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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

DATE: 24-JAN-2000

SUBJECT: PP#s 6F04754 & 9E06025. Pyridate (i.e. TOUGH®) in/on Brassica Head and Stem Subgroup, Collards and Mint. **HED Risk Assessment**. Chemical 128834. DP Barcodes: D257832 & D262641. Case #s: 292143 & 287949. Submission #s: S565495 & S508455.

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the use of pyridate formulated as TOUGH® in/on collards, mint and the Brassica head and stem subgroup.

A summary of the findings and an assessment of human health risk resulting from the proposed use of pyridate are provided in this document. Cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity is not addressed in this document. The hazard assessment was provided by Melba Morrow, D.V.M. of Registration Action Branch 1 (RAB1), the residue chemistry data review by George F. Kramer, Ph.D. of RAB1, the dietary risk assessment by Jennifer E. Rowell of RAB1, the occupational/residential review by Dana Vogel of RAB1, and the water exposure assessment by Subijoy Dutta of the Environmental Fate & Effects Division (EFED).

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1.0 EXECUTIVE SUMMARY

Sandoz Agro, Inc. has submitted petitions in support of a Section 3 registration for the use of TOUGH® Herbicide in/on collards, mint and the Brassica head and stem subgroup. The active ingredient in TOUGH® is pyridate [O-(6-chloro-3-phenyl-4-pyridazinyl)-S-octyl-carbonothioate]. The proposed tolerances, expressed as the parent compound and the metabolite CL-9673 [6-chloro-3-phenyl-pyradazine-4-ol], and conjugates of CL-9673, all expressed as pyridate, are:

Brassica head and stem subgroup	0.03 ppm
Collards	0.03 ppm
Mint tops (leaves and stem)	0.03 ppm
Mint oil	0.03 ppm

Permanent tolerances are currently established for the combined residues of pyridate, the metabolite CL-9673, and conjugates of CL-9673, all expressed as pyridate, in/on cabbage, corn (fodder, forage, grain, and silage), and peanut (hulls and nutmeat), each at 0.03 ppm [40 CFR §180.462].

Pyridate is proposed for foliar applications on the above crops for the postemergent control of weeds such as Florida beggarweed, pigweed, lambsquarters, kochia, cocklebur, sicklepod, velvetleaf, morning glory, and triazine-resistant weeds.

Hazard Identification

The toxicological database for pyridate is adequate to support registration and the proposed tolerances. There are no data gaps.

Pyridate is in toxicity category III for acute oral, acute dermal, primary dermal irritation and toxicity category IV for acute inhalation and primary ocular irritation. The compound is slightly irritating to the skin and is a positive sensitizing agent when tested using the Magnusson Kligman method for assessing dermal sensitization.

In subchronic toxicity studies in rats, the primary effects reported in both sexes were hypoactivity and salivation. In dogs dosed with pyridate for 13 weeks, the primary effects were emesis and ataxia. In the same 13 week study in dogs, neurotoxicity and death were reported at the highest dose tested (200 mg/kg/day). In a 21-day dermal toxicity study in rats, no systemic effects were reported following the dermal administration of pyridate at the limit dose of 1000 mg/kg/day.

In a chronic toxicity study in dogs, neurotoxic symptoms were observed and characterized by excessive salivation, ataxia, mydriasis, dyspnea, tremors, increased respiration and prostration. In a chronic/carcinogenicity study in rats fed pyridate in the diet, a decrease in body weight was reported. There was no significant increase in tumor incidence in rats or mice which could be associated with the administration of pyridate. Mice received the limit dose of 7000 ppm (882.6 mg/kg/day in males and 1044.6 mg/kg/day in females).

The developmental toxicity study in Wistar HAN rats resulted in increased incidences of missing

and ossified sternebrae and decreased fetal body weight. Maternal toxicity was characterized by a decrease in the mean body weight and food consumption and clinical signs which were indicative of neurotoxicity (ventral body position, dyspnea, sedation and loss of reaction to external stimuli). Developmental and maternal NOAELs were 165 mg/kg/day. In the developmental toxicity study in New Zealand White rabbits, no developmental effects were reported at the NOAEL of 600 mg/kg/day and maternal toxicity was characterized by decreased body weight and body weight gain, decreased food consumption, increased incidences of dried feces and increased incidences of abortion at the LOAEL of 600 mg/kg/day. The maternal NOAEL was 300 mg/kg/day.

The 3-generation reproduction study in rats resulted in a decrease in maternal body weight gain and a decrease in pup weight gain at postnatal days 14 and 21. Both parental and offspring toxicity were reported at the high dose of 67.5 mg/kg/day.

A pattern of neurotoxicity was observed in several studies, including the rat developmental study, the subchronic dog and rat study and the chronic dog study. When the chemical was presented to the FQPA Safety Factor Committee (SFC) on October 4, 1999, a decision was made to request a developmental neurotoxicity study although the HIARC had determined in an earlier report (November 3, 1997) that the doses selected for risk assessment for the various exposure scenarios were protective of neurotoxicity.

There are no concerns for mutagenicity, as all tests were negative. Metabolism studies in rats demonstrated that pyridate was rapidly absorbed and excreted, with 95% of the compound being eliminated by 24 hours. Following multiple oral exposures, bioaccumulation in the liver, spleen and fat were reported. Metabolic patterns were similar for both sexes following a single dose; however, following multiple doses, female rats eliminated radioactivity slower than male rats.

Dose Response Assessment

The Hazard Identification Review Committee (HIARC) met on October 21, 1997 and selected doses and endpoints for dietary and non-dietary exposure risk assessments. On October 4, 1999; the FQPA SFC recommended that the safety factor for protection of infants and children be reduced to 1X since the database for pyridate was complete and the data provided no indication of increased susceptibility.

For acute dietary risk assessment, the HIARC recommended the use of the subchronic (90-day) dog study. The no observable adverse effect level (NOAEL) was 20 mg/kg/day and the lowest observable adverse effect level (LOAEL) was 60 mg/kg/day based on ataxia and emesis observed within 1-3 hours of dosing beginning on the first day. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variations) was used to determine the acute Reference Dose (aRfD) of 0.2 mg/kg/day.

For chronic dietary risk assessment, a NOAEL of 10.8 mg/kg/day was used based on the results from the chronic/carcinogenicity study in rats where decreased body weight gain was reported at the LOAEL of 67.5 mg/kg/day. This dose was supported by the results of the three-generation reproduction toxicity study in which the NOAEL was 10.8 mg/kg/day based on the reported

decrease in pup weights at 67.5 mg/kg/day on post-natal day 14 and 21 in both generations. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variation) was used to determine the chronic Reference Dose (cRfD) of 0.11 mg/kg/day.

