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Inspection Branch

Pesticides Directorate

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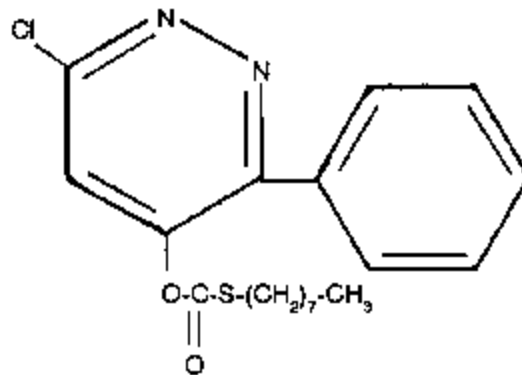
Direction des pesticides

Canada

Decision Document

E91-01

PYRIDATE



HERBICIDE

Product Management Division

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FOREWORD

PYRIDATE

As part of the ongoing efforts to produce a summary of the data received and to outline the regulatory action on the active ingredient pyridate, a Decision Document has been prepared. This document reflects input from specialists within Agriculture Canada and from key departmental advisors. Based on the review of all available information and in consideration of the agronomic benefit to Canadian farmers, a regulatory decision has been made to grant registration for pyridate and the end-use product Lentagran 45 WP herbicide.

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April 1991

TABLE OF CONTENTS

	<u>Page</u>
1. Summary	1
2. Pesticide Name and Properties	2
3. Development and Use History	3
4. Regulatory Position and Rationale	3
5. Biological Properties	4
6. Use Summary and Benefits	4
6.1 Corn and Tomato Use	5
6.2 Weeds Controlled	5
6.3 Time and Rate of Application	5
7. Toxicology and Occupational Exposure: Health and Welfare Canada	5
7.1 Toxicological Evaluation	5
7.2 Dietary Exposure	10
7.3 Occupational Exposure and Risk Assessment	11
8. Environmental Aspects: Environment Canada (Commercial Chemicals Branch and Canadian Wildlife Service)	14
8.1 Environmental Aspects	14
8.2 Environmental Chemistry and Fate	15
8.3 Environmental Toxicology	18
8.4 Wildlife Habitat Impact Assessment	21
9. Effects on Fish, Fish Habitat and Fishery Resources: Fisheries and Oceans Canada	21
9.1 Fish	21
9.2 Fish Food and Habitat	22
9.3 Movement into and Transformation in Aquatic Environments	23
9.4 Impact Assessment	23

PYRIDATE

1. Summary

The purpose of this document is to provide a summary of the data reviewed and to outline the regulatory action on the active ingredient pyridate.

Agriculture Canada, with the assistance of advisors from Environment Canada, Health and Welfare Canada, and the Department of Fisheries and Oceans, has completed a review of the available data supporting pyridate. The data base is modern and reasonably complete. Additional data are needed to complete a full assessment of chronic toxicity of CL 9673 (the primary transformation product of pyridate), to aquatic invertebrates. The need for further data on non-target plant information has been identified.

With respect to dietary exposure, the data indicate that when Lentagran 45 WP, the end-use product, is used on corn and tomatoes in accordance with the proposed label directions, total residues at harvest are unlikely to exceed 0.1 ppm. Such residues are not considered to pose a hazard to consumers.

With regard to occupational hazard and safety, it is considered that an adequate margin of safety (MOS) exists for label uses with the 45% formulation.

With respect to environmental impact, pyridate was shown to be predominantly transformed by chemical hydrolysis to CL 9673. Transformation was relatively rapid even under conditions of low soil moisture. Consequently, pyridate was considered to be of little environmental concern.

When comparing the exposure under field situations to levels causing acute toxicity, the acute risk to birds and wild mammals, from the use of Lentagran 45 WP, was considered to be low.

The submitted data indicated that Lentagran 45 WP was moderately toxic to mysid shrimp and daphnia (Daphnia magna). There were no observed effects on bees. Pyridate was judged to be of low toxicity to the earthworm.

Results of acute toxicity tests on fish consistently indicate LC₅₀'s > 22 mg/L. These results suggest that direct acute toxic effects on fish are unlikely at the concentrations of pyridate and CL 9673 that may occur in water bodies following a single direct over spray of Lentagran 45 WP.

Lentagran 45 WP is an effective herbicide for the control of various weeds in corn and tomatoes. The data indicate that the product is efficacious for the intended purpose. It provides adequate control or suppression of all label-claimed weed species without injury to corn and tomatoes, the host crops.

Based on the information available, the herbicide has been granted registration status until December 31, 1992.

2. Pesticide Name and Properties

2.1 Pesticide Name

Common Name: pyridate

Chemical Name (ISO): Carbonothioic-acid-0-(6-chloro-3-phenyl-4-pyridazinyl)-S-n-octyl ester

Trade Name: Lentagran 45 WP

CAS Registration No.: 55512-33-9

2.2 Physical and Chemical properties

2.2.1 Technical Products

Empirical Formula: $C_{19}H_{23}ClN_2O_2S$

Molecular Weight: 378.91

Melting Point (technical): 20-25°C

Vapour Pressure: 1.33×10^{-9} mbar @ 20°C

Octanol/Water Partition Coefficient (K_{ow}):

Pyridate > 1000

CL 6973 (main metabolite) < 1000

Water Solubility: 1.49 + 0.24 ppm

Solvent Solubility:

100 mL of the solvent	Pyridate in g.
methanol	> 100
ethyl acetate	> 100
toluol	> 100
acetone	> 100
hexane	> 100
heptane	> 100

Thermal Stability: Pyridate is stable at room temperature and at elevated temperature (54°C) Hydrolysis Rate: half-life 6.8-66.7 hours at pH 5-9

2.2.2 Formulated Product

Product Name: Lentagran 45 WP

Guarantee: 45%

Flammability: Not applicable

Storage Stability: Stable at room temperature
for at least 2 years

3. Development and Use History

Pyridate belongs to the pyridazine group whose herbicidal properties were first reported in 1976. The members of this group of herbicides are inhibitors of plant growth and control a wide spectrum of weeds.

Pyridate is manufactured by Agrolinz Austria (formerly Chemie Linz AG). The Canadian agent for Agrolinz is United Agri Products.

The Canadian development program was conducted by United Agri Products (formerly Pfizer Canada Ltd.). The registrant for both technical pyridate and Lentagran 45 WP is Agrolinz and the data has been provided through Agrolinz Inc. of Memphis, Tennessee, the U.S. agent for Agrolinz.

