by McKenzie Labs; Stewart Agricultural Research; Collins Agricultural Consultants, Inc. 207 p.

42950103 Rhone-Poulenc Ag Co. (1993) BUCTRIL/Wheat/Magnitude of Residue in Processing Fractions: Lab Project Number: USA92B03: 44210. Unpublished study prepared by Food Protein Research & Development Ctr., Texas A&M Univ. System; CYAL, Inc. 244 p.

43108801 Koktavy, K. (1994) Storage Stability of Bromoxynil on Frozen Raw Agricultural Commodity Substrates Spiked With Bromoxynil Octanoate: Lab Project Number: EC/91/179. Unpublished study prepared by McKenzie Laboratories, Inc. 544 p.

43151701 Yenne, S. (1994) Metabolic Fate and Distribution of (carbon 14)-Bromoxynil Octanoate in Cotton and Genetically Modified Cotton Addendum to MRID No 42677703: Lab Project Number: ECV90-122. Unpublished study prepared by Rhone-Poulenc Ag Co. 16 p.

43307001 Krautter, G. (1994) Bromoxynil Octanoate: Magnitude of Residues in Meat and Milk of Lactating Dairy Cows: Lab

Project Number: 805: 1608. Unpublished study prepared by PTRL East, Inc. 289 p.

43307701 Johnson, T.; Theissen, R. (1994) Metabolic Fate and Distribution of (Carbon 14) Bromoxynil Octanoate in Sweet Corn: Supplementary Report to MRID 424369-01: Lab Project Number: 571: 1410. Unpublished study prepared by PTRL East, Inc.; Rhone-Poulenc Ag Co. 168 p.

43307702 O'Neal, S.; Tripp, M. (1994) (Carbon 14) Bromoxynil Octanoate: Metabolic Fate and Distribution in Alfalfa: Lab Project Number: 705: 1538: 705E. Unpublished study prepared by PTRL East, Inc.; Plant Sciences, Inc.; Rhone-Poulenc Ag Co. 325 p.

43389001 Krautter, G. (1994) Bromoxynil Octanoate: Magnitude of Residues in Meat and Eggs of Laying Hens: Lab Project Number: 807: 1618. Unpublished study prepared by PTRL East, Inc. 230 p.

43506901 Cappy, J. (1995) BUCTRIL/Sorghum/Magnitude of Residue: Additional Data to Support MRID 427187-02: Lab Project Numbers: USA91B03: 91-001. Unpublished study prepared by McKenzie Labs, Inc. 351 p.

43922301 Rhoads, W. (1996) Multiresidue Study: PAM I Multiresidue Protocol Testing for 3,5-Dibromo-4-Hydroxybenzoic Acid (DBHA): Final Report: Lab Project Number: EC-95-319: 1266: RHONE-POULENC-1266. Unpublished study prepared by Colorado Analytical Research & Development Corp. 292 p.

43980901 Cappy, J. (1996) BUCTRIL 4EC: Magnitude of Residues In/On Transgenic BXN Cottonseed and Gin Trash: Final Study Report: Lab Project Number: US95B01R: 45036: 44940. Unpublished study prepared by Rhone-Poulenc Ag Co. 438 p.

43980902 Cappy, J. (1996) BUCTRIL 4EC: Magnitude of Residues In/On Transgenic BXN Cottonseed and Cottonseed Processed Fractions: Final Study Report: Lab Project Number: US95B02R: 45037: 95-0243. Unpublished study prepared by Rhone-Poulenc Ag Co.; Food Protein Research and Development Center, Texas A&M University System. 473 p.

43980903 Schults, J. (1996) Independent Laboratory Method Validation of Bromoxynil and its Metabolites in Cotton Gin Trash: Final Report: Lab Project Number: MK01-96: 44940: U:\RHONE\MK01-96.DOC. Unpublished study prepared by McKenzie Laboratories, Inc. 77 p.

43980904 Pittman, J. (1996) Bromoxynil--Validation of Method of Analysis for Bromoxynil Octanoate and its Metabolites in/on Cotton Seed and Cotton Gin Trash: Final Report: Lab Project Number: EC-95-325: 867A: 45017. Unpublished study prepared by

PTRL East Inc.; Rhone-Poulenc Ag Co. 210 p.

44168802 Pittman, J. (1996) Bromoxynil--Validation of Method of Analysis for Bromoxynil Octanoate and Its Metabolites in/on Cotton Seed and Cotton Gin Trash: Supplement to Study No. EC-95-325, MRID 43980904: Lab Project Number: EC-95-325: 45182. Unpublished study prepared by Rhone-Poulenc Ag Co. and PTRL East, Inc. 16 p.

44183301 Cappy, J. (1996) Buctril 4EC: Magnitude of Residues in/on Transgenic BXN Cottonseed and Gin Trash: Amended Final Report: Lab Project Number: US95B01R: 45036: 95-0224. Unpublished study prepared by Rhone-Poulenc Ag Co. 553 p.

44248501 Yang, J. (1997) Storage Stability of Bromoxynil Phenol Residues and its Metabolite, 3,5-Dibromo-4-hydroxybenzoic Acid Residues in Cottonseed, Gin Trash, C-95-319: 1266: Residues in Cottonseed, Gin Trash, and Seed Processed Fractions: Interim Report: Lab Project Number: EC-96-344: 90020: US95B01R. Unpublished study prepared by Rhone-Poulenc Ag Co. 200 p.

44352201 Yang, J. (1997) Storage Stability of Bromoxynil Phenol Residues and Its Metabolite, 3,5-Dibromo-4-hydroxybenzoic Acid Residues in Cottonseed, Gin Trash, and Seed Processed Fractions: Lab Project Number: EC-96-344: 45327: 90020. Unpublished study prepared by Rhone-Poulenc Ag Co. 239 p.

44449901 Petit, J. (1997) Independent Laboratory Validation of Analytical Method: Bromoxynil: Method of Analysis for Bromoxynil and its Metabolite, 3,5-Dibromo-4-hydroxybenzoic Acid in Cottonseed, Gin Trash and Seed Processed Fractions Using GC-MSD: Lab Project Number: 019-02: 97P-019-02: EC-97-408. Unpublished study prepared by Centre Analytical Labs., Inc. 86 p. {OPPTS 860.1340.

92013024 Andrawes, N. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00115594. Distribution of Residues and Metabolism of Carbon-14-Bromoxynil Octanoate in Foliar-treated Corn. Prepared by UNION CARBIDE CORPORATION. 14 p.

92013025 Andrawes, N. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00165547. Metabolism of (Carbon-14) Bromoxynil in/on Field Corn, ASD #82/029, Ref. No. 82/136/BHL/AG. Prepared by Rhone-Poulenc Inc. 19 p.

92013026 Tew, E. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00139591 and Related MRIDs 00075674, 00084589. Bromoxynil Residue Data on Sorghum Plants, Fodder and Grain: ASD 83/038. Prepared by RHONE-POULENC AG CO. 15 p.

92013027 Tew, E. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00150382. Residue and Metabolism: Bromoxynil in or on Seedling Alfalfa: Project No. 854R11. Prepared by Union Carbide Agricultural Products Co. 8 p.

92013028 Tew, E. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00075674. Bromoxynil and MCPA Residue Results in/on Wheat and Soil Following a Single Tank Mix Application: PDD Report No. 81/005; Ref No. 81/167/BHL/AG. Prepared by RHONE-POULENC AG CO. 9 p.

92013031 Guyton, C. (1990) Rhone-Poulenc Ag Company Phase 3 Reformat of MRID 00075674. Bromoxynil and MCPA Residue Results in/on Wheat and Soil Following a Single Tat Number: USA90B26. Unpublished Soil Following a Single Tank Mix Application: PDD Report No. 81/005; Ref. No. 81/167/BHL/AG. Prepared by RHONE-POULENC INC. 128 p.

92013032 Baron, J. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00118506. Bromoxynil-Magnitude of the Residue on Mint: Project No. 1291. Prepared by Interregional Research Project No. 4. 13 p.

92013022 Andrawes, N. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00115657 and Related MRIDs 00124227. Carbon-14-Bromoxynil Field Rotational Crop Study: The Potential Uptake of Carbon-14-Bromoxynil and/or Its Metabolites in Various Crops from Soil Treated with Carbon-14 Bromoxynil Octanoate. Prepared by RHONE-POULENC AG CO. 13 p.

92013023 Andrawes, N. (1990) Rhone-Poulenc Ag Company Phase 3 Summary of MRID 00149623. BROMINAL - Confined Accumulation Study on Rotational Crops following Carbon-14 -Bromoxynil Octanoate Treatment of Sandy Loam Soil: Project No. 854R10, File No. 33251. Prepared by RHONE POULENC AG CO. 18 p.

43279401 Carringer, R. (1994) Buctril Field Crop Rotation study: Final Study Report: Lab Project Number: AA930050: 44429. Unpublished study prepared by CYAL, Inc. 298 p.

13544

010340

Chemical:	**Bromoxynil; 3,5-Dibromo-4-hydroxybenzonitrile octano**
PC Code:	**035301; 035302**
HED File Code	**14000 Risk Reviews**
Memo Date:	**06/24/98**
File ID:	**DPD246944**
Accession Number:	**412-02-0005**

HED Records Reference Center
10/25/2001