The acute and chronic Population Adjusted Doses (aPAD and cPAD) are modifications of the acute and chronic RfDs to accommodate the FQPA Safety Factor. The PAD is equal to the acute or chronic RfD divided by the FQPA Safety Factor. As the FQPA Safety Factor was reduced to 1X, the PADs are equal to the RfDs.

Pyridate is not carcinogenic in either the rat or the mouse. Therefore, no carcinogenic risk assessment is required.

Non-Dietary Exposure

A dermal absorption study was not available for evaluation. The HIARC estimated a dermal absorption rate of 20% based on the interpretation of data from oral and dermal rat studies.

For short-term MOE calculations, the HIARC recommended the use of the NOAEL of 20 mg/kg/day from the 90-day feeding study in dogs. At the LOAEL of 60 mg/kg/day, clinical signs indicative of neurotoxicity (ataxia and emesis) were observed within 1-to 3 hours following the first dose. These signs persisted for the duration of the study.

For intermediate-term dermal exposure, the NOAEL of 20 mg/kg/day from the 90-day oral toxicity study in dogs should be used. The NOAEL in this study was 20 mg/kg/day based on the occurrence of ataxia and emesis at the LOAEL of 60 mg/kg/day.

For chronic dermal exposure, the HIARC selected the endpoint from the chronic/carcinogenicity study in the rat. In this study, the NOAEL was 10.8 mg/kg/day based on the decrease in body weight gain reported at the LOAEL of 67.5 mg/kg/day.

The HIARC recommended the use of oral NOAELs for inhalation exposure assessments. The NOAEL of 20 mg/kg/day from the 90-day feeding study in dogs was selected for short and intermediate exposure scenarios. The NOAEL of 10.8 mg/kg/day from the chronic/carcinogenicity study in rats was selected for long-term inhalation exposure.

Dietary Risk Estimates from Food Sources

Tier 1 acute and chronic dietary exposure analyses for pyridate were performed with the Dietary Exposure Evaluation Model (DEEM™) using published and proposed tolerance level residues and 100% crop treated (CT) for all commodities. Therefore, the acute risk was analyzed at the 95th percentile. The acute and chronic dietary risk estimates are less than 1% of the PADs for the general U.S. population and all population subgroups. **The results of the analyses indicate that the acute and chronic dietary risks associated with the existing and proposed uses of pyridate do not exceed HED's level of concern for the U.S. population or any population subgroup.**

Dietary Risk Estimates from Drinking Water Sources

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for pyridate at this time. In conjunction with a Section 3 risk assessment for the use of pyridate on garbanzo beans (John Simons/Environmental Risk Branch 2, memo dated 11/21/97), EFED provided estimates of ground and surface water concentrations for pyridate. EFED estimates acute and chronic Estimated Environmental Concentration (EECs) for ground water (using SCI-GROW) at 5 ppb. EFED estimated acute and chronic EECs for surface water (using GENEEC) are 97 ppb and 75 ppb, respectively. According to HED drinking water guidance (HED SOP 98.4) the 56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment is **25 ppb**.

Currently, HED uses drinking water levels of comparison (DWLOCs) as a surrogate to estimate risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that pesticide from food, water and residential uses (if any). The EEC of pyridate in surface water is less than HED's DWLOCs for pyridate (2000-7000 ppb and 1100-3800 ppb, respectively) as a contribution to both acute and chronic aggregate exposures.

Occupational Exposure and Risk Assessment

An MOE of 100 is adequate to ensure protection for occupational exposures to pyridate via the dermal and inhalation routes. Since pyridate is applied only a few times per year, long-term exposures from the proposed uses are not expected. In the absence of chemical specific data, handler exposure addressing mixer/loaders and applicators have been assessed using surrogate data available in the Pesticide Handlers Exposure Database (PHED Ver 1.1, 1997) Surrogate Table. Since PHED does not contain mixer/loader scenarios for emulsifiable concentrate (EC) formulations, the liquid mixer/loader scenario from the PHED Surrogate Table was used as a conservative scenario for the EC formulation use. The oral MOEs are 260 and greater for all handling activities. Therefore, exposure to handlers is below HED's level of concern.

Post-application exposures are expected for the proposed use. Post-application activities related to mint consist of scouting and mechanical harvesting (Personal Communication from R. Lundy of the Mint Industry Research Council to D. Vogel, 4/8/99). For brassica, post-application exposures result from scouting and cultural practices since pyridate is mainly applied prior to head development. In both cases, there is minimal potential for post-application exposure. Therefore, since the final application can be made no less than 45 days prior to harvest, potential post-application exposure is greatest for workers performing scouting activities. The MOE for scouts (100) is below HED's level of concern. Additionally, the label indicates that Tough® is rainfast, quickly absorbed by leaves, rapidly decomposed in soil, and has no effective pre-emergent or residual activity. Since the products do not persist in the environment, the amount of residue available for transfer is expected to be low. Therefore, post-application exposure estimates are expected to overestimate the potential exposures from the proposed uses of pyridate.

Residential Exposure and Risk Estimates

There are **no residential** or non-occupational uses for pyridate; therefore exposures are not likely, nor are residential postapplication exposures expected.

Aggregate Exposure and Risk Assessment/Characterization

Because there are no uses of pyridate that could result in residential exposures, this aggregate risk assessment takes into consideration dietary food and water exposure, only.

Acute aggregate risk estimates do not exceed HED's level of concern. For the U.S. population and all subgroups, including infants and children, <1% of the aPAD is occupied by dietary (food) exposure. The EECs of pyridate in surface and ground water are less than HED's levels of comparison for pyridate in drinking water as a contribution to acute aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of pyridate in drinking water do not contribute significantly to the acute aggregate human health risk at the present time considering the present and proposed uses in this action.

Chronic aggregate risk estimates do not exceed HED's level of concern. For the U.S. population and all subgroups, including infants and children, <1% of the cPAD is occupied by dietary (food) exposure. The EECs of pyridate in surface and ground water are less than HED's levels of comparison for pyridate in drinking water as a contribution to chronic aggregate exposure. Therefore, HED concludes with reasonable certainty that residues of pyridate in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time considering the present uses and uses proposed in this action.

Recommendation for Tolerances

Provided that a revised Section F is submitted, the residue chemistry and toxicological databases are adequate to support the following tolerances for pyridate and the metabolite CL-9673 [6-chloro-3-phenyl-pyradazine-4-ol], and conjugates of CL-9673, all expressed as pyridate, in terms of human health risk:

Brassica, head and stem, subgroup	0.03 ppm
Collards	0.03 ppm
Peppermint, tops	0.20 ppm
Spearmint, tops	0.20 ppm

However, the registrations should be made conditional upon submission of an acceptable developmental neurotoxicity study. The registrant must also submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether pyridate share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for pyridate need to be modified or revoked.