The Canadian field testing program with pyridate was initiated in 1982 and the original submission for registration was received in 1984.

Pyridate is currently registered for use in many countries including Austria, Germany, Switzerland, U.K., Italy, Benelux, France and the USSR.

4. Regulators Position and Rationale

Pyridate has low acute, oral, dermal and inhalation toxicities in rats and/or rabbits. Studies indicate that pyridate is not mutagenic or teratogenic and exhibits low toxicity to fish, wildlife and honeybees. Subchronic feeding and reproduction studies as well as chronic feeding studies in rats, mice, and dogs are also favourable. The data indicate that when pyridate is used in corn and tomatoes, in accordance with label directions, residues are not considered to pose a hazard to consumers.

No data on the toxicity of pyridate or Lentagram 45 WP to terrestrial or aquatic vascular plants were submitted, and therefore the risk to these wildlife food resources cannot be estimated. Exposure to aquatic or terrestrial vascular plants adjacent to field edges is anticipated because of possible spray drift or over spray. To mitigate against this risk, the requirement for spray-free buffer zones at the edges of fields has been placed on the product label to protect this habitat. Data on plant toxicity are being generated and will be submitted to assess risk to plant life.

The exposure of aquatic organisms to CL 9673, the transformation product of pyridate, is likely to be longer than the duration of the acute toxicity tests and no results

of chronic toxicity tests were submitted. Studies of the chronic toxicity of CL 9673 to aquatic invertebrates are currently being generated.

Weed control in crops like corn and tomatoes is often the critical management step in an effort to maximize economic return. The ability to control nightshade species is an important feature of Lentagran 45WP. Until now, there have been very few chemical control measures available that effectively control this weed species. In addition, Lentagran 45WP can be combined with triazine herbicide atrazine to control a broad spectrum of triazine-tolerant weeds. Finally, crop tolerance with Lentagran 45WP is considered to be excellent.

Agriculture Canada has concluded that application of the end-use product, Lentagran, if used according to label directions, will not pose an unacceptable risk to the user or to the environment. The risk reduction measures such as a restriction for ground application equipment only and the provision of a buffer zone to protect non-target plants were part of the decision-making process. At the same time, the Department recognizes the need for a final environmental assessment after a review is completed of the additional data described.

5. Biological Properties

Pyridate is rapidly absorbed by leaves. Once inside the sensitive weed species, activity is evident by marginal yellowing, followed by browning and yellowing of the entire leaf. This visible evidence generally occurs within 4-7 days of application. Activity is more rapid at higher temperatures and under good growing conditions. Crop tolerance is due to the rapid inactivation of pyridate by the crop.

6. Use Summary and Benefits

6.1 Corn and Tomato Use

Pyridate herbicide has been field-tested extensively in Canada over the past eight years alone and in combination with other herbicides. Pyridate as a 45% wettable powder formulation provides postemergence weed control of many broadleaved weeds in tomatoes and corn. The ability to control nightshade species will greatly improve yields, grades, and tomato quality where these weeds are a problem. In corn, pyridate controls triazine resistant weeds.

The combination of pyridate and atrazine as a tank mix broadens the spectrum of weeds that are controlled and also adds some control of postemergent grass.

Pyridate, whether applied post-emergence alone or in combination with atrazine or cyanazine, has excellent crop tolerance and provides good control of weeds.

The end-use product Lentagran is to be applied using ground application equipment only.

6.2 Weeds Controlled or Suppressed

	CORN OPTION 1 1 kg Lentagran WP	CORN OPTION 2 2 kg Lentagran WP	TOMATOES 1-2 kg Lentagran WP
BROADLEAVED WEEDS			
Buckwheat, wild	XS		XS
Ladysthumb	XS		XS
Lambsquarters, common	X	X	X
Mustard, wild	X		X
Nightshade	X		X
Pigweed, redroot	X	X	X
Purslane	X		X
Ragweed, common	X		X
Smartweed	X		X
Shepherdspurse	X		X
Velvetleaf	X		X
GRASSES			
Barnyardgrass	XS		XS
Crabgrass, hairy	XS		XS
Foxtail, green	XS		XS
Foxtail, yellow	XS		XS

X = Controlled XS = Suppressed

6.3 Time and Rate of Application

The product is applied in the spring to actively growing weeds in the 1-4 true leaf stage at the rate of 1-2 kg/ha. For best results, thorough coverage of the weeds is essential. Large crop and weed-leaf canopies may shelter smaller weeds and prevent adequate coverage. A delay in spraying, which permits weeds to grow beyond the proper application time, may result in reduced control. The product is not applied more than once per season.

7. Toxicology and Occupational Exposure: Health and Welfare Canada:

7.1 Toxicological Evaluation

a) Acute toxicity - Technical

The acute oral LD₅₀ in male and female dogs is >3000 mg/kg b.w.
Pyridate is of low toxicity to Wistar rats (male LD₅₀ - 5993 mg/kg b.w.,

female LD₅₀ - 3544 mg/kg b.w.), Sprague-Dawley rats (male LD₅₀ - 2715 mg/kg b.w., female LD₅₀ - 2195 mg/kg b.w.) and Swiss mice (male LD₅₀ - 11,550 mg/kg b.w., female LD₅₀ - 28,400 mg/kg b.w.) by the oral route. The dermal LD₅₀ in rabbits is >2000 mg/kg b.w. Inhalation toxicity in rats exceeds 4.4 mg/L. It is a mild eye irritant, a moderate skin irritant, and produces a sensitizing response in guinea pigs.

Acute toxicity - Lentagran 45 WP formulation (45% Active Ingredient)

Lentagran 45 WP is of low toxicity to rats by the oral route (male LD₅₀ - 2205 mg/kg b.w., female LD₅₀ - 2377 mg/kg b.w.) and to rabbits by the dermal route (LD₅₀ > 2000 mg/kg b.w.). It does not appear to be acutely toxic via the inhalation route, with the LC₅₀ exceeding 2.14 mg/L in rats. The formulated product is a mild eye irritant, non-irritating to rabbit skin but produces a sensitizing response in guinea pigs.

Human Skin Sensitizing Potential

A challenge study was performed on 19 humans exposed from 3 months to several years to pyridate at the parent company and no sensitizing reaction was recorded.

b) Short-Term Studies:

3 Week Dermal Rat: The main effect of pyridate in this study was mild to moderate skin irritation at the test site. The study indicates that dermal exposure of rats to 1000 mg/kg b.w./day does not demonstrate systemic toxicity.

90 Day Oral Rat: Groups of 20 Sprague-Dawley rats/sex/dose level, 8 weeks of age were gavaged with 0, 0.04, 0.08, or 0.16 mL pyridate /kg b.w./day in 0.1 mL rape oil/kg. Five rats/sex/dose level were killed at 4 weeks and the remainder at 13 weeks. There was male mortality (3/20) at 0.08 mL/kg b.w./day, but not at 0.16 mL/kg b.w./day. In females, mortality (2/20) occurred at 0.16 mL/kg b.w./day. Serious exudates in the lungs were observed in both sexes at 0.08 mL/kg b.w./day and above. These exudates were associated with lipid pneumonia, and may not be compound related. A No-Observed-Effect-Level (NOEL) of 0.04 mL/kg b.w./day (equivalent to 46.2 mg/kg b.w./day) was determined.

90 Day Oral Dog: Groups of 6 dogs/sex/dose level were dosed daily by gavage with 0, 0.04, 0.08 or 0.16 mL pyridate /kg b.w./day in 0.5 mL rape oil/kg. At 0.08 mL/kg b.w./day and above diarrhea, unsteady gait and impaired equilibrium were noted. A possible dose-related

increase in eye abnormalities was also observed at .08 mL/kg b.w./day and above. A NOEL of 0.04 mL/kg b.w./day (equivalent to 46.2 mg/kg b.w./day) was determined.

One Year Oral Dog: A study using 6 dogs/sex/dose level fed dietary concentrations of 0, 60, 240 or 2000 ppm for 372 days indicated a NOEL of 240 ppm (6 mg/kg b.w./day) based on an increased incidence of vomiting, a slight decrease in male body weight gain, an increase in reticulocyte counts in both sexes, and an increase in urinary pH in males at the 2000 ppm level.

c) Long-Term Studies

Chronic toxicity/Oncogenicity Rat: A rat study at dietary concentrations of 0, 80, 400 or 2500 ppm comprised groups of 10 rats/sex/dose level fed for 1 year, 15 rats/sex/dose level fed for 2 years and 50 rats/sex/dose level fed for a lifetime (ca 120 weeks. Haematological changes (reduced haemoglobin, packed cell volume and erythrocyte counts) were observed in females at 80 and 2500 ppm, but not at 400 ppm. The biological significance of these non-dose related changes are questionable. Changes (reduction of alanine aminotransferase and lactic dehydrogenase) were observed in females at all dose levels. These changes were not observed at all time periods: severity of change in lactic dehydrogenase (LDH) was, however, more marked at 400 and 2500 ppm. Male relative thyroid weights at 12 months only, were decreased at all dose levels, the decrease being greatest at 400 and 2500 ppm. The No Observed Adverse Effect Level (NOAEL) was determined to be 400 ppm (20 mg/kg b.w./day pyridate + hydroxylation product (CL 9673), or 15 mg/kg b.w./day pyridate, based on degradation in the diet). Pyridate was not considered to be oncogenic in the rat.

Chronic toxicity/Oncogenicity Mouse: A mouse study at dietary concentrations of 0, 200, 1000 or 5000 ppm comprised 15 mice/sex/dose level maintained for 80 weeks (chronic study) and 50 mice/sex/group maintained for 104 weeks (oncogenic study). A NOEL of 200 ppm (28.6 mg/kg b.w./day) was determined, based on increased relative liver weight in males at 1000 and 5000 ppm. Pyridate was not considered to be oncogenic in mice.

Reproduction: In a rat multigeneration study (3 generations, 2 litters/generation), utilizing dietary concentrations of 0, 80, 400 or 2500 ppm, a NOEL of 80 ppm was determined. At 400 ppm (20 mg/kg b.w./day), an increase in relative kidney weights, and a decrease in relative thyroid weights was observed. The NOEL of 80 ppm (4 mg/kg b.w./day) applies to pyridate and hydrolysis product in the diet. The NOEL for pyridate was determined to be 3 mg/kg b.w./day.

d) Teratology:

RAT:

A teratology study in Him:OFA(SD)SPF rats was conducted using 20 mated female rats/dose level at 0, 33.3, 100 and 300 mg/kg b.w./day. There were three deaths at 300 mg/kg b.w./day, and one death at 100 mg/kg b.w./day. No NOEL was determined since the incidence of major and minor malformations, especially dilation of brain lateral ventricles, and effects on kidneys (dilation of renal pelvis, hydronephrosis) was high in all test groups, although incidences were not clearly dose related. Because of these equivocal results which were not statistically significant, a repeat study was performed.

The repeat study utilized groups of 25 mated female Wistar HAM rats dosed at 55, 165, 400, or 495 mg/kg b.w./day. Thirty five mated females served as controls. Maternal mortality, clinical signs of toxicity, and reduced foetal weight were observed at 400 mg/kg b.w./day and above. There was no evidence of malformation induction at any dose level. The NOEL, based on maternal toxicity was 165 mg/kg b.w./day.

RABBIT:

A dose-range finding study resulted in mortality in non-pregnant rabbits (3/dose level) at doses of 50 mg/kg b.w./day and above. No effects were observed at 15 mg/kg b.w./day.

In a teratogenicity study (in which additional control animals had to be initiated because of very poor fertility in this group), groups of 13 mated females dosed at 0, 3.3, 10, or 30 mg/kg b.w./day showed no adverse effects. A NOEL of 30 mg/kg b.w./day was determined.

A second rabbit teratology study using 16 mated females/dose level at doses of 0, 10, 30 and 90 mg/kg b.w./day did not show any adverse effects. A NOEL of 90 mg/kg b.w./day was, therefore, determined.

e) Pharmacokinetics and metabolism:

Following a single oral dose of ¹⁴C pyridate 62.7% of the ¹⁴C was excreted in urine, and 24.6% in the faeces within 5 days. In vitro studies with artificial gastric juice (7.5 g pepsin/1000 mL phosphate buffer at pH 1.5) indicate an absence of breakdown of pyridate. However, in artificial intestinal juice (30 g pancreatin/1000 mL phosphate buffer) pyridate is hydrolysed, the rate of hydrolysis increasing with increasing pH.

The elimination of pyridate is biphasic in rats, with half lives of 3 and 40 hours. Tissue concentrations are highest in kidney, liver and blood at 3 hours, but later are highest in thyroid, ileum, colon, carcass and skin.

Following multiple dosing (20 doses 5 mg/rat) accumulation of the test material occurred in all organs with higher levels in females than in males. Tissue levels after 20 doses were about 5 times those detected after a single dose. After 4 days withdrawal, levels decreased to those observed after a single dose. Urinary excretion remains constant, regardless of number of doses. Faecal levels were not investigated, but data indicate pyridate is re-circulated via the bile. Three metabolites have been identified, and a metabolic pathway has been proposed.

f) Mutagenicity:

Point mutation: Ames \pm S9 activation: negative
DNA effects: Rat hepatocyte Unscheduled DNA
Synthesis: negative
Cell transformation: negative
Chromosomal aberrations: Micronucleus: negative
Drosophila: negative
Somatic cell mutation assay: negative

g) Summary:

The lowest NOEL was observed in the rat multigeneration reproduction study. This was 4 mg pyridate + hydroxylation product (CL 9673)/kg b.w./day. The actual level of pyridate in the diet at the NOEL of 4 mg/kg b.w./day was approximately 3 mg/kg b.w./day. The ADI for pyridate is based on a 100 fold safety factor applied to the NOEL for pyridate (3 mg/kg bw/day).

7.2 Dietary Exposure

a) Acceptable Daily Intake (ADI) Assessment:

ADIs have been assessed at 0.04 and 0.03 mg/kg b.w./day for pyridate + CL 9673 and for pyridate alone, based on the NOEL level observed in the multigeneration reproduction study and the use of a 100 fold safety factor.

b) Residue Levels

Pyridate plant metabolism has been extensively studied in rice, corn,

broccoli, and peanuts. The recommended application coincides with the 1 to 3 leaf stage of the actively growing weeds. This application then allows for two routes of uptake, one through the leaves and one through the roots from the soil.

The soil metabolism data indicates that pyridate is rapidly hydrolyzed to CL 9673 under soil conditions. The CL 9673 then forms CL 9673-O-methyl and both compounds are mineralized to volatile (CO₂) and bound metabolites. The bound metabolites were not associated with CL 9673. This data coupled with the metabolism data showing that residues of pyridate and its metabolites do not translocate, make this a minor route of residue uptake for the crops proposed.

Pyridate is rapidly absorbed by plants due to its lipophilic side chain. Once pyridate is absorbed this lipophilic side chain is rapidly hydrolyzed and the metabolite formed, designated CL 9673, is the herbicidally active species. CL 9673 apparently causes blocking of the photosynthetic process. The parent pyridate is itself not a photosynthetic inhibitor.

CL 9673 is metabolized further in the plant by conjugation to form the – and O- glycosides, with the N-glycoside being the major conjugation route. The ability to detoxify CL 9673 by this conjugation route appears to be the basis for plant resistance. Although the intermediate metabolites were not confirmed due to low yields, the major conjugate (CL 9673-N-glycoside) appears to undergo ring cleavage with the resulting products incorporated into bound natural products, i.e., sugars, proteins, pectins, and lignins. These natural products could not be hydrolyzed and therefore are not considered to be of importance to the terminal plant residues. None of the pyridate or its metabolites residues were found to translocate from the treated sites, therefore new growth did not appear to have significant pyridate residues.

The terminal residues of interest therefore have been identified as pyridate, CL 9673, and hydrolyzable CL 9673 residues. Analytical methodology has been developed to determine these residues as CL 9673 using column switching HPLC with detection in the UV simultaneously at 280 and 300 nm. This methodology gives a detection limit of 0.03 ppm with recoveries averaging 70% in corn and 90% in tomatoes.

The plant and animal metabolic profiles appear to be similar except for the conjugation species. As in plants, the first step in animal metabolism is the hydrolysis of pyridate to CL 9673. As stated above, in plants, the O- and the N-glycosides are formed, in the rat however,

the O- and the N-glucuronides are formed. Two factors tend to palliate this difference. Firstly, the terminal residues are very low (<0.03 ppm) and the conjugated metabolites form only a small portion of these terminal residues. Secondly, the plant glycoside conjugates hydrolyze to CL 9673 which is an animal metabolite. The difference in conjugation species is therefore not considered to be of concern.

An evaluation of Canadian data along with all available metabolism data indicates that residues are unlikely to exceed 0.03 ppm in tomato or corn. The field trial residue data presented by the petitioner was not considered to be adequate to support the use of pyridate on cole crops at this time.

The residue and metabolism studies indicate that the use of pyridate will not result in detectable residues in corn and corn byproducts. The feeding of these products to cattle therefore are not likely to result in residues of pyridate or pyridate metabolites in meat, milk, poultry, or eggs or in byproducts of these commodities.

c) Risk Assessment: Dietary Exposure

The maximum theoretical daily intake (TDI) of residues from tomatoes and corn would not exceed 0.00007 mg/kg bw/day or 0.23% of the ADI. Even if the residues approached 0.1 ppm, the TDI would not exceed 0.00023 mg/kg bw/day or 0.77% of the ADI.

7.3 Occupational Exposure and Risk Assessment

a) Occupational Exposure

The registrant submitted an occupational exposure study which was conducted in Germany with Lentagran 45 WP. Six farmers were monitored on 2 different occasions while spraying pyridate on corn. The workers were monitored for dermal exposure (skin and hand deposition) and respiratory exposure during mixing/loading, application, and clean up procedures. Biological monitoring was also conducted in the form of spot sample collection. In order to quantitate exposure from biological monitoring data, cumulative 24 hour urine samples should be collected until background levels are achieved. In consideration of the pharmacokinetics and metabolism of the compound, the total excreted values are used to arrive at an estimate of systemic dose. In this study, total cumulative urine samples were not collected; thus, the biological monitoring component of the study was not useful for quantitative exposure estimation. Consequently, the resulting exposure estimate is based on dermal deposition and inhalation results.

Total exposure was calculated by adding the dermal (patch and hand rinse) and inhalation results. Assuming that a typical 70 kg Canadian farmer sprays Lentagran 45 WP at the highest label rate of 1.35 kg active ingredient (a.i.) /ha wearing cotton coveralls and no gloves, treatment of 48 ha/day (120 acres/day) is estimated to result in a total exposure of 7.6 (2.2-22.3) mg pyridate/kg b.w./day. The majority of dermal deposition was to the hands.

The precision of this quantitative estimate is questionable due to the low dermal patch field recovery and storage stability results. Furthermore, no field recovery nor storage stability data were submitted for hand rinse solution; therefore, the hand results were not corrected. However, because the dermal patch storage stability recoveries were very low, there is reason to believe that storage of hand rinse solution may have resulted in similar low recoveries. Hence, the measured hand rinse values could be an underestimate of actual hand deposition.

The calculated exposure estimates are based on farmers applying pyridate at the highest recommended label rate, without protective gloves. The primary component of the estimate involves dermal deposition. In the absence of a dermal absorption study, it was necessary to assume 100% absorption through the skin, however, this assumption is likely an overestimate. It is expected that the use of appropriate protective gloves would reduce hand deposition considerably.

Water soluble bags are proposed for packaging this product. Data on the integrity of water soluble packaging were provided by the registrant for review. The conditions of the test were within those of Canadian use, but did not include the extremes of temperature and humidity that are encountered in Canadian climate. Thus, the Health Protection Branch is unable to rely entirely on the water soluble packaging as a means of reducing worker exposure. Each water soluble bag will be further packaged in an outer, water-proof bag. It is not known to what extent the protective outer bag will protect the water soluble film.

b) Risk Assessment: Occupational and Bystander Safety

The toxicity database on pyridate does not indicate mutagenic, oncogenic, teratogenic or reproductive effects. Pyridate is also of low acute toxicity. For the assessment of risk to workers exposed to pyridate for at most 20 days per year, the 90 day toxicity studies in rats and dogs are considered most appropriate, and a NOEL of 46.2 mg/kg bw/day for both studies is used in the calculation of a margin of

safety. The lower NOEL in the reproduction study is considered of little biological significance.

Based on the NOEL (46.2 mg/kg/b.w./day) and the calculated daily exposure estimate (7.6 mg/kg/b.w./day) for a 70 kg Canadian farmer wearing cotton overalls and no gloves, spraying at the highest label rate of 1.35 kg active ingredient/ha, and treating 48 ha/day (120 acres/day), the margin of safety (MOS) calculation is as follows:

$$\text{MOS} = \frac{\text{NOEL}}{\text{Exposure}} = \frac{46.2 \text{ mg/kg b.w./day}}{7.6 \text{ mg/kg b.w./day}} = 6$$

When interpreting this margin of safety assessment, it should be noted that the exposure estimate assumes 100% dermal absorption. A comparison of the subchronic oral and subchronic dermal studies indicates that while no effect levels in a 90 day oral dog and 90 day oral rat studies were both 46.2 mg/kg b.w./day, a 21 day dermal rat study showed no systemic toxicity at 1000 mg/kg b.w./day. Thus, dermal absorption is likely to be at least an order of magnitude lower than oral absorption. Taking this into consideration, the margin of safety is expected to be at least an order of magnitude higher. Although the Health Protection Branch is reluctant to rely on the proposed water soluble packaging as the only means of exposure reduction, this packaging, in combination with the following precautionary measures, are likely to further reduce exposure, and increase the MOS:

1. Because hand deposition accounts for the majority of the total dermal deposition, it is expected that the use of protective gloves would reduce exposure during mixing, loading, spraying and clean up, particularly if the packaging does not remain intact during mixing and loading.
2. In order to confirm that water soluble packaging will significantly reduce exposure, the integrity of the packaging should be further investigated during extremes of temperature and humidity. Otherwise, a label warning statement about storage of the formulation (i.e., "Do not store in freezing temperatures, or in conditions of high humidity") is necessary.

Taking the dermal absorption assumption into account, and assuming that the precautionary measures are instituted, it is felt that the Margin of Safety (MOS) in this assessment would fall in an acceptable range.

8. Environmental Aspects:

Environment Canada (Commercial Chemicals Branch and Canadian Wildlife Service)

8.1 Environmental Aspects

The primary transformation product of pyridate is CL 9673 (6-chloro-3-phenyl-4-hydroxy-pyridazine). Pyridate is basically the carrier form while CL 9673 is the physiologically active ingredient. In view of the rapid transformation of pyridate to CL 9673, information is also provided on the environmental fate and toxicology of CL 9673.

Pyridate was shown to be predominately transformed by chemical hydrolysis to CL 9673. The submitted data indicated that soil transformation was relatively rapid, even under conditions of low soil moisture, and consequently pyridate was considered to be of little environmental concern.

CL 9673 was shown to be primarily transformed by biological processes. Under normal agricultural conditions CL 9673 would be biotransformed by the end of the growing season; however, test results indicated that under conditions of very low rainfall, residues of CL 9673 may carryover to the next year. CL 9673 was shown to be highly soluble in water at pH 7, and therefore, would be expected to leach readily in soils of neutral to alkaline pH.

When comparing the exposure expected under field situations to levels causing acute toxicity, the acute risk to birds and wild mammals, from the use of Lentagran WP, was considered to be low.

The submitted data indicated that Lentagran WP was moderately toxic to mysid shrimp (Mysidopsis bahia) and daphnia (Daphnia magna). Pyridate was moderately toxic to mysid shrimp. CL 9673 was slightly toxic to daphnia. There were no observed effects on bees (Apis mellifera). Pyridate was judged to be of low toxicity to the earthworm Eisenia foetida foetida.

No aquatic or terrestrial plant toxicology studies were submitted.

8.2 Environmental Chemistry and Fate

a) Physicochemical Properties

The water solubility of pyridate was reported to be 1.49 mg/L. The water solubility of CL 9673 ranged from 59.8 mg/L at pH 4.0 to 1638.2 mg/L at pH 7.0. The octanol/water partition coefficient (Kow) for pyridate and CL 9673 were reported to be 11,100 - 4000 and 3.2 - 71.2, respectively; the Kow for CL 9673 decreased with increasing pH.

The vapour pressures of pyridate and CL 9673 were reported as 7.5×10^{-9} and 4.3×10^{-10} torr, respectively, at 25°C. Based on their vapour pressures and water solubilities, pyridate and CL 9673 are considered to have little potential to volatilize.

b) Transformation Processes

Hydrolysis

Fifty per cent of the initial pyridate in an aqueous solution was reported to hydrolyse to CL 9673 within 66.7 h at pH 5 and 22 - 25°C; the DT_{50} (time

for disappearance of 50% of the compound) decreased to 6.8 h at pH 9. Pyridate hydrolysed when adsorbed to soil ($DT_{50} < 5$ d at pH # 6.2) or silica gel (31% decrease in 6 h) but did not hydrolyse when adsorbed to cellulose powder. The data supplied indicated that CL 9673 did not hydrolyse.

Phototransformation

The experimental data indicated that the illumination source determined, qualitatively and quantitatively, the phototransformation products formed. The different light sources used in the various experiments made comparisons of the DT_{50} 's from the different studies difficult.

In view of the rapid hydrolysis rate of pyridate, phototransformation in aquatic situations was judged to be of little importance in the transformation of pyridate. Under artificial illumination, aquatic phototransformation of CL 9673 was pH dependent; the 10% level was reached in < 5 h at pH 5 and > 261 h at pH 9. Under sunlight, at pH 5.0, CL 9673 was completely degraded after 3 d and 11% of the initial radioactivity from labelled CL 9673 was recovered as $^{14}CO_2$. No data were provided on phototransformation at pH 7 or 9. In acidic aquatic systems (pH 5), the data indicated that an unidentified phototransformation product of CL 9673 had the potential to accumulate to significant quantities (> 10%).

Data were supplied on the phototransformation of pyridate and CL 9673 when adsorbed to silica gel, cellulose powder, and soil. There were insufficient data points in the silica gel and cellulose powder experiments to calculate the DT 's confidently. The data implied that phototransformation would not be a significant route for the transformation of adsorbed pyridate. The data indicated that the DT_{50} for CL 9673 adsorbed to silica gel was probably similar to that

obtained for the aquatic phototransformation studies ($DT_{50} = 46$ h at pH 7.0). Adsorption to cellulose resulted in increased persistence of CL 9673 ($DT_{50} = 1057$ h) over that observed in the aquatic studies.

Biotransformation

The soil biotransformation studies indicated that at moisture contents of 17-70% of the maximum water holding capacity (MWC) (75% field capacity) of a silt loam, pyridate was rapidly transformed to CL 9673 ($DT_{50} < 1$ d). Transformation was probably due to chemical hydrolysis and not to biotransformation. In air dried silt loam, the DT_{50} was # 14 d;

almost complete transformation of pyridate occurred by approximately 100 d.

At soil moisture contents greater than the permanent wilting point of the silt loam (35% MWC), CL 9673 was biotransformed (< 10% of initial), within 90 d, to CO_2 (33 - 42%) and to unidentified humic material (32 - 39%). No other major transformation products were observed. At 7°C and 55% MWC, the DT_{50} for CL 9673 was 1 year. Other data indicated that the amount of CL 9673 biotransformed in 4 soils after 30 d at 70% field capacity was found to be inversely correlated with the % organic matter (O.M.) content; the amounts recovered ranged from 70.0% to 45.8% for soils with O.M. contents from 0.7% to 3.1%, respectively.

Under anaerobic soil conditions, the data indicated that CL 9673 was slowly biotransformed to a large proportion of non-polar transformation products. Biotransformation in anaerobic sediments would not be an effective route for the dissipation of CL 9673 and it would be persistent beyond the growing season.

It is hypothesized that, in agricultural soils, biotransformation would be the major route of CL 9673 dissipation; however, under conditions of very low rainfall, CL 9673 would persist to the following year. Although CL 9673 was persistent under dry soil conditions, the amount of soil moisture at which significant persistence would occur would also be unfavourable for crop production.

c) Mobility

Adsorption-Desorption

Due to the physicochemical properties of pyridate, the adsorption-desorption methodology proposed in the Canadian

Environmental Chemistry and Fate guidelines (T-1-255) guidelines would be inappropriate for pyridate. Various studies indicated that pyridate rapidly partitioned from the water phase into the soil and that binding to the soil constituents was not permanent. Pyridate was also rapidly transformed by hydrolysis in soil.

The adsorption partition coefficient (K_d) for CL 9673 was reported as 1.08 - 0.82. The K_d values were found to depend upon the soil % organic carbon (O.C.) content and pH. At a defined pH, the K_d increased with increasing % O.C.. As the % O.C. increased the pH became more important than the % O.C. at estimating the K_d ; as the pH decreased, the K_d increased.

Leaching

The leaching studies undertaken with pyridate were not appropriate to determine the leaching potential of this compound; however, in view of the high K_{ow} , low solubility, and rapid hydrolysis of pyridate, leaching of pyridate was judged to be of low probability.

The submitted data indicated that the leaching potential of ^{14}C -CL 9673 was a function of both the % O.C. and the pH, with pH being the more important factor. For 3 soils with equivalent pH (6.1-6.5), the amount of CL 9673 leached increased with decreasing % O.C (0.5-2.7). For soils with % organic matter (OM) # 3.1, the relative amount of CL 9673 remaining in the soil after the leaching studies could be predicted from the pH of the soils; 41.8% was recovered from a sandy loam (pH = 5.0), 22.7% from a silty clay loam (5.9), 15.7% from a sand (6.6), and 8.7% from a silt loam (7.4). Of the total radioactivity recovered from these soil columns, 57.7 - 80.1% was located in the 0-5 cm layer. Of the total radioactivity recovered from the column leachates, 87-100% was CL 9673.

Based upon the pesticide characteristics used by Cohen et al. (1984) to identify a pesticide with the potential to leach to groundwater, i.e., water solubility > 30 ppm, $k_d < 5$, DT_{50} hydrolysis > 25 wk, etc., CL 9673 would be judged to have a potential to leach to groundwater. The present data indicated that with normal rainfall, significant leaching of CL 9673 to groundwater would occur in soils of neutral or alkaline pH, with moderate % O.M. (# 2.3%).

Field Dissipation

Field dissipation studies with Lantagran WP, performed in southern Ontario during a year of abnormally high precipitation, indicated that the DT_{50} for CL 9673 in bare and cropped soils (2.6% O.C., pH = 7.2)

would be < 33 d. Data from European field transformation studies with low pH (< 6.3) soils indicated that the 10% levels for pyridate and CL 9673 would be realized in < 35 and < 93 days, respectively.

The field dissipation studies implied that the dissipation of pyridate and CL 9673 was delayed until sufficient rainfall was realized. The laboratory and field data suggested that the longer the interval between the application of CL 9673 and a rainfall event, the less CL 9673 would leach from the soil during the rainfall event.

8.3 Environmental Toxicology

a) Wild Birds

The main route of exposure of wild birds is likely to be ingestion of contaminated vegetation, although dermal and inhalation exposure will occur during the spray event. No information was provided on the metabolism or pharmacokinetics of pyridate or CL 9673 in avian species.

The acute oral toxicity of pyridate was studied in the Pheasant, Bobwhite Quail, Mallard Duck, and Peking Duck. Acute dietary toxicity was studied using the Japanese Quail and Bobwhite Quail. These studies showed that the acute oral and dietary toxicity to birds was low. When comparing exposure expected under the field situation to levels causing acute toxicity, risk to birds is considered low. No avian reproduction studies were submitted, nor do they appear warranted at this time.

b) Wild Mammals

The likely routes of exposure to wild mammals is through ingestion of contaminated vegetation although dermal and inhalation exposure will occur during the spray event. No studies on wild mammals were submitted, thus toxicity must be extrapolated from toxicity observed in laboratory species.

Pyridate was absorbed and rapidly distributed in rats following oral dosing. It was rapidly metabolized, predominantly to CL 9673.

Acute oral toxicity studies in rats showed pyridate to be of low toxicity. Reported LD₅₀'s ranged from 992 to 5993 mg a.i./kg-bw. The formulated product, Lentagran WP appeared to be more toxic than technical pyridate, but is still of low toxicity. Dermal exposure of rabbits and inhalation exposure of rats also showed pyridate to be of low toxicity to mammals. When comparing the exposure expected under

field situations to levels causing acute toxicity, acute risk to wild mammals from the use of Lentagran WP is expected to be low.

c) Amphibians and Reptiles

No data were submitted to assess the risk to amphibians and reptiles from the proposed uses of Lentagran WP.

d) Aquatic Invertebrates

The submitted data indicated that pyridate and Lentagran were moderately toxic to mysid shrimp (Mysidopsis bahia); 96 h LC₅₀ values were 2.9 - 4.8 mg/L for pyridate and 3.8 mg/L for Lentagran. Lentagran was moderately toxic to daphnia (Daphnia magna); the 48 h LC₅₀ values were 3.3 - 7.1 mg/L. CL 9673 was shown to be slightly toxic to daphnia; the 48 h LC₅₀ value was 26.2 mg/L.

e) Terrestrial Invertebrates

Earthworms

Earthworm toxicity studies were initiated with Eisenia foetida foetida over a 14 day period. A no observed effect limit of \$ 250 mg pyridate/kg dry artificial soil was obtained and the 14 day LC₅₀ was calculated to be 799 mg/kg. Pyridate is judged to be of low toxicity to Eisenia foetida foetida.

Bees

There were no observed effects on Apis mellifera at up to 100 g pyridate/g bee weight, the highest concentration tested. The 48 h LD₅₀ was \$ 100 g/g. A study carried out by the Austrian Bundesanstalt fur Pflanzenschutz (results only submitted) indicated a tarsal (dermal) LD₅₀ > 160 g/g. Field studies with Lentagran WP demonstrated no effects and no deaths over a 2 day period. The application of Lentagran WP and atrazine produced no deaths, but resulted in a 33-85% decrease in flying activity.

f) Microbial Processes

Small effects were noted for starch mineralization, cellulose degradation and protein mineralization, but the effects were temporary and were consequently judged to be environmentally non-significant.

Increases in the ammonium concentrations, up to 45.5% at 3 ppm and 313.6% at 30 ppm, were observed within 4 days after application.

After 1 week the soils showed either increased or decreased levels of ammonium. Nitrate concentrations increased up to 27.6% after 6 weeks in 2 of the 4 soils studied.

g) Plants

No aquatic or terrestrial plant toxicology studies were submitted.

Plant metabolism studies were undertaken with both broccoli (Brassica oleracea cv. botrytis var. Italica) and corn. Pyridate was sprayed on the leaves at 1.8 kg/ha as Lentagran 50 (broccoli) or Lentagran 45 (corn). The data indicated that translocation of CL 9673 did not occur in the plants. It appeared that transformation of CL 9673, to non-mobile transformation products, occurred before CL 9673 could be translocated. No significant pyridate transformation products were found in the soil after the plants were harvested. In a hydroponic study with corn, translocation was not observed; after 8 d, 85% of the radioactivity was extracted from corn roots, with 40% of that extracted identified as CL 9673. A hydroponic study with barley indicated that 35.9% of the radioactivity, from pyridate, was translocated to the aerial parts of barley.

h) Algae

The 96 h EC₅₀ for Scenedesmus subspicatus was 82.1 mg/L for pyridate in comparison to 1.1 mg/L for potassium dichromate. At 50 mg/L, no effect was observed on the algal concentration over a 96 h period. Bioconcentration studies were initiated with Chlorella fusca but the methodology was flawed and the results obtained were inconsistent.

8.4 Wildlife Habitat Impact Assessment

Effects on wildlife can result from alterations in their habitat, by either changes in the amount, type or quality of food available or reduction in cover, required for nesting and protection. Given that exposure is estimated to be several fold lower than that causing effects on terrestrial invertebrates (bees, earthworms) or aquatic invertebrates (Daphnia, mysid shrimp), risk to birds, due to food removal, is expected to be low.

The concentration of pyridate expected in a shallow pond (0.5 m depth) immediately following a direct over spray and assuming complete mixing within the water column, is estimated to be 0.27 mg a.i./L. Comparing levels resulting from this worst-case scenario with levels causing toxicity in Scenedesmus subspicatus (96 h EC₅₀ = 82.1 mg a.i./L), effects on algae

under a field situation are not anticipated. Risk to wildlife due to effects on this resource are not anticipated.

The amounts of CL 9673 recovered from soils with "aged" CL 9673 appeared to be correlated with the % O.M. content of the soils; the higher the % O.M. content the lower the quantity of CL 9673 recovered.

The data submitted for earthworm and bee toxicology indicated that pyridate was relatively non-toxic to the earthworm Eisenia foetida foetida and to the honey bee Apis mellifera. Field studies indicated that Lentagran WP, at recommended application rates, would have no effect on the honey bee.

The previously and presently submitted data indicated that transformation of pyridate occurred mainly as a result of hydrolysis. Pyridate was very rapidly hydrolysed and the reviewer considers that pyridate would have a very short life under normal agricultural practices. Even under extremely dry soil conditions, pyridate would be transformed to CL 9673 by the end of the growing season.

Studies with pyridate added to two soils (pH @ 6.2) produced DT₅₀'s of < 45 d.

9. Effects on Fish, Fish Habitat and Fishery Resources:
Fisheries and Oceans Canada

9.1 Fish

Reports of static acute toxicity tests upon fish indicate that pyridate and its major transformation product, CL 9673, are marginally toxic to fish. Although no tests used CL 9673 as the test compound, it is considered to have been present in all tests since transformation of pyridate in aqueous solution to CL 9673 is rapid. The tests were conducted upon rainbow trout, catfish, bluegill sunfish, carp, golden orfe and sheepshead minnows and resulted in 96 h median lethal concentrations (LC_{50s}) of 22 mg/L or more. Although the tests were poorly reported, the consistency among the results suggests that they are reasonably representative of the median lethal concentration expected with direct input of pyridate to aquatic systems. They cannot, however, be considered definitive of the toxicity of CL 9673 to fish because the concentrations of neither pyridate nor CL 9673 were analytically monitored during the tests.

9.2 Fish Food and Habitat

The information available indicates that pyridate and CL 9673 are acutely toxic to aquatic invertebrates at concentrations less than 1 mg/L; however, the minimum toxic concentration has not been established since concentrations

less than 1 mg/L have not been tested. The reported static acute toxicity tests on daphnids and mysid shrimp exposed to pyridate technical and its WP formulation resulted in 48 h LC_{50s} in the range <1 to 7.1 mg pyridate/L. The only reported test of the acute toxicity of CL 9673 to daphnids was rejected because: 1) the test substance was reported to be unstable in the test medium, a situation which should not have been the case since CL 9673 is extremely soluble in water; and 2) mortalities occurred in the controls and lowest concentrations, but not in the highest concentration within 24 hours.

No studies of the chronic toxicity of CL 9673 to aquatic invertebrates have been submitted.

CL 9673 is expected to dissipate by photolysis and aerobic biotransformation, but test results indicate that the rate may be sufficiently slow that the exposure of aquatic organisms to CL 9673 must be considered chronic. This was demonstrated by a laboratory test of the photolysis of CL 9673 in buffered solution exposed to xenon light. In that test photolysis occurred with half-lives from less than one day at pH 5 to more than ten days at pH 9. The report also suggested that the rate of photolysis of CL 9673 under sunlight may be even slower; about one third of that indicated for the laboratory xenon light apparatus. Slow transformation of CL 9673 also occurred in tests of its biotransformation in water/soil suspensions under aerobic conditions. These resulted in dissipation times (DT_{50s}) of greater than 80 days. Soil tests showed that anaerobic biotransformation of CL 9673 is considerably slower than aerobic biotransformation.

9.3 Movement Into and Transformation in Aquatic Environments

LENTAGRAN 45 WP is intended for post-emergent application to maize, cole crops and tomatoes to control weeds at an early growth stage. The proposed label indicates application rates of up to 1350 g a.i./ha and does not prohibit more than one application in a season. The number of permissible applications each year, and their timing, should be included on the label to provide for regulatory control of the environmental exposure of the product, and to facilitate proper estimation of environmental exposure.

Aerial application of pyridate is not prohibited by the label directions and, if permitted, will increase the probability of pyridate and CL 9673 entering aquatic systems by direct over spray and spray drift.

Laboratory and field tests demonstrated characteristics of pyridate and CL 9673 which indicate that CL 9673 may enter aquatic systems in runoff. These characteristics are:

- 1) pyridate, in soil, rapidly transforms to CL 9673 (half-lives of <1 to 2 days were demonstrated);

- 2) CL 9673 dissipates slowly on soil (DT_{50} s ranged from 8 to 60 days);
- 3) CL 9673 is water soluble (1638 mg/L);
- 4) CL 9673 has a low coefficient of adsorption on some agricultural soils ($K_d = 0.3$ to 6.32).

Studies of CL 9673 run-off may be required once the toxicity of CL 9673 is established.

Pyridate entering aquatic environments is expected to rapidly transform to CL 9673 by hydrolysis. This has been demonstrated, in laboratory tests, to occur with half-lives of from 67 to 7 hours at pH 5 to 9 respectively at 22°C. Exposure to light has been shown to increase the rate of transformation.

9.4 Impact Assessment

Pyridate and CL 9673 are not expected to have any direct acute toxic impact on fish since the reported median lethal concentrations for fish are two orders of magnitude greater than the maximum expected environmental concentration (EEC) in aquatic systems. The predicted concentration, which would result from a single direct over spray of LENTAGRAN 45WP into a shallow (20 cm deep) stream, was estimated to be about 0.675 mg pyridate/L.

Aquatic invertebrates, which provide food for fish, may be at risk from the use of LENTAGRAN 45WP. The laboratory acute toxicity tests on daphnids indicated that no effect concentrations (which have not been established) may be less than 1 mg pyridate/L and may be in the range of the estimated environmental concentration (EEC). This risk cannot be adequately evaluated at this time due to lack of definitive tests of the minimum toxic concentration of CL 9673 to aquatic invertebrates. Since the characteristics of CL 9673 indicate that its exposure to aquatic organisms may be chronic, a study of the chronic toxicity of CL 9673 to aquatic invertebrates is needed.

Since the only described mode of action of pyridate (interference by CL 9673 with photosynthetic carbon fixation) is specific to plants, it is unusual that the results of algal growth inhibition test and the daphnid acute toxicity tests indicated that these compounds were more toxic to invertebrates than algae. This anomaly raises the concern of whether the available test results are reasonable indications of the toxicity of CL 9673, particularly for algae. An explanation for this anomaly, supported by suitable studies, is required, and any alternative modes of action should be described.

Because pyridate is lethal to certain plants at application rates, and because no information is available on the sensitivity of non-target plant species to

pyridate or CL 9673, it must be assumed that riparian and emergent aquatic vegetation will be affected by substantial spray drift of pyridate. Such vegetation is essential for the maintenance of fish habitat. The potential for such impact can be minimized if suitable buffer zones around aquatic habitat are maintained.

Bioconcentration of residues in fish should not be a concern. Although flow-through bioconcentration tests upon bluegill indicated significant bioconcentration of pyridate, it was rapidly transformed and depurated. Also pyridate concentrations will rapidly decline under natural aquatic conditions as it transforms to CL 9673. That compound did not bioconcentrate significantly in tests using catfish.

Assessment of the potential risks to fish food species and their habitat resulting from use of products containing pyridate cannot be completed because the toxicity of CL 9673 is not clearly established.

A growth inhibition test using technical pyridate on the algal species Scenedesmus subspicatus resulted in an EC₅₀ of 84 mg/L. That was based on initial nominal concentrations, however, (concentrations of pyridate and CL 9673 were not analytically monitored during the test) and the results cannot be considered definitive of the toxicity of these compounds to algae.

No information was submitted to indicate the effects of pyridate on aquatic macrophytes.