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Food Production
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Direction générale,
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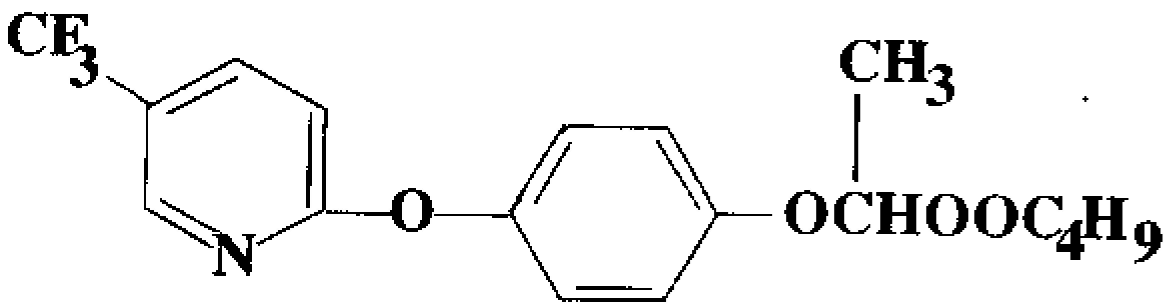
Pesticides Directorate

Direction des pesticides

Decision Document E88-01

FLUAZIFOP-BUTYL



Herbicide

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FOREWORD

FLUAZIFOP-BUTYL

As part of the ongoing efforts to provide a summary of the data received and outline the regulatory action on the active ingredient, fluazifop-butyl, a Decision Document has been prepared. This document reflects input from specialists within Agriculture Canada and key interdepartmental advisors. Based on the reviews of all available information and in consideration of its agronomic benefits to Canadian farmers, a regulatory decision has been made to grant registration for fluazifop-butyl and the end-use product Fusilade 250EC.

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June 27, 1988

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FLUAZIFOP-BUTYL

1. **SUMMARY**

The purpose of this document is to provide a summary of the data reviewed and outline the regulatory action on the active ingredient fluazifop-butyl and the end-use formulation Fusilade 250EC.

Agriculture Canada, with the assistance of advisors from Environment Canada, Fisheries and Oceans Canada and Health and Welfare Canada has completed a review of the available data supporting fluazifop-butyl and Fusilade 250EC. The data base is considered complete with respect to current regulatory data requirements. However, the interpretation of results from teratology studies with laboratory animals has been a focal point in this important ongoing regulatory issue. Health and Welfare Canada has expressed concern about the potential risk to the unborn children of pregnant women exposed to Fusilade 250EC during occupational use.

An occupational exposure study conducted in western Canada with Fusilade 250EC indicates that the judicious use of full protective clothing reduces exposure as does strict adherence to precautions during handling, mixing and loading.

Consumer dietary exposure to food crops treated with Fusilade 250EC is not a concern. Residue levels in most crops are less than 0.1 ppm, with the exception of strawberries and soybeans, where a Maximum Residue Level (MRL) of 1.0 ppm has been established under the Food and Drug Regulations.

With respect to environmental impact, fluazifop-butyl is not expected to pose any hazard to wildlife. The effects on wildlife habitat are expected to be minimal. Similarly, there is little likelihood of adverse effects on fish and fish habitat. The herbicide exhibits low persistence and mobility properties and would pose no risk to non-target organisms at expected environmental concentrations.

A review of agronomic and economic benefits of fluazifop-butyl centres on the importance of this herbicide for annual grass and quackgrass control, particularly cost effective control of volunteer cereals in rapeseed (Canola) and flax, and quackgrass in a wide variety of broadleaved crops. The availability of a variety of herbicides to growers is considered an important ingredient for more efficient production, because each herbicide is better suited than another to certain weed and/or crop conditions.

Based on the review of all information and in consideration of the benefits to Canadian producers, as expressed by them, their associations and independent researchers,

Agriculture Canada has registered technical fluazifop-butyl and the end-use product Fusilade 250EC. The potential risk to the unborn child has been identified in a label warning. This hazard can be reduced by following the label instructions regarding protective clothing and precautions during mixing, loading and application. Women capable of bearing children are warned of the risk of using this product during pregnancy. They are advised to pay particular attention to use directions to reduce exposure. Failure to judiciously follow label directions will increase exposure and risk (i.e., reduce margin of safety).

Identification of the significant hazard(s) and of measures to alleviate them are required by virtue of Section 27.2 (k) of the Pest Control Products Regulations. The position reached with fluazifop-butyl, concerning labeling of hazards and precautions, is considered to be a prudent one which will allow the user to make an informed choice when selecting pest control products.

2. PESTICIDE NAME AND PROPERTIES

2.1 Pesticide Name

Common name: fluazifop-butyl
Chemical name: butyl(RS)-2-[4-(5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate
Trade name: Fusilade 250EC
CAS Registry No.: 069806-504

2.2 Physical and Chemical Properties

Empirical formula: $C_{19}H_{20}O_4NF_3$
Molecular weight: 383
Physical form: oily liquid
Color: straw coloured to brown
Odor: Odorless
Melting point: Approximately 5°C
Boiling point: Approximately 170`C at 0.5 mm Hg
Vapor pressure: 5.5×10^{-5} Pa at 20°C
Octanol/water partition coefficient (Kow): 5.1
Solubility: 2 ppm in water
2% in propylene glycol
Miscible with methanol, acetone, cyclohexanone, hexane, xylene and methylene dichloride
Specific gravity: 1.21 at 20°C
Stability: As undiluted material, no detectable decomposition at 50°C for 3 months or at ambient temperature or 37°C for 6 months.
In dilute aqueous solution hydrolyzes to parent acid, fluazifop
at pH 4, 40°C 10% degradation in 30 days
at pH 6, 49°C half-life = 35 days
at pH 7, 40°C half-life = 17 days
at pH 9, 40°C half-life = 0.2 days

NOTE: Fluazifop-butyl exists as a racemic mixture consisting of the R and S enantiomers. The product chemistry information provided above is for the racemic mixture. Due to the submission of bridging data for the active isomer, fluazifop-p-butyl (Fusilade 125EC), and the completed review by some advisors, this form of the product is referred to in certain sections.

3. DEVELOPMENT AND USE HISTORY

Fluazifop-butyl is manufactured by Imperial Chemical Industries PLC, United Kingdom. In Canada, product development has been carried out by Chipman Inc. of Stoney Creek, Ontario. Chipman Inc. is also the registrant in Canada for both technical fluazifop-butyl and the end-use formulation Fusilade 250EC.

Fluazifop-butyl is registered in several countries including the United Kingdom and the United States. In the United States, registration has been granted for use on many crops including soybeans carrying residue tolerances of 1.0 ppm for soybeans, 2.0 ppm for soybean oil and 2.0 ppm for soybean meal.

In Canada, fluazifop-butyl, formulated as Fusilade 250EC, was first granted temporary registration in 1984, and subsequently in 1985 for use on flax, potatoes, sugarbeets, sunflowers and legume forages. New concerns centering on Health and Welfare Canada's interpretation of teratology studies in the rat, (i.e., effects on the developing fetus) and a lack of agreement between the registrant and regulatory officials on label wording to alleviate potential risk to the user, precluded registration in 1986. The registration was reinstated for 1987, following

agreement on precautionary labeling. In 1987, use expansion was granted for use in rapeseed (canola), soybeans, tobacco, onions, tomatoes, strawberries and forest and ornamental nurseries.

In addition, the registrant is continuing research into further methods of exposure reduction. These include the development of a dry flowable formulation (i.e., water dispersible granules) and registration of the active isomer (fluazifop-p-butyl). These methods will effectively reduce usage rates of the fluazifop-butyl by 50% and will potentially reduce user exposure.

4. REGULATORY POSITION AND RATIONALE

Fluazifop-butyl is a post-emergence grass herbicide for use in a wide variety of broadleaved crops and onions. Currently there are only two (2) other post-emergence grass control products available for broadleaved crops, namely, diclofop-methyl (Hoe-grass) and sethoxydim (Poast).

Improved control of certain species with fluazifop-butyl provides growers with a more cost-effective treatment, depending on grassy weeds present. It also provides for a more competitive marketplace for pest control products. Both these factors have been major talking points expressed by growers and their associations. Without product availability, Canadian farmers are in an unfavourable position vis-à-vis competitors in other countries, particularly the U.S. where fluazifop-butyl is registered.

The data base supporting fluazifop-butyl and Fusilade 250EC is both modern and complete. However, concern was expressed by Health and Welfare Canada in 1984 with respect to potential risk through occupational exposure from mixing and loading concentrated product. Interpretation of the results from teratology studies conducted with laboratory rats indicated to Health and Welfare Canada advisors that a potential hazard existed to the developing fetus of pregnant users.

However, the use of protective equipment and clothing, rate adjustments, formulation changes, etc. may well mitigate this concern. In the absence, at that time, of an adequate exposure study, the potential occupational hazard could not be assessed.

An occupational exposure study conducted in western Canada indicated that the Margins of Safety (MOS) achieved could only be attainable by fully respecting label requirements for protective clothing and gloves. Failure to wear protective gloves during the mixing/loading would decrease the MOS, as would breakthrough of the gloves. The importance, therefore, of adherence to label instructions during use is paramount.

Agriculture Canada recognizes that the entire scientific judgement on this matter, and indeed all biological/ scientific studies, is subject to varied interpretation and opinion. One example of this is the establishment of the NOEL for teratogenicity of fluazifop-butyl. In the United States, the Environmental Protection Agency (EPA) has chosen 10 mg/kg/day. Health and safety advisors in Canada have settled on 5 mg/kg/day. The result of these differing opinions might well be the reason behind the EPA not requiring a teratology warning on the U.S. Fusilade label (ie. adequate margin of safety), but rather a general health warning and strong emphasis on protective clothing.

With respect to consumption of treated food, Health and Welfare Canada considers the use of fluazifop-butyl acceptable. Residues in flax, onions, potatoes, sugarbeets, sunflowers, tobacco and tomatoes are not expected to exceed 0.05 ppm when used according to registered application rates and pre-harvest intervals. Residues may occur at harvest in both soybeans and strawberries. An MRL of 1.0 ppm is considered acceptable and has been established under the Food and Drug Regulations for strawberries and soybeans, which would include edible soybean products and soybean oil for human consumption. Significant residues are not expected in rapeseed oil or in meat or milk of livestock consuming soybean or rapeseed meal from crops treated with fluazifop-butyl.

In considering all the input from many parties, including user groups, who have indicated a strong desire for an alternative and in some situations more cost-effective postemergence herbicide, Agriculture Canada has concluded that the use of fluazifop-butyl, if used according to label directions will not pose an unacceptable risk to the user. The registrant has, in view of the one (1) user in the exposure study with a low MOS, provided product labeling which includes statements regarding use by women capable of bearing children and use and handling precautions for all

users. Section 27.2.(k) of the Pest Control Products Regulations requires the label to "identify significant hazard" and "measures to alleviate same". The following label statements for fluazifop-butyl technical and Fusilade 250EC, effect this intent:

WARNING

> Experimental feeding studies in rats have demonstrated that the active ingredient in this product can produce birth defects and other adverse effects in the developing fetus of rats. Women capable of bearing children should be particularly careful when handling this product. Occupational exposure to this product will be reduced by strict adherence to the handling precautions and use directions provided.

PRECAUTIONS

1. Harmful if swallowed. Causes eye and severe skin irritation. Failure to follow the directions may cause a health hazard.

2. All users must follow all handling precautions, use directions, and clean-up procedures noted on the label.

3. Wear coveralls, boots, and PVC (liquid proof) gloves when spraying, or when adjusting, repairing, or cleaning equipment.

4. Wear coveralls, boots, PVC (liquid proof) gloves and safety goggles when handling the concentrate.

5. Avoid spray mist by staying upwind from the spray and/or by wearing a suitable mask or respirator. Wash thoroughly with soap and water after handling and before eating or smoking. Remove contaminated clothing and wash before re-use.

6. Use PVC gloves supplied with product and dispose of them after use or if damaged. Dispose of gloves immediately if contaminated on the inside. Wash hands thoroughly with soap and water before using a new pair of gloves.

7. Be sure sprayer tank is clear of debris and all sprayer nozzles and screens are clean and clear of obstructions before loading the sprayer with Fusilade. This precaution eliminates contamination of clothing and skin caused by the need to clear blocked nozzles after spraying commences.

8. Avoid drift onto other crops and non-target areas. Corn, cereals and turf are highly susceptible to Fusilade.

9. Do not apply by aircraft.

10. Do not apply within 15 m of fish-bearing waters and wildlife habitats.

11. Seed only broadleaf crops listed on this label, if it is necessary to reseed a crop within 60 days of applying Fusilade.

12. Do not graze or harvest crops for forage or hay in the year of treatment.

5. BIOLOGICAL PROPERTIES

Fluazifop-butyl is highly active particularly when applied post-emergence.

It is absorbed through leaf surfaces and then transported in both the xylem and phloem to the growing points of leaves, shoots, roots or rhizomes. It affects the meristematic tissues in these growing points. Laboratory studies suggest that fluazifop-butyl interferes with the plants adenosinetriphosphate (ATP) production.

Symptoms of injury in susceptible species are often not evident until a week after application although growth usually ceases within 48 hours. Nodes and growing points become necrotic; young leaves show chlorosis followed by necrosis. There is a general loss of vigour and often pigment changes that are normal associated with senescence. Death of susceptible plant species is usually complete after three to five weeks.

6. **AGRONOMIC PROPERTIES/BENEFITS**

6.1 Agronomic Properties

Fluazifop-butyl has been field tested extensively in Canada both alone and in tank mixes with other herbicides for broad spectrum weed control. A wide variety of broadleaved crops have been shown to exhibit tolerance to this herbicide.

Table 1 summarizes the grass species controlled, rates of fluazifop-butyl required for control and the crops currently registered for use.

TABLE 1

FLUAZIFOP-BUTYL; SPECIES CONTROLLED, RATES AND CROPS REGISTERED

Grass Species Controlled	Rate (kg ai/ha)	Crops Registered	Maximum Interval to Harvest (PHI-days)
Volunteer corn	0.15	Flax	80
		Rapeseed (Canola)*	80
Johnsongrass, Persian	0.20	Soybeans	90
darnel, Barnyard grass,		Sugarbeets	90
Volunteer spring wheat		Sunflowers	120
and spring barley		Tobacco*	45
		Legume forages**	****
Wild oats, Wild proso	0.25	(alfalfa, red clover	
millet, Crabgrass		and birdsfoot	
		trefoil)	
		Onions*	42-60
Green, Yellow and Giant	0.25	Potatoes***	90
foxtail - EASTERN		Tomatoes	60
CANADA		Strawberries	30
Green, Yellow and Giant		Nurseries	
foxtail - WESTERN		(Forest	
	0.35	and Ornamental)	
CANADA			
Quackgrass	0.50		

* a maximum of 0.25 kg ai/ha is permitted in rapeseed (canola) and tobacco. In onions, where more than one application is made per season, use a maximum of 0.25\kg ai/ha per application and a PHI of 42 days. A single application up to 0.50 kg ai/ha may be made in onions with a PHI of 60 days.

** may be tank mixed with 2,4-DB

*** may be tank mixed with metribuzin

**** do not harvest for feed or graze livestock in the year of treatment

6.2 Time of Application

Fusilade is less effective on grass weeds which are stressed by lack of moisture, flooding, low temperature and/or very low relative humidity. Regrowth by tillering may occur if application is made under any of the above stress conditions. In wide row crops, where the crop canopy may be slow to close, cultivation may be necessary to control grasses that emerge after treatment.

a) Annual Grasses: Fusilade should be applied to actively growing annual grasses at the full 2-leaf to 5-leaf stages (except green and yellow foxtail). For green and yellow foxtail, apply at full 2-leaf to 4-leaf stages. Established grasses beyond the 5-leaf stage (including regrowth after clipping or tilling) will not be controlled. Most effective control is achieved when application is made before annual grasses produce tillers. Application made to annual grasses that have tillered and are under moisture and/or temperature stress may not provide acceptable control.

b) Quackgrass: For seasonal control of quackgrass, apply to actively growing plants that have 3 to 5\fully developed leaves. Applications made to plants greater than 20 cm in height, or which have reached the heading stage, may not provide adequate control.

   For annual crops, rhizomes of quackgrass should be thoroughly fragmented by tillage (disc or cultivator) prior to the application of Fusilade to obtain effective control. Tillage required to fragment rhizomes can be done in the fall or in the spring before seeding. Do not cultivate for 5 days after application.

   In perennial crops, effective seasonal control can be achieved providing that quackgrass is not under moisture and/or temperature stress, and that application is confined to the optimum leaf stage. Crop competition generally enhances control of quackgrass. Treated areas should not be cultivated for 5 days after application.

6.3 Spraying Instructions

A sprayer equipped with standard flat fan nozzles is recommended. The use of flood jet or hollow cone nozzles is not recommended because of uneven and inadequate spray coverage.

Recommended water volume per hectare: 100-300 L
Recommended spray nozzle pressure: 200-300 kPa*

higher pressures (up to 425 kPa) are recommended for applications to dense weed infestations or to dense crop canopies to ensure thorough coverage.

Adjuvant: add Agral 90 at a rate of 1 L per 1000 L of spray solution (0.1% volume). Do not add Agral 90 in tank mixes. When band spraying, use a proportionately smaller sprayer volume per hectare. Use ground sprays only.

6.4 Broadleaved Weeds

Fluazifop-butyl will not control broadleaved weeds. Therefore a recommended herbicide for control of broadleaved weeds should be applied separately unless a tank mix is otherwise recommended on the label. Fluazifop-butyl should not be applied following a postemergence application of a broadleaved weed herbicide as reduced grass control can be expected. Where Fusilade is to be used in sequence with a postemergent broadleaved weed herbicide, apply Fusilade first and wait 3 days before applying the other herbicide. Where tank mixes are used, apply labeled rates of both fluazifop-butyl and the tank mix partner. Do not add adjuvant to tank mixes.

6.5 Agronomic Benefits

The major market anticipated for fluazifop-butyl is in the oilseed production areas of western Canada. Of the crops grown in this area, rapeseed (canola) and flax are the major crops likely to receive fluazifop-butyl treatment. As these crops are grown mostly for the export market, the Canadian oilseed grower must successfully compete with other oilseed producing countries for markets. Thus, Canadian oilseed producers should be given the benefit of any new technology which can contribute to the maximization of production efficiency.

Grass weeds have been a significant contributor to yield loss in oilseed crops in western Canada. Wild oats (Avena fatua) and volunteer cereals (Hordeum vulgare and Triticum sp.) are commonly a problem in both rapeseed (canola) and flax fields, with green foxtail (Seteria viridis) being a problem primarily in flax. Wild oat is the most common grass weed found throughout each of the three prairie provinces, while volunteer cereals are found in most oilseed fields due to the common practice of cereal/oilseed rotation.

Data on crop losses in rapeseed (canola) and flax due to volunteer cereal infestations shows that even with moderate infestation levels, crop yields and thus profitability to the oilseed grower, can be significantly reduced. At eight (8) volunteer wheat or barley plants per square metre, significant yield losses resulted. Equal numbers of volunteer cereals were found to be 1.5 times as competitive as wild oats. Volunteer wheat at this level of infestation reduced flax yields by 25 per cent. Volunteer barley reduced yields by 30 per cent. Both volunteer wheat and volunteer barley reduce rapeseed (canola) yields 10 to 13 per cent in the same trials. The overall economic importance of volunteer cereals is presented in Table\2.

Wild oats are found in all Canadian provinces but cause the greatest economic losses in the three prairie provinces. It has been estimated that 17.3\million hectares of arable land in this region are infested with wild oats of which 13 million hectares have a moderate to heavy infestation (150 plants/m^2 or greater). Annual crop losses and herbicide costs due to wild oats in western Canada alone have been estimated at $280 million. Yield reductions due to wild oats (150-2000 plants/m^2) have been estimated at 46% in rapeseed and 86% in flax. Even at relatively light infestations (12 plant/m^2) wild oats can significantly reduce yields of flax. In addition to direct crop competition effects, wild oats population may also affect crop quality. Removal of wild oats from flax and rapeseed, either manually or with a herbicide, increases the quality of the oil in both crops. Wild oats, although less competitive than volunteer cereals at equal populations, would still result in a substantial increase in lost value, particulary if present with volunteer cereals.

The importance of controlling volunteer cereals and wild oats in oilseed crops in western Canada has been summarized in the foregoing paragraphs. Information on the impact of other grass species on crop yield and quality of these and other crops may also be available. However, only the major uses and grass species have been discussed as indicative of the importance of grass control materials.

TABLE 2

ECONOMIC SIGNIFICANCE OF VOLUNTEER CEREALS

Crop	Areas Planted 1987 ha (000's)	Potential Areas Infested Volunteer Cereal ha (000's)	Est.* Yield Loss %	Average Yield/ ha (kg)	Yield Loss tonne/ ha	Value /tonne Fall 1987	Total Potential Lost Value $Million
Rape-seed (canola)	2,641	1,676	10	1,434**	0.14	$259.50	60.9
Flax-seed	755	549	25	1,359	0.34	$219.00	40.9
TOTAL	3,296	2,225					101.8

* Based on 7 to 8 volunteer cereal plants/m^2.
** Average yields from statistics compiled for 1987.

In eastern Canada, crop loss estimates due to specific grass species are not currently available. However, yield responses from grass herbicides are evident throughout research reports from the Expert Committee on Weeds (Eastern Section). The major crops on which fluazifop-butyl would be used include soybeans and potatoes, where the major grass weed problems are the foxtails, barnyard grass, crabgrass and quackgrass.

The production of a variety of "minor" crops in eastern Canada would also be made easier with the availability of grass control herbicides (i.e., tobacco, strawberries, ornamentals).

6.6 Availability of Alternative Products

Traditionally, growers have made use of preplant incorporated (ppi) herbicides for grass control in crops such as rapeseed, flax and soybeans. However, the availability of post-emergence grass herbicides can reduce costs for time and fuel (i.e., no incorporation step), reduce soil erosion from wind and water (i.e., no tillage required) and provide control of volunteer cereals which is not obtainable with ppi products.

Currently there are three (3) postemergence herbicides which have parallel uses: diclofop-methyl (Hoe-Grass), fluazifop-butyl and sethoxydim (Poast). Fluazifop-butyl is the only one of the three active ingredients currently registered for tobacco, strawberries and ornamentals and therefore, for the short term, it has some advantages over the others. However, in all other instances there is more than one product registered. Therefore a brief discussion of the differences will aid in determining which product is best to use. A comparison of the grass species controlled by each is presented in Table 3.

TABLE 3

Annual Grass Species	diclofop-methyl	fluazifop-butyl	sethoxydim
barnyard grass	X	X	X
crabgrass		X	X
fall panicum		X	X
foxtail (green, yellow)	X	X	X
Johnsongrass		X	
Persian darnel	X	X	X
proso millet		X	X
volunteer cereals (wheat, barley, oats)		X	X
volunteer corn	X	X	X
wild oats	X	X	X
witchgrass			X
Perennial Grass Species			
quackgrass		X	X

Of the major grass weeds in oilseed crops, diclofop-methyl will control wild oat and foxtail (green, yellow) but not volunteer wheat and barley. Fluazifop-butyl, on the other hand, will control volunteer wheat and barley, as well as wild oats and green foxtail. Sethoxydim will control wild oats and green foxtail and is also registered for volunteer cereal control. In order to establish benefit from the use of fluazifop-butyl, one must consider the unique differences in ability to control certain species and the relative suggested retail prices for these products. Based on 1987 suggested retail prices, sethoxydim and diclofop-methyl would give more economical control of foxtails and wild oats than fluazifop-butyl, while the latter would be more cost effective for control of volunteer wheat and barley and wild oats. Therefore, as there may be a marked price advantage for control of foxtail with sethoxydim, there is a comparable saving where fluazifop-butyl is used to control volunteer cereals.

It is important to note that rarely does only one grass species exist in any one field. The savings comparisons are for illustrative purposes, and may vary, depending on grass species present in actual field situations. For example, if volunteer cereals, foxtail and wild oats were a problem, the use of sethoxydim would represent a saving; whereas if volunteer cereals and wild oats were a problem, the use of fluazifop-butyl would yield a saving.

In eastern Canada, it is anticipated there will be a minor market for fluazifop-butyl relative to that in western Canada. Nevertheless, the importance of product availability to individual situations must be considered.

The largest potential use in eastern Canada would be in soyabeans and pototoes. The major grass weed problems in these crops include the annual grasses, foxtail, barnyard grass, crabgrass and the perennial grass, quackgrass. For these annual grasses sethoxydim, based on 1987 suggested retail prices would be more cost-effective. However, for postemergence quackgrass control fluazifop-butyl may have some cost advantage.

Many of the so called "minor" crops can benefit from the use of postemergence grass herbicides. In an Ontario study on onions, with no pest control, yield losses in each of the trial years were 100 percent.

Common practice in onion production, particularly in the muck soil area of Bradford, Ontario and St.\Clothilde, Quebec is to plant wheat or barley windbreaks. The purpose of such windbreaks is to protect the tender and climatically sensitive onions in the early leaf stages. Once through this sensitive stage these cereal wind abatement crops must be removed/controlled to prevent growth competition. Both sethoxydim and fluazifop-butyl will control these cereals. However, as mentioned previously under volunteer cereal discussion, fluazifop-butyl would be more cost-effective, based on 1987 suggested retail prices.

Johnsongrass, which is a perennial grass in the United States, is primarily an annual under Ontario climatic conditions and is currently of minor or localized importance. However, as fluazifop-butyl controls this weed, its ability to curtail further spread particularly in soyabeans and other broadleaved crops, may be an important factor.

Overall, each of the three postemergence grass herbicides has a distinct niche depending on crops in which they are registered for use or the specific grass species present and their relative ability to control certain grass species. In choosing between these herbicides, growers must compare their own crop/weed situations with the strengths and weaknesses of each herbicide. For example, fluazifop-butyl is registered on sunflowers and forage legumes, while sethoxydim is not. Where the herbicides are registered on the same crop, the choice depends on the weeds present, their stage of growth and whether a tank-mix for broad spectrum control of both broadleaved and grass weeds is desired. The cost per hectare of controlling weeds can vary with the effectiveness of the herbicides use, as discussed above.

Given the foregoing discussion, it is also important to consider the impact on alternate product pricing particularly when only one product is available for a given use. The availability of fluazifop-butyl will provide growers with an additional weed management tool which will offer a competitive pricing situation amongst products and allow for a potential increase in productivity through decrease in input costs (depending on weed species present).

7. TOXICOLOGY

An extensive toxicology data package was submitted by the registrant, Chipman Inc. The following data were considered in the assessment of potential human health hazards.

7.1 Acute toxicity

a) Technical grade fluazifop-butyl

Oral LD_{50} values varied between species, ranging from 620 mg/kg in male New Zealand White rabbits, to greater than 3000 mg/kg in both sexes of Wistar rats. The oral LD_{50} in male ICR-JCL male mice was 1490 mg/kg, and in females 1770 mg/kg. In male guinea pigs, the oral LD_{50} was 2660 mg/kg.

Percutaneous toxicity exceeded 2 mL/kg in both sexes in New Zealand White rabbits and 5 mL/kg in Wistar rats. The LC_{50} in a rat inhalation study exceeded 5.25 mg/L. The compound was minimally irritating to rabbit eyes, and mildly irritating to skin. Dermal sensitization and delayed contact hypersensitization studies in guinea pigs were negative.

b) Formulations - Fusilade 250EC

The oral LD_{50} in Wistar rats was 4660 mg/kg for combined sexes and the dermal LD_{50} greater than 2000\mg/kg. The formulation was a severe skin irritant, but only a mild eye irritant in rabbits. Eye irritation was slight when the formulation was diluted to normal spray strength.

The inhalation toxicity potential was studied in rats. The results indicate low toxicity by this route with an LC_{50} of 5000 mg/m^3 based on actual Fusilade\250EC concentration.

7.2 Short-Term Toxicity

Technical grade fluazifop-butyl fed in the diet to Wistar rats for 13 weeks resulted in a dose-related increase in kidney degeneration in male animals, apparent at all dose levels (minimum dose 0.7 to 0.8 mg/kg/day), with liver damage also occurring at higher dose levels. At the high dose level, haematological data are indicative of mild anaemia. The kidney and liver pathology are supported by serum enzyme and plasma protein changes. A No Observed Effect Level (NOEL) could not be determined.

Further short-term studies in the rat were evaluated in order to address the question of effects on the kidney. Based on the results of the 90-day rat studies, it was concluded that 10 ppm (0.5 mg/kg/day) can be considered to be a NOEL for nephrotoxicity.

A 13-week study with technical fluazifop-butyl fed to beagle dogs via capsule indicated a no observed adverse effect level (NOAEL) of 5\mg/kg/day. At this dose level, the only observed effect was a sporadic decrease in plasma cholesterol levels in males. The 250\mg/kg/day dose level resulted in ophthalmic lesions sufficiently severe to warrant sacrifice of 3 out of 8 dogs after 4 weeks on test. Histopathologic changes were observed in eyes, G.I. tract, liver and testes of these sacrificed animals.

A short term dermal toxicity study in rabbits treated 5\times weekly for 6 h/day over 3 weeks indicated a NOEL of 100 mg/kg/day. Higher doses resulted in indications of anaemia, and at 2000 mg/kg/day, increased kidney weight, liver hypertrophy and an increased incidence of spermatid giant cells in the testes.

7.3 Long-Term Toxicity and Carcinogenicity

There was no evidence of tumorigenicity in either rats or mice treated with the fluazifop acid for the majority of the lifespan. A NOEL of 0.3 mg/kg/day was determined for both species, the next higher dose (1 mg/kg/day) causing kidney changes in male rats, decreased testicular weight in both species and liver cell enlargement in male mice.

Long-term toxicology studies in rats and mice were submitted in which the butyl-ester form of the technical material was tested. The results were consistent with the findings on the acid form of the technical material and confirmed that fluazifop-butyl is not carcinogenic. For the mouse long-term study, a NOEL was determined to be 5 ppm based on effects on the liver at dose levels of 20 ppm and higher. The rat study achieved a NOEL of 10 ppm based on kidney effects at 80 ppm and higher.

Although minor changes were observed in bone marrow at 5 mg/kg/day in a 55-week dog study, these changes were considered to be of sufficient significance or frequency to prevent this level from being deemed a NOEL. A higher dose resulted in major changes in bone marrow and clinical chemistry and the top dose level (125 mg/kg/day) in a wide range of effects including mortality and changes in clinical chemistry, hematology, ophthalmoscopy, etc.

7.4 Mutagenicity

Under the test conditions utilized, no evidence of mutagenic activity was observed in the Ames test, mammalian cell transformation test, or the mouse dominant lethal test. Results of a rat cytogenetic study are equivocal.

7.5 Reproduction

Results from a two-generation reproduction study are limited since only 1 litter/generation was obtained and reported.

A three-generation reproduction study was conducted with the ester form of fluazifop-butyl in rats. A teratology segment was also included in the experimental design. The NOEL for general toxicity to parental animals was determined to be 10 ppm based on body weight reductions at 80 and 250 ppm and increased kidney and decreased testes weights at 250 ppm. Levels of 80 and 250 ppm were also associated with effects on offspring as manifested by reduced pup weights and an increased incidence of hydronephrosis. The results from the teratologic phase of the study indicated that reduced ossification occurred at the lowest dose level (10 ppm). However, since this effect was limited to the F_3B, a NOEL of 10 ppm appears appropriate.

7.6 Teratology

Several studies were submitted to assess the developmental toxicity potential of fluazifop-butyl.

a) Rabbit: A NOEL of 10 mg/kg/day was determined in a teratology study, the NOEL being based on embryotoxicity. The top dose (90 mg/kg/day) resulted in an increase in the incidence of abortion, which was not statistically significant. Dose-related decreases in ossification of skull bones, the hyoid and long bones, are also indicative of embryotoxicity. There are no data indicative of teratogenicity. However, aborted material does not appear to have been examined.

b) Rat: Three studies were available to assess the teratogenic potential of fluazifop-butyl in a rodent species: a conventional size teratogenicity study in the rat, a study of unusually large size ("mega-study") designed to further investigate the findings of the first study and a teratogenicity assessment as part of the multigeneration rat study.

All three studies indicated that fluazifop-butyl has the potential for adverse effects on the developing fetus.

The conventional size rat study indicated an increase of the incidence of a major malformation, i.e. diaphragmatic hernia, which in the experience of the testing laboratory was exceedingly rare in this species and strain. The follow-up "mega-study" confirmed this result by showing a high and significant increase of diaphragmatic hernia at the high dose (200 mg/kg/day). However, a low and statistically non-significant incidence of diaphragmatic hernia was observed at dose levels below 200 mg/kg/day and in controls in the mega-study as well as in the initial rat study and in the multigeneration rat study. The toxicological significance of this low incidence cannot be fully answered by the available teratogenicity data.

In addition, the mega-study provided evidence of an increase in major malformations (at 200 mg/kg/day) other than diaphragmatic hernia. There was also a treatment-related, dose-dependent increase in anomalies of skeletal structures at 10 mg/kg/day and 200 mg/kg/day. Because these anomalies can be interpreted to be part of the spectrum of teratogenic manifestations, it is prudent to consider a NOEL for teratogenicity other than diaphragmatic hernia, at 5\mg/kg/day.

The overall NOEL of 1 mg/kg/day for this study, however, is based on fetotoxic effects as demonstrated by significant dose-dependent increases in skeletal variants and retardations as well as effects on the development of kidney and urinary tract.

8. **FOOD RESIDUE STUDIES**

Fluazifop-butyl herbicide is rapidly absorbed by plants and metabolized to fluazifop (acid) and conjugates of fluazifop. Analytical methods capable of determining fluazifop-butyl, fluazifop and fluazifop conjugates were used to determine residues in crops.

On flax, onions, potatoes, sugarbeets, sunflowers, tobacco and tomatoes, total residues at harvest are not expected to exceed 0.05 ppm, when fluazifop-butyl is used according to registered application rates and pre-harvest intervals. On these crops, the Health Protection Branch (HPB) does not propose to establish any specific residue limits under the Food and Drug Regulations, but will control excess residues under the general Regulation B.15.002(1).

Residues may occur in strawberries harvested from a treated crop and the HPB has established a maximum residue limit (MRL) of 1.0 ppm (calculated as fluazifop acid) under the Food and Drug Regulations.

On soybeans, although residues from the proposed Canadian uses are not expected to exceed 0.2 ppm, higher application rates and later applications are expected for use on soybeans in the United States. In view of the importation of soybeans and soybean products by Canada from the United States, the HPB has established an MRL of 1.0 ppm (calculated as fluazifop acid) to cover residues on soybeans, which would include edible soybean products and soybean oil sold in Canada for human consumption. On soybean meal imported from the United States, and used as a protein supplement in animal feeds, residues may occur at levels up to 2.0 ppm.

On rapeseed, residues may occur in whole rapeseed at levels up to 1.0 ppm, when applications are made up to the 5-leaf stage of the crop. Commercial processing studies on rapeseed containing residues of fluazifop have shown that residues in refined rapeseed oil would not exceed 0.05 ppm, although residues in rapeseed meal may occur at levels up to 2.0 ppm. The HPB does not propose to establish any specific MRL's for fluazifop on whole rapeseed because this commodity is not sold or used as such for human food purposes in any significant quantity. Low residues in rapeseed oil are not considered likely to pose any hazard to consumers and will be controlled under the general Regulation B.15.002(1).

Residues in soybean and rapeseed meal at levels up to 2.0\ppm are subject to control by Agriculture Canada under the Feeds Act. If residue limits in such meals do not exceed 2.0 ppm, they are unlikely to result in any significant residues occurring in meat or milk of livestock consuming feeds containing soyabean or rapeseed meal as a protein supplement.

9. **OCCUPATIONAL EXPOSURE**

The registrant submitted an occupational exposure study with Fusilade 250EC formulation in which dermal deposition and absorbed dose were estimated for workers wearing work clothing, a faceshield during mixing/loading and new PVC gloves during the mixing/loading operations.

Based on exposure to the head-neck region and protected hands and assuming that each worker mixes, loads and applies 60 kg of fluazifop-butyl [treats 300 acres (125 ha)] in a day, a dermal deposition of approximately 1 mg/kg body weight (bw) for a worker wearing protective gloves would result. For a worker not wearing gloves, dermal deposition would be 3 mg/kg bw/day. In only 2 out of 13 workers was fluazifop at a non-detectable (0.001 mg/L) concentration at the end of the seven-day collection period. Therefore, these results are not strictly quantitative.

The study also indicated that urinary excretion might not be complete by day 7. It was, therefore, considered prudent to include the results of the worker with the highest excreted dose (0.03 mg/kg bw) in the Margin of Safety (MOS) calculations. For comparison, the MOS as based on dermal deposition, are also presented.

For a calculation of MOS for workers, carrying out mixing/loading/spraying operating, the following toxicological endpoints are of relevance:

1. Fetotoxic and teratogenic effects with respective NOEL's at 1 and 5 mg/kg/day.
2. Nephrotoxic effects as determined from short-term rat studies with NOEL of 10 ppm or 0.5 mg/kg/day.

<u>MOS CALCULATION BASED ON DERMAL DEPOSITION OR ABSORBED DOSE</u>

toxicological end point	(NOEL)	dermal deposition with gloves	deposition without gloves	max.	mean / absorbed dose with gloves	
fetotoxicity	(1 mg/kg/day)	no MOS	no MOS	x 33	x 143	
*teratogenicity	(5 mg/kg/day)	x 4.3	x 1.8		x 167	x 714
nephrotoxicity	(0.5 mg/kg/day)	no MOS	no MOS	x 17	x 72	

*not considering diaphragmatic hernia at dose levels below 5 mg/kg/day

These margins of safety are best-case estimates and can only be achieved by fully respecting label requirements for protective clothing and gloves, e.g., failure to wear protective gloves during the mixing/loading would decrease the MOS, as would breakthrough of the glove.

10. **ENVIRONMENTAL ASPECTS**

10.1 Environment Chemistry, Fate and Toxicology (Invertebrates)

a) Summary: A review of the environmental chemistry, fate and toxicology data submitted to support the registration of Fusilade 250EC and Fusilade 125EC has led to the opinion that, on mineral soils, fluazifop-butyl, fluazifop-p-butyl, and R and S-fluazifop would have low persistence, low off-target mobility, and would pose no risk to non-target organisms at expected environmental concentrations. The mobility and persistence of compound X (5-trifluoromethyl-pryid-2-one), a major transformation product, was not determined under field conditions, however, this product is not expected to be toxic, based on results of studies with non-target indicator species. Insufficient evidence was presented to show the persistence of residues on organic soils following the proposed multiple/split application schedule.

b) Transformation: Fluazifop-butyl and fluazifop-p-butyl were rapidly hydrolyzed to fluazifop in both soil and water. S-fluazifop inverted to R-fluazifop in both soil and water. No significant epimerization of the R-enantiomer of fluazifop was detected. The dissipation rate of fluazifop in soil was not dependent on optical configuration. The DT_{50} of fluazifop was less than 3 weeks under both laboratory and field conditions in mineral soils. In organic soils, fluazifop has a DT_{50} of 16 weeks under laboratory conditions and 3 weeks under field conditions. The reason for this discrepancy is not known. Fluazifop was persistent in non-aerated, flooded soils. Under aerobic soil conditions, the major transformation product compound X (5-trifluoromethyl-pryid-2-one) dissipated, however, a DT_{50} could not be determined from the submitted studies.

c) Mobility: Fluazifop-butyl was strongly adsorbed to soil and did not leach under laboratory or field conditions. Fluazifop had a low soil adsorption coefficient and had a high water solubility and therefore, could be considered potentially mobile. However, in field studies, fluazifop was not recovered from soil below a depth of 15 cm. In soil column leaching studies, using high rates of "rainfall", very little fluazifop was recovered in leachate fractions from 35 cm columns. The apparent low mobility of fluazifop may be explained by its rapid transformation in soil under aerobic conditions.

Compound X was shown to be mobile in soil column leaching studies and is expected to be mobile under field conditions, but only at low concentrations.

d) Non-target Invertebrates: Technical and formulated fluazifop-butyl and fluazifop-p-butyl were not toxic to honey bees at expected environmental concentrations. Residues of fluazifop-butyl did not affect: earthworm weight, numbers of species diversity; soil microbial processes including ATP production, CO_2 evolution, ammonification, nitrification and cellulose degradation; numbers of soil microrganisms; soyabean growth and nitrogen fixation; and soil microarthropod numbers of species diversity.

In pesticide screening trials fluazifop-butyl, fluazifop and compound X did not show activity against: non-graminaceous plants, photosynthesis in plant cell suspension, eight species of invertebrate pests, or seven plant pathogens. Compound X did not show herbicidal activity against graminaceous plants.

Formulated fluazifop-butyl, technical fluazifop and technical and formulated fluazifop-p-butyl were not toxic to *Daphnia magna* at expected environmental concentrations. No differences in toxicity to *Daphnia magna* were seen where ratios of R-fluazifop: S-fluazifop were varied. Formulated fluazifop-butyl was not toxic to fiddler crab, pink shrimp or crayfish at expected environmental concentrations.

10.2 Environmental Toxicology

a) Summary: When applied at label rates, there is no indication that this herbicide will pose any hazard to wild birds or mammals, or terrestrial and aquatic invertebrates. Effects on wildlife habitat are expected to be minimal.

b) Wild Birds: Fluazifop-butyl is of low toxicity to avian species when administered orally. The acute oral LD_{50} for adult mallard ducks was greater than 17280 mg/kg bw. Exposure of birds via contaminated food is unlikely to cause mortality. The five-day dietary LC_{50} concentration for 14-day old mallard ducklings and day-old ring-necked pheasants was greater than 25000\ppm and 18500 ppm, respectively.

When two domestic hens were dosed daily for 14 days with labelled fluazifop-butyl at concentrations at least 10 times higher than those generally detected on treated crops, 97% of the total radioactivity was recovered in the feces. Metabolism and clearance was rapid; only very low levels were detected in the eggs. Little fluazifop-butyl accumulated in the tissues of mallards and Bobwhite quail given daily oral doses of 0.15 mg/kg and 0.20 mg/kg bw, respectively, for up to 28 days suggesting this active has a low bioaccumulation potential.

Reproduction of mallard ducks and Bobwhite quail was not affected in any way by diets containing 5 and 50\ppm of fluazifop-butyl. Spraying fertile mallard duck eggs with Fusilade 250EC at application rates equivalent to 0.5 and 2.5 kg ai/ha on days 0, 2, 4, 10, 14 or 20 of the incubation period produced no adverse affects on duckling hatchability, growth or survival to 14 days of age.

The results of this comprehensive assessment suggest that fluazifop-butyl poses no hazard to wild birds when applied at label rates. No further avian testing is warranted.

c) <u>Wild Mammals</u>: The acute oral toxicity of fluazifop-butyl to laboratory mammals is low. Oral LD_{50} values ranged from 621 mg/kg in rabbits, 1490-1770 mg/kg in mice and 2659 mg/kg in guinea pigs to 3328 mg/kg in rats. The acute (4-hour) inhalation LD_{50} for rats was greater than 5.24 mg/L and dermal toxicity was low. The acute toxicity of the formulated product Fusilade\250EC was less than that of the ai as exemplified by an oral LD_{50} of 4662 mg/kg in rats.

The absorption, excretion and tissue retention of labelled fluazifop-butyl has been studied using oral and intravenous administrations of 1 mg/kg and 1000\mg/kg. Fluazifop was the only metabolite detected in the blood. Clearance was independent of the route of administration. The half-lives of elimination of 1 mg/kg fluazifop were 2.7 hours for females and 26-33 hours in males. The major route of excretion is via the urine, the proportion differing between the sexes and the dose. There is no indication that the enzymes involved in the biotransformation are induced or become saturated by repeated exposure.

Fluazifop-butyl is fetotoxic to rats and rabbits at dietary levels of 5 and 90 mg/kg BW, respectively, and has some teratogenic potential. However, a dietary concentration of 10 ppm caused no effects on growth, development or reproductive performance or any indication of embryopathy.

When applied at recommended rates, it is not expected that wild mammals will be at risk due to exposure to fluazifop-butyl via any route.

d) Amphibians and Reptiles: No data are available to evaluate the hazard posed by use of fluazifop-butyl to amphibians and reptiles.

e) Aquatic Invertebrates: Fluazifop-butyl, formulated as Fusilade 250EC was not acutely toxic to Daphnia magna (48-hour EC_{50} = 6.36\mg/L, NOEL\= 3.0 mg/L). The NOEL for crayfish was 0.76\mg ai/L. When applied at label rates of 0.25-1.0 kg/ha, it is not likely to be toxic to either species in natural wetlands.

f) Terrestrial Invertebrates: Under conditions tested, fluazifop-butyl does not appear to be toxic to terrestrial invertebrates. Bees were not affected by either the technical or formulated product when exposed by contact and ingestion. Earthworm weight, numbers and species composition were not affected by applications of the formulated product Fusilade 250EC at one and 10 times the recommended rate, when exposed soil was sampled one, six and twelve months after application.

g) Plants: Fluazifop-butyl is toxic to annual grasses but not to broadleaf plants or sedges. No symptoms of injury were observed in species of Typha, Scirpus, Myriophyllum, Potamogeton and Lemna, all important macrophytes associated with wetland habitats, seven and twenty-one days after spraying with fluazifop-butyl and Fusilade 250EC at rates equal to or exceeding the maximum label rate.

The 96-hour EC_{50} for growth inhibition for the green algae Scenedesmus quadricauda and Selenastrum capricornutum were 3.16 mg/L and greater than 56 mg fluazifop-butyl per L, respectively. If one assumes a scenario of a small shallow pond of 0.01\ha surface area and 0.5 m in depth, being directly oversprayed at a maximum label rate of 1000 g\ai/ha, an initial environmental concentration of fluazifop-butyl of 0.2\mg/L could be expected in the pond water. Hence, the use of this active at label rates is unlikely to affect freshwater algal communities.

h) Habitat Impact Assessment: There is no indication that use of Fusilade 250EC or Fusilade 125EC at label rates will detrimentally affect wetland wildlife habitats exposed via direct spray, drift or run-off. Expected environmental concentrations in wetlands are lower than those which have been shown to be toxic to emergent macrophytes, algae, aquatic invertebrates.

Some alteration of the species composition of headland plant communities may occur if annual grasses are eliminated. However, the significance of this impact cannot be predicted at this time.

10.3 Fish and Fish Habitat

The Fusilade 250EC formulation of fluazifop-butyl is moderately toxic to fish. The 96 hr LC_{50}'s are 1.43 m 1^{-1} ai for Rainbow Trout (Salmo gairdneri) and 0.66 mg ai 1^{-1} for Mirror Carp (Cyprinus carpio). The NOEL's are 0.15 mg ai 1^{-1} for trout and 0.025 mg ai 1^{-1} for carp. The latter concentrations could be exceeded by a direct overspray of water 0.5 m deep at an application rate of 1 kg ha^{-1}.

Fluazifop-p-butyl in the Fusilade 125EC formulation is highly toxic to fish. The 96-hour LC_{50} for rainbow trout (Salmo gairdneri) is 0.55\mg\ai/L and for mirror carp (Cyprinus carpio) it is 0.74 mg ai/L (95% confidence interval 0.65 to 0.86\mg/L). Because there was no concentration at which the number of rainbow trout deaths was0% and <100%, no 95% confidence interval can be calculated for the LC_{50} for that species.

Fusilade 250EC is moderately toxic to Daphnia magna. The 48 hr EC_{50} is 6.5 mg 1^{-1} and the NOEL is 3.0 mg 1^{-1}. These concentrations are not likely to be achieved in the field under normal use conditions.

Fluazifop-p-butyl is highly toxic to Daphnia magna in the Fusilade 125EC formulation. The 48-hour EC_{50}'s for two European formulations are 0.26 and 0.76\mg/L.

Fluazifop-butyl is moderately toxic to the alga Scenedesus quadricauda. The growth rate 48-hour EC_{50} 3.17 mg/L (95% confidence interval 2.18-4.57 mg/L) and the biomass 96-hour is 1.87\mg/L (95% confidence interval 1.5-2.34 mg/L). The degradation product fluazifop effected a 15% decrease in the cell density of Selenastrum capricornutum at a concentration of 46.8 mg/L.

In a continuous flow system bluegill (Lepomis macrochirus) were found to concentrate fluazifop-butyl to 320 x the water concentration based on whole body concentrations. The maximum body concentration was reached in 1 day. The degradation product fluazifop concentrated 2.1 x in channel catfish (Ictalurus punctatus). Depuration times were rapid. The channel catfish lost 80% of the residues in 1 day; the bluegill lost 97% of the residues in 3 days. Hydrolysis of fluazifop-p-butyl to the much less toxic fluazifop (no observed effect level for rainbow trout during a 96-hour acute toxicity test of 96 mg ai/L) is very rapid. The half-life was <24 hours in soil/water system experiments. In some of the acute toxicity tests, from 44 to 80% of the fluazifop-butyl had hydrolyzed before the time zero analysis. The parent compound is not very mobile in soil, but fluazifop shows some tendency to leach from soils.

Because aerial application is not permitted, it is unlikely that concentrations in water bodies would ever reach the 400 ug/L possible in the worst case of a direct spray on a water body of 0.25 m depth at a use rate of 1 kg/ha.

Even though this concentration is at or near LC_{50} and EC_{50}'s for fish and aquatic invertebrates, the hydrolysis rate is fast, there is little potential for bioaccumulation and the toxicity of the initial breakdown product, fluazifop, is low. Therefore, there is little likelihood of adverse effects on fish and fish habitat.

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