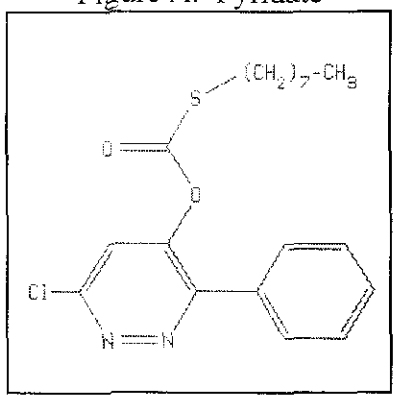
2.0. PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

The manufacturing process and other product chemistry data required for registration have been previously reviewed and found adequate (see PP#8F3603, 2/6/91). Technical pyridate contains 91% ai; impurities are not expected to pose a residue problem.

1. Description of Chemical

Pyridate is a herbicide used for post emergence control of several weed species.

Figure A. Pyridate



Molecular Formula: $C_{19}H_{23}ClN_2O_2S$
Molecular Weight: 378.92
Caswell No.: 716A

CAS Registry No.: 55512-33-9
Shaughnessy/Chemical No.: 128834

Table 1. Description of Pyridate

IUPAC name	6-chloro-3-phenylpyridazin-4-yl S-octyl thiocarbonate
Color	White-crystalline solid when pure; technical is a brown, oily liquid
Density	1.555 g/ml at 20°C (technical)
Melting Point	27°C
Boiling Point	>220°C at 0.105 mm Hg
Vapor Pressure	1.01×10^{-7} mm Hg at 20°C
Stability	Not degraded by UV light
Solubility	water: 1.5 mg/L at 20°C acetone: >10g/100 ml at 20°C benzene: >10 g/100 ml at 20°C methanol: >12 g/100 ml at 20°C toluene: >10 g/100 ml at 20°C

pK_a	none
Octanol/Water Partition Coefficient	K_{ow} = > 1000

3.0. HAZARD CHARACTERIZATION

3.1. Hazard Profile

Table 2. Acute Toxicity of Pyridate

STUDY TYPE	RESULTS	TOX. CATEGORY
81-1 Acute Oral-rat Acc.# 072340	LD50= 5993 mg/kg (m) 3544 mg/kg (f)	III
81-2 acute dermal- rabbit Acc. # 073280	LD 50 > 2000 mg/kg	III
81-3 Acute Inhalation-rats Acc # 073280	LC 50 > 4.37mg/L	IV
81-4 Primary Eye Irritation- rabbits Acc. # 072340	non-irritant	IV
81-5 primary dermal irritation-rabbit Acc # 072340	slightly irritating	III
81-6 Dermal sensitization Guinea pigs MRID # 40357102	positive by Magnusson Kligman method	N/A

Table 3. Toxicology Profile for Pyridate		
STUDY	MRID, Classification and Doses	RESULTS
82-1(a) 90-day feeding - rat (1987)	40157401 GUIDELINE 0, 62.5, 177, 500 or 500/600 mg/kg/day	NOAEL = 62.5 mg/kg/day LOAEL = 177 mg/kg/day based on hypoactivity and salivation
82-1(b) 90-day feeding - dog (1987)	40101604 GUIDELINE 0, 20, 60 or 200 mg/kg/day	NOAEL = 20 mg/kg/day LOAEL = 60 mg/kg/day based on emesis and ataxia
82-2 21-day dermal - rat (1988)	40980401 GUIDELINE 0 or 1000 mg/kg/day (limit dose)	NOAEL > 1000 LOAEL not determined
83-1 chronic feeding - dog (1989)	41093901 MINIMUM 0, 5, 20, 60or 100 mg/kg/day	NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on excessive salivation, mydriasis, ataxia, dyspnea, tremors and prostration
83-2 carcinogenicity - mouse (1983)	42168001 MINIMUM 0, 400, 800, 1600 or 7000 ppm	NOAEL and LOAEL not established; no effects at limit dose of 7000 ppm
83-3(a) Developmental - rabbit (1987)	40463201 GUIDELINE 0, 150, 300 or 600 mg/kg/day	NOAEL, maternal: 300 mg/kg/day NOAEL, developmental: > 600 mg/kg/day LOAEL maternal : 600 mg/kg/day based on reduced body weight gain
83-3(b) Developmental - rats (1986)	00262546 GUIDELINE 0, 55, 165 or 400 mg/kg/day	maternal NOAEL: 165mg/kg/day developmental NOAEL: 165 mg/kg/day maternal LOAEL: 400 mg/kg/day based on increased mortality and decreased body weight. developmental LOAEL: 400 mg/kg/day based on increased incidence of missing or unossified sternebrae, decreased fetal body weight
83-4 3 generation reproduction - rat (1982)	00072347 MINIMUM 0, 2.2, 10.8 or 67.5 mg/kg/day	systemic NOAEL: 10.8 mg/kg/day Reproductive NOAEL: 10.8 mg/kg/day Systemic LOAEL: 67.5 mg/kg/day based on decreased body weight Reproductive LOAEL: 67.5 mg/kg/day based on decreased pup weight during lactation
83-5 Chronic feeding/rat	00072342 00072343 MINIMUM	NOAEL = 10.8 mg/kg/day LOAEL = 67.5 mg/kg/day, based on decreased body weight.
84-2(a)	40101602	not mutagenic at doses ranging from 1 to 10,000 ug/plate, with or

84-2(a) Gene Mutation Assay (1987)	40186502 Acceptable	non-clastogenic in Chinese hamster ovary cells, with or without activation up to 250 ug/mL
84-2(b) Structural Chromosomal Aberrations (1980)	00072348 Acceptable	non-clastogenic at doses from 0.073 to 0.725 g/mL
84-2(b) Structural chromosomal Aberration (1986)	401166401 Acceptable	Compound did not induce structural chromosomal aberrations with or without activation at doses up 4 g/kg
84-2(c) Other Genotoxic effects- Unscheduled DNA synthesis (1986)	40857001 40982601 Acceptable	No increase in UDS at doses ranging from 0.1 to 1000 ug/mL

3.2. Dose Response Assessment

The HIARC met on October 21, 1997 and selected doses and endpoints for dietary and non-dietary exposure risk assessments. A summary of the selected doses and endpoints is presented in Table 4. An FQPA Assessment for pyridate was conducted on October 4, 1999. The FQPA SFC recommended that the safety factor for protection of infants and children be removed (1X).

3.2.1. Dietary Exposure

Acute Dietary (all populations). The aRfD = 0.2 mg/kg/day. For acute dietary assessment, the HIARC recommended the use of the subchronic (90-day) dog study. In this study, groups of beagle dogs (4/sex/dose) received gelatin capsules containing pyridate at doses of 0, 20, 60 or 200 mg/kg/day for 90 days. The NOAEL was 20 mg/kg/day and the LOAEL was 60 mg/kg/day based on ataxia and emesis observed within 1-3 hours of dosing beginning on the first day. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variations) was used to determine the acute RfD of 0.2 mg/kg/day.

Chronic Dietary. The cRfD = 0.11 mg/kg/day. For chronic dietary risk assessment, a NOAEL of 10.8 mg/kg/day was used based on the results from the chronic/carcinogenicity study in rats where decreased body weight gain was reported at the LOAEL of 67.5 mg/kg/day. This dose was supported by the results of the three-generation reproduction toxicity study in which the NOAEL was 10.8 mg/kg/day based on the reported decrease in pup weights at 67.5 mg/kg/day on post-natal day 14 and 21 in both generations. An uncertainty factor of 100 (10X for interspecies extrapolation and

10X for intraspecies variation) was applied.

3.2.2. Non-Dietary Exposure

Dermal absorption. A dermal absorption study was not available for evaluation. The Committee estimated a dermal absorption rate of 20% based on the interpretation of data from oral and dermal rat studies. In an oral developmental toxicity study in rats, the maternal NOAEL was 165 mg/kg/day, based on mortality, significantly decreased mean body weight and food consumption and clinical signs. In the 21-day dermal toxicity study in rats, no dermal or systemic toxicity was observed at the limit dose of 1000 mg/kg/day. In extrapolating to the dermal route from the oral route, the following assumptions were made: 1) the toxicity seen via the oral route is due to direct transport of pyridate from the absorption site to the target organs and, 2) the metabolism following oral and dermal routes is similar. Under these assumptions, no more than 16% of the pyridate applied to the skin is absorbed. The Committee decided to use a conservative dermal absorption value of 20% in the absence of definitive dermal absorption data.

Short-Term Dermal Exposure. For short-term MOE calculations, the HIARC recommended the use of the NOAEL of 20 mg/kg/day from the 90-day feeding study in dogs. At the LOAEL of 60 mg/kg/day, clinical signs indicative of neurotoxicity (ataxia and emesis) were observed within 1-to 3 hours following the first dose. These signs persisted for the duration of the study. A dermal absorption factor of 20% should be used for this risk assessment. An MOE of 100 is adequate for this assessment.

Intermediate-Term Dermal Exposure. For intermediate-term dermal exposure, the NOAEL of 20 mg/kg/day from the 90-day oral toxicity study in dogs should be used. The NOAEL in this study was 20 mg/kg/day based on the occurrence of ataxia and emesis at the LOAEL of 60 mg/kg/day. A dermal absorption factor of 20% should be used for this risk assessment. An MOE of 100 is adequate for this assessment.

Chronic Dermal Exposure. The HIARC selected the endpoint from the chronic/carcinogenicity study in the rat for long-term dermal exposure. In this study, the NOAEL was 10.8 mg/kg/day based on the decrease in body weight gain reported at the LOAEL of 67.5 mg/kg/day. A dermal absorption factor of 20% should be used for this risk assessment. An MOE of 100 is adequate for this assessment.

Inhalation Exposure. The HIARC recommended the use of oral NOAELs for inhalation exposure assessments. The NOAEL of 20 mg/kg/day from the 90 day feeding study in dogs was selected for short and intermediate exposure scenarios. The NOAEL of 10.8 mg/kg/day from the chronic/carcinogenicity study in rats was selected for long term inhalation exposure. An MOE of 100 is adequate to ensure protection from exposures to pyridate by the inhalation route. The risk assessments for inhalation exposure should be as follows:

> (i) The inhalation exposure should use a 100% default absorption rate and be converted to a mg/kg/day dose.

(ii) The dermal exposure component, using a 20% dermal absorption rate, should be combined with the converted inhalation dose.

(iii) The dose should then be compared to the oral NOAELs of 20 mg/kg/day for short and intermediate term exposure and 10.8 mg/kg/day for long term exposures.

3.2.3. Cancer

Pyridate is not carcinogenic in either the rat or the mouse. Therefore, no carcinogenic risk assessment is required.

3.2.4. Food Quality Protection Act (FQPA) Considerations

On October 4, 1999; the FQPA SFC determined that the safety factor be removed in assessing the risk posed by this chemical. This was based on the fact that the data base for pyridate was complete and that the data provided no indication of increased susceptibility. However, in their deliberations, the Committee recommended that a developmental neurotoxicity study be conducted since pyridate is a known neurotoxicant which produces both clinical signs of neurotoxicity (ataxia and emesis) and cholinesterase (nystagmus and mydriasis) depression at high doses in adult dogs at 200 mg/kg/day and hypoactivity in rats at 500 mg/kg/day.

Table 4. Toxicological Doses and Endpoints for Pyridate

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT and TOXICOLOGICAL EFFECT	STUDY
Acute dietary (all populations)	NOAEL = 20 UF = 100 FQPA SF = 1	LOAEL = 60 mg/kg/day based on ataxia and emesis. Acute PAD = 0.2 mg/kg/day	90-Day Feeding Study in Dogs
Chronic Dietary	NOAEL = 10.8 UF = 100 FQPA = 1	LOAEL = 67.5 mg/kg/day based on decreased body weight gain in male rats. Chronic PAD = 0.11 mg/kg/day	Chronic/ Carcinogenicity Study in rats
Dermal Absorption	A dermal absorption factor of 20% was extrapolated from an oral developmental toxicity study in rats in which the maternal NOAEL was 165 mg/kg/day based on mortality, decreased mean body weight and food consumption and clinical signs and a 21 day dermal study in rats in which no dermal or systemic toxicity was observed at the limit dose of 1000 mg/kg/day. The absorption rate was 165 mg/kg/d /1000mg/kg/day or 16%. HIARC elected to use a more conservative value of 20% for the dermal absorption rate.		
Short-term dermal	NOAEL = 20 MOE = 100	LOAEL = 60 mg/kg/day based on ataxia and emesis.	90-Day Feeding Study in Dogs
Intermediate term dermal	NOAEL = 20 MOE = 100	LOAEL = 60 mg/kg/day based on ataxia and emesis.	90-Day Feeding Study in Dogs

EXPOSURE SCENARIO	DOSE (mg/kg/day) UFs	ENDPOINT and TOXICOLOGICAL EFFECT	STUDY
Long term dermal	NOAEL = 10.8 MOE = 100	LOAEL = 67.5 mg/kg/day based on decreased body weight gain in male rats.	Chronic/ Carcinogenicity Study in rats
Inhalation (Short and intermediate)	NOAEL = 20 MOE = 100	LOAEL = 60 mg/kg/day based on ataxia and emesis.	90-Day Feeding Study in Dogs
Inhalation (Long term)	NOAEL = 10.8 MOE = 100	LOAEL = 67.5 mg/kg/day based on decreased body weight gain in male rats.	Chronic/ Carcinogenicity Study in rats

The aPAD and cPADs are modifications of the acute and chronic RfDs to accommodate the FQPA Safety Factor. The PAD is equal to the acute or chronic RfD divided by the FQPA Safety Factor. As the FQPA Safety Factor was reduced to 1X, the PADs are equal to the RFDs.

4.0. EXPOSURE ASSESSMENT

4.1 Summary of Registered and Proposed Uses

4.1.1. Mint

The petitioner has included a proposed label for a 55.8% EC formulation (EPA Reg. No. 100-877; Product name = TOUGH®) containing pyridate as the active ingredient.

The 55.8% EC formulation is proposed for foliar applications to mint at a rate of 0.9375 lb ai/A/application. Two applications may be made up to a maximum of 1.875 lb ai/A/year. The minimum retreatment interval is 14 days. Applications may be made using ground equipment in 20-30 gal/A (GPA) of water. A 49-day preharvest interval (PHI) is proposed.

The petitioner has adequately described the proposed uses of pyridate on mint. The proposed use directions are adequate to assess whether the submitted residue data reflect the maximum residues likely to occur in foods.

4.1.2. Collards and the Brassica Head and Stem Subgroup

The petitioner has included a proposed label for a 45% wettable powder (WP) formulation (EPA Reg. No. 55947-162; Product name = TOUGH®) containing pyridate as the active ingredient. The formulation is proposed for use on collards and the following crops belonging to the Brassica head and stem subgroup: broccoli, Chinese broccoli, cauliflower, cabbage, cavalo broccolo, Brussels sprouts, and kohlrabi.

The 45% WP formulation is proposed for foliar applications at a rate of 0.9 lb ai/A/application. Split applications may be made up to a maximum of 1.8 lb ai/A/year. In seeded crops, applications are to be made when the crop has at least 4 fully developed leaves and before head formation. In transplanted crops, applications are to be made only after plants have become well established (~3 weeks after transplanting) and before head formation. Applications may be made using ground equipment in 20-30 gal/A (GPA) of water; use in irrigation systems is prohibited. The proposed WP formulation may be used as part of a sequential treatment to control broadleaf weeds following a preplant incorporated or preemergence herbicide. A 45-day preharvest interval (PHI) and feeding restriction is proposed for cabbage, Brussels sprouts, and kohlrabi, and a 60-day PHI and feeding restriction is proposed for collard greens, broccoli, Chinese broccoli, cauliflower, and cavalo broccolo.

The petitioner has adequately described the proposed uses of pyridate on collards and crops belonging to the Brassica head and stem subgroup. The proposed use directions are adequate to assess whether the submitted residue data reflect the maximum residues likely to occur in foods.

4.2 Dietary Exposure

4.2.1. Food Exposure

Residue chemistry data pertaining to the proposed uses of pyridate on collards, mint, and crops belonging to the Brassica head and stem subgroup were submitted and reviewed by HED (Memos, G. Kramer 9/20/99; Barcode D228354 & 9/20/99; Barcode D259325).

4.2.1.a. Nature of the Residue - Plants and Livestock (OPPTS GLN 860.1300):

Plants: No new plant metabolism studies were submitted with this petition. Acceptable metabolism studies on broccoli, corn, and peanuts have previously been submitted and evaluated under PP#8F3603 (E. Haeberer, 12/14/89). The residues of concern in plants consist of pyridate, the metabolite CL-9673, and conjugates of CL-9673, all expressed as pyridate.

Livestock: There are no livestock feed items associated with the proposed uses of pyridate on collards, mint, and crops belonging to the Brassica head and stem subgroup. Therefore, the requirements for livestock metabolism studies do not apply to this petition. It is, however, noted that in conjunction with PP#8F3603 (E. Haeberer. 12/14/89), metabolism studies on lactating goats, cows, and laying hens were submitted and evaluated. It was concluded that the nature of the residue in ruminants is adequately understood. The total residues of concern in ruminants consist of pyridate, the metabolite CL-9673, and conjugates of CL-9673, all expressed as pyridate. Based on the proposed uses of pyridate described in PP#8F3603, HED additionally concluded that no secondary residues are anticipated in eggs or poultry tissues.

4.2.1.b. Residue Analytical Method - Plants (OPPTS GLN 860.1340):

The analytical method used is a total residue procedure. Pyridate, CL-9673, and conjugated CL-9673 are hydrolyzed to CL-9673 and measured as such by UV-HPLC. Pyridate and its main metabolites CL-9673 and conjugated CL-9673 are extracted from plant material by blending with an alkaline solution of ammonium acetate, acetone, and morpholine, whereby pyridate is converted to CL-9673. The extract is evaporated until free from acetone and partitioned between an alkaline solution of ammonium acetate and dichloromethane. The aqueous fraction undergoes an acidic hydrolysis for cleavage of CL-9673 conjugates. The CL-9673 residues are extracted into dichloromethane, which is applied to a "Bond-Elut" Si cartridge. Compound CL-9673 is eluted with a dichloromethane/methanol solution. The eluent is taken to dryness and ammonium acetate buffer is added. After pH adjustment to pH 5.0, 250 microliters of the aqueous phase are injected onto the HPLC. The HPLC uses a column switching technique to transfer the eluent from a dimethylamine column onto a C-18 column where a 15 minutes linear gradient is used to further separate the compounds. Ultraviolet absorbance detection is performed at 280 and 300 nm wavelengths to quantitate the level of CL-9673. The limit of quantitation (LOQ) is 0.03 ppm.

The method has undergone validation in EPA laboratories (PP#4G3047, L. Propst, 10/5/88) and is suitable to gather residue data and to enforce tolerances. It was sent to FDA for inclusion in PAM II (PP#8F3603, F. D. Griffith, Jr., 5/2/90). The multiresidue recovery data (MRID# 40917908) have been sent for inclusion in PAM I (PP#1G3956, F.D. Griffith, Jr., 6/27/91).

4.2.1.c. Multiresidue Methods (MRM) (OPPTS GLN 860.1360):

Data pertaining to the behavior of pyridate and the metabolite CL-9673 using FDA multiresidue protocols (PAM Vol. I) have previously been submitted. Pyridate and the metabolite CL-9673 could not be chromatographed as per GC methodology in MRM Protocol C. In accordance with the "decision tree" for MRM testing, no further evaluation was performed. The MRM submission was forwarded (E. Haeberer, 12/20/89) to FDA for evaluation and inclusion in PAM Vol. II.

4.2.1.d. Storage Stability Data (OPPTS GLN 860.1380):

Collards and the Brassica Head and Stem Subgroup:
Samples of broccoli and collards that were collected from the field trials were frozen (-50 to -8.3 C) within 2.5 hours of harvest and shipped frozen within 94 days of harvest to Agrolinz Melamin GmbH (Leonding, Austria) for residue analysis. All samples were stored frozen at the analytical laboratory until analysis. The total storage intervals between harvest and analysis of samples were 44-114 days (~2-4 months) for broccoli and 67-155 days (~2-5 months) for collards.

To validate the storage intervals and conditions of broccoli and collard samples, the petitioner conducted a storage stability study. Untreated samples of broccoli and collards

were separately fortified with pyridate and CL-9673, each at 0.06 ppm and 0.5 ppm. Recoveries following 1 and 138 days (~4.6 months) of frozen storage for broccoli, and 1 and 140 days (~4.6 months) of frozen storage for collards were reported. Unfortified broccoli and collard samples were fortified (fresh fortification samples) following frozen storage with the 138 and 140 day samples.

The storage stability data from the current submissions indicate that fortified residues of pyridate are relatively stable under frozen storage conditions in/on broccoli for up to 138 days and in/on collards for up to 140 days. Residues of the metabolite CL-9673 are relatively stable in/on broccoli for up to 138 days but are unstable (i.e., 55-69% decline in residues) in/on collards after 140 days.

The observed residue instability of the metabolite CL-9673 in/on collards would typically trigger HED to question the validity of the field trials conducted for collards. In lieu of the fact that some treated collard samples were analyzed within 2 months of harvest with residues below the method's LOD (0.003 ppm), HED concludes that, overall, the results of the field trials are supported by adequate storage stability data. Additional storage stability data for broccoli, corn, cabbage and alfalfa were reviewed in conjunction with PP#8F3603 (E. Haeberer, 12/14/89). It was concluded that residues of pyridate and the metabolite CL-9673 are stable for up to two years under freezer storage in/on various plant commodities, and that depletion of residues appears to vary depending upon the matrix involved.

Mint:
Samples of fresh mint foliage and oil that were collected from the field trials shipped frozen to Agrolinz Melamin GmbH (Leonding, Austria) for residue analysis. All samples were stored frozen at the analytical laboratory until analysis. The total storage intervals between harvest and analysis of samples were 199-264 days.

To validate the storage intervals and conditions, the petitioner conducted a storage stability study. Untreated samples of fresh foliage and oil were separately fortified with pyridate and CL-9673 at 0.3 ppm and 0.164 ppm, respectively. Recoveries following 0 and 280 days of frozen storage were determined. The storage stability data from the current submissions indicate that fortified residues of pyridate are relatively stable under frozen storage conditions in/on fresh foliage and oil for up to 280 days. Residues of the metabolite CL-9673 are relatively stable in/on oil for up to 280 days but are unstable (i.e., 80% decline in residues) in/on fresh foliage after 280 days. Freshly fortified controls were not analyzed concurrently with the stored samples so that the apparent degradation could have been a result of problems with the method. To further characterize storage stability, the field trial samples with quantifiable residues were reanalyzed after an additional 14 months of frozen storage. No evidence of degradation was observed.

HED concludes that, overall, the results of the field trials are supported by adequate storage stability data. Additional storage stability data broccoli, corn, cabbage and alfalfa were reviewed in conjunction with PP#8F3603 (E. Haeberer, 12/14/89). It was concluded that residues of pyridate and the metabolite CL-9673 are stable for up to two years under

freezer storage in/on various plant commodities, and that depletion of residues appears to vary depending upon the matrix involved.

4.2.1.e. Meat, Milk, Poultry and Eggs (OPPTS GLN: 860.1480):

There are no feed items associated with mint, collards, and crops belonging to the Brassica head and stem subgroup. Therefore, secondary residues are not expected to occur in meat, milk, poultry, or eggs as a result of the proposed use.

4.2.1.f. Crop Field Trials (OPPTS GLN 860.1500):

Collards and the Brassica Head and Stem Subgroup:
Geographic representation of residue data is adequate. Seven trials, reflecting the proposed maximum use pattern, were conducted in Regions 2 (4 trials), 3 (1 trial), 6 (1 trial), and 10 (1 trial). The number and location of the collard field trials are adequate according to current guidance (OPPTS GLN 860.1500) to support the proposed use on collards.

The submitted residue data for collards are adequate to support the proposed tolerance of 0.03 ppm. The combined residues of pyridate, the metabolite CL-9673, and CL-9673 conjugates were less than the method's LOQ of 0.03 ppm in/on collards harvested 58-61 days following the last of two foliar applications of the 45% WP formulation at 0.66-1.0 lb ai/A/application (1x the maximum proposed single and seasonal rates). The combined residues in/on collards following treatments at 2x were <0.03-0.055 ppm.

Mint:
Geographic representation of residue data is adequate. A total of five trials reflecting the proposed maximum use pattern for mint were conducted in Regions 5 (3 trials), 11 (1 trial), and 12 (1 trial). The current guidance (OPPTS GLN 860.1500, Table 5) specifies that a minimum of five trials should be conducted on mint in Regions 5 (2 trials) and 11 (3) trials. Since the trial performed in Region 12 was on the border of Region 11 and a total of five trials were performed, it is not necessary for the petitioner to conduct a additional field trial in Region 11.

The submitted residue data for mint are adequate. They indicate that the combined residues of pyridate, the metabolite CL-9673, and CL-9673 conjugates **will exceed** the proposed tolerance level of 0.03 ppm in/on mint harvested 39-48 days following the last of two foliar applications of pyridate at 0.9 lb ai/A/application (1X the maximum proposed single and seasonal rates). The appropriate tolerance for the combined residues of pyridate, the metabolite CL-9673, and CL-9673 conjugates in/on mint is 0.20 ppm. Also, separate tolerances are required for "peppermint, tops" and "spearmint, tops." **A Revised Section F is required.**

4.2.1.g. Processed Food/Feed (OPPTS GLN: 860.1520):

Collards and the Brassica Head and Stem Subgroup:
There are no processed food/feed items associated with collards and crops belonging to the Brassica head and stem subgroup. Therefore, data pertaining to the magnitude of pyridate residues in processed commodities are not required in support of this petition.

Mint:
Samples of mint for processing were collected in conjunction with the residue trials. Residues in/on all treated mint oil samples were <0.03-0.042 ppm at 1X and <0.03-0.065 at 2X.

The average concentration factor for pyridate in mint oil (1.28 ± 1.31X) is not significantly greater than 1X. Tolerances for mint oil are thus not required. **A Revised Section F, in which the proposed tolerance for mint oil is deleted, is required.**

4.2.1.h. Confined/Field Accumulation in Rotational Crops (OPPTS GLNs 860.1850 and 860.1900):

A confined rotational crop study with pyridate was previously submitted and accepted by EFGWB/EFED (Memorandum dated 3/16/90, R. Mahler). To summarize, confined rotational crop data using [^{14}C]pyridate at an application rate of 1.6 lb ai/A (1.6x) showed no detectable uptake (<0.01 ppm) of residues (pyridate, the metabolite CL-9673, or CL-9673-Ome) by lettuce, carrots, or barley after rotational intervals of 1 and 2 months. These findings were supported by data showing rapid metabolism in soil of pyridate residues. Based on the results of this study, no field rotational crop study was required, and no label restrictions are needed.

4.2.1.i. International Harmonization of Tolerances:

There is neither a Codex proposal, nor Canadian or Mexican limits for residues of pyridate in the subject crops. Therefore, a compatibility issue is not relevant to the proposed tolerance. Copies of the International Residue Limit Status (IRLS) sheets are attached to this memorandum.

4.2.2. Dietary Exposure Analysis

Acute and chronic DEEM^{TM} analyses for pyridate were performed in order to provide an estimate of the dietary exposure and associated risk for pyridate resulting from existing and proposed tolerance levels (Memo, J. Rowell 11/23/99; Barcode D259289). The DEEM^{TM} analyses evaluated the individual food consumption as reported by respondents in the USDA 1989-92 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity.

4.2.2.a. Acute Dietary Exposure Analysis

A Tier 1 acute analysis was performed for the general U.S. population and all population subgroups using published and proposed tolerance levels for all commodities. 100% CT information was used for all commodities. Therefore, the acute risk was analyzed at the 95th percentile. Dietary exposures and associated acute risk estimates for the general U.S. population and population subgroups which represent the highest dietary exposures for their respective subgroups (i.e., children, infants, females, and males) are shown in Table 5.

Table 5. Summary of Results of Acute DEEM Analysis for Pyridate at 95th Percentile.

	95th Percentile		99th Percentile		99.9th Percentile	
Subgroups	**Exposure (mg/kg/day)**	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**	**Exposure (mg/kg/day)**	**% aPAD**
U.S. Population (48 states)	0.000151	<1	0.000269	<1	0.000453	<1
Non-nursing Infants (<1 year old)	0.000278	<1	0.000442	<1	0.000682	<1
Children (1-6 years old)	0.000303	<1	0.000442	<1	0.000696	<1
Females (13+years old/nursing)	0.000149	<1	0.000252	<1	0.000254	<1
Males (13-19 years old)	0.000141	<1	0.000216	<1	0.000353	<1

At the 95th percentile, the %aPADs were <1. For acute dietary risk, HED's level of concern is >100% aPAD. The results of the acute analysis indicate that the acute dietary risk estimates associated with the existing and proposed uses of pyridate do not exceed HED's level of concern.

4.2.2.b. Chronic Dietary Exposure Analysis

The chronic analysis was performed using published and proposed tolerance levels and 100% CT for all commodities. Dietary exposures and associated chronic risk estimates for the general U.S. population and population subgroups which represent the highest dietary exposures for their respective subgroups (i.e., children, infants, females, and males) are shown in Table 6.

Table 6. Summary of Results from Chronic DEEM Analysis of Pyridate.

Subgroups	**Exposure (mg/kg/day)**	**% cPAD**
U.S. Population (48 states)	0.000048	<1
Non-nursing Infants (<1 year old)	0.000121	<1
Children 1-6 yrs old	0.000114	<1
Females 13+ old (not pregnant/not nursing)	0.000046	<1
Males 13-19 yrs old	0.000057	<1

The chronic risks were all <1%. For chronic dietary risk, HED's level of concern is >100% cPAD. The results of the chronic analysis indicate that the chronic dietary risk estimates associated with the existing and proposed uses of pyridate do not exceed HED's

level of concern.

4.2.2.c. Cancer Dietary Exposure Analysis

Pyridate is not carcinogenic in either the rat or the mouse. Therefore, no carcinogenic risk assessment is required.

4.2.3. Drinking Water Exposure

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for pyridate at this time. Therefore, information was provided by EFED in conjunction with its use on garbanzo beans (John Simons/Environmental Risk Branch 2, memo dated 11/21/97).

4.2.3.a. Groundwater EECs

Although pyridate does not possess the environmental fate parameters associated with a compound that could leach to ground water, the fate parameters of its degradate CL-9673 seem to indicate that it has the potential to leach to ground water (K_d of 0.3 - 3.5), especially in soils of low organic matter. In unusual conditions such as flooding, where anaerobic conditions exist in the top soil layers for up to 60 days, CL-9673 could persist and possibly leach to ground water or run off to surface water.

Pyridate is not listed in the EPA Pesticides in Ground Water Database, nor is there an EPA Maximum Contaminant Level or health advisory.

The drinking water exposure from the ground water screening model, SCI-GROW, yields a peak EEC of 5 ppb in ground water. There may be exceptional circumstances under which ground water concentration could exceed the SCI-GROW estimates. However, such exceptions should be quite rare since the SCI-GROW model is based exclusively on maximum ground water concentrations from studies conducted at sites and under conditions which are most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW are based on the largest 90-day average recorded during the sampling period. The EEC of 5 ppb can be considered as both the acute and chronic values.

4.2.3.b. Surface water EECs

The GENEEC model was used to estimate surface water concentrations for pyridate resulting from its use on garbanzo beans. The modeling results indicate that pyridate has the potential to move into surface waters, especially during times of unusually heavy rainfall. The peak GENEEC EEC of pyridate in surface water is 97 ppb, and the average 56-day EEC is 75 ppb. This estimate is based on a maximum application rate of 0.9 lbs ai/acre (the 1X rate for mint, collards, and crops belonging to the Brassica head and stem subgroup). The GENEEC values represent upper-bound estimates of the concentrations that might be found in surface water due to pyridate use.

Note: HED policy specifies that the 56-day GENEEC value be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment would be 25 ppb.

4.2.3.c. Environmental Fate Assessment

Pyridate hydrolyzes rapidly with half-lives of 66.7, 17.8, and 6.8 hours at pH 5, 7, and 9, respectively. The degradate, CL-9673, appears to be stable to hydrolysis with a reported half-life of >35 days (>95% remained as CL-9673 after 35 days).

Pyridate does not undergo any significant aqueous or soil photolysis, but is rapidly hydrolyzed to CL-9673, which is in turn readily photolyzed in water with a half life of 3.7 to 14 days and on soil with a half life of 16 days. These half lives indicate that pyridate and its primary degradate will be short lived in the environment when exposed to sunlight. CL-9673 has terrestrial field dissipation half lives of 7-29 days.

In anaerobic conditions, the degradate is persistent with a half-life for anaerobic soil metabolism of 330-630 days. The soil partition coefficient (K_d) for CL-9673 is 0.3-3.5, indicating it is not sorbed.

Neither pyridate nor CL-9673 is volatile, with a vapor pressure for pyridate of 7.49×10^{-9}, and a Henry's Constant of 2.49×10^{-9}, meaning pyridate is less volatile than water. A fish study indicated that pyridate bioaccumulates (464 times), but 99% of residues were eliminated in 14 days.

In summary, the data indicate that in terrestrial and aquatic environments, pyridate rapidly hydrolyzes to CL-9673 with half-lives usually $\leq$3 days. Although pyridate is also rapidly hydrolyzed under anaerobic soil conditions to CL-9673, CL-9673 is persistent and undergoes very little degradation with half-lives from 330-630 days in anaerobic soil conditions. Aerobic half-lives of CL-9673 are about 10-30 weeks in soils (incorrectly given as 10-30 days in the EPA one-liner database). CL-9673 is rapidly degraded under the influence of light as indicated by the 14-day half-life in the water and 16-day half-life in soil. In general, pyridate and its primary degradate, CL-9673, will not persist in aerobic conditions, while CL-9673 will persist in anaerobic conditions.

4.2.3.d. Drinking Water Risk (Acute and Chronic)

A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs.

HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against

conservative model estimates of a pesticide's concentration in water.

DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

HED has calculated DWLOCs for both acute and chronic risks. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from DEEM™) was subtracted from the aPAD to obtain the acceptable acute exposure to pyridate in drinking water. To calculate the DWLOC for chronic (non-cancer) exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM™) was subtracted from the cPAD to obtain the acceptable chronic (non-cancer) exposure to pyridate in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures, which are listed in Table 7.

Table 7. Default Body Weight and Drinking Water Consumption Figures

DEEM Population	Body Weights (kg)	Drinking Water Consumption (liters/day)
General U.S. Population/48 States Males	70	2
Females 13-50	60	2
Infants/children	10	1

Calculation:

$$\text{DWLOC}_{\text{(acute or chronic)}}(\text{mg/L}) = \frac{[\text{water exposure}_{\text{(acute or chronic)}}(\text{mg/kg/day}) \times \text{body weight (kg)}]}{[\text{consumption (L)} \times 10\text{-}3\ \text{kg/mg}]}$$

The DWLOCs for the acute and chronic scenarios are listed in Table 8. For the acute and chronic scenarios, the population subgroups chosen were the U.S. population (70 kg. body weight assumed), the female subgroup with the highest food exposure (60 kg. body weight assumed), the infant/child subgroup with the highest food exposure (10 kg. body weight assumed), the male subgroup with the highest food exposure (70 kg. body weight assumed), and the other general population subgroups (70 kg. body weight assumed) which have higher dietary exposure than the general U.S. population.

Table 8. Acute and Chronic Drinking Water Levels of Comparison for Pyridate

Scenario/Population Subgroup	DWLOC, ppb
Acute	
U.S. Population (48 states)	7000
Non-nursing Infants (<1 year old)	2000
Children (1-6 years old)	2000
Females (13+years old/nursing)	7000
Males (13-19 years old)	7000
Chronic	
U.S. Population (48 states)	3900
Non-nursing Infants	1100
Children 1-6 yrs old	1100
Females (13+years old/nursing)	3900
Males 13-19 yrs. old	3900

The estimated peak concentration of pyridate in surface water is 97 ppb. This value is less than HED's DWLOCs for pyridate (2000-7000 ppb) as a contribution to acute aggregate exposure. The estimated average concentration of pyridate in surface water is 25 ppb. This value is less than HED's DWLOCs (1100-3900 ppb) for pyridate as a contribution to chronic aggregate exposure.

4.3. Occupational Exposure

4.3.1. Summary of Use Patterns and Formulations

For the proposed uses, two formulations will be utilized for post-emergent weed control of broadleaf weeds and grasses. The Tough® 45WP (45% pyridate) formulation will be used for brassica crops, while Tough® EC (55.8% pyridate) will be used for mint crops. Pyridate will be applied by groundboom sprayer equipment to both mint and brassica crops. Applications will be made at a maximum rate of 0.90 and 0.94 lbs ai/acre for brassica and mint, respectively. No more than two applications will be made at a 14-day interval for mint. Split applications may be made up to a maximum rate of 1.8 lbs ai/acre/year for brassica. No applications will be made within 45 to 60 days of harvest. Table 9 summarizes the use pattern of pyridate for the proposed uses.

Table 9. Use Pattern Summary of Pyridate on Mint and Brassica

Factors	Mint	Brassica
Formulation	Tough® EC (55.8% ai) - emulsifiable concentrate	Tough® 45WP (45% ai)- wettable powder in water soluble bags
Pests	broadleaf weeds and grasses	
Application methods	groundboom sprayer	
Maximum application rate (AR)	0.90 lb a.i per acre	0.94 lb a.i. per acre
Maximum number of applications	2 applications made a minimum of 14-day intervals	Split applications up to 1.8 lbs ai acre/year
Manufacturer	Novartis	

4.3.2. Occupational Exposure Assessment

An MOE of 100 is adequate to ensure protection for exposures to pyridate via the dermal and inhalation routes. Since pyridate is applied only a few times per year, long-term exposures from the proposed uses are not expected. Pyridate is not carcinogenic in either the rat or the mouse. Therefore, no carcinogenic risk assessment is required.

4.3.2.a. Mixer/Loader/Applicator Exposure Assessment

HED has identified toxicological endpoints of concern for occupational exposures. In the absence of chemical specific data, handler exposure addressing mixer/loaders and applicators have been assessed using surrogate data available in the Pesticide Handlers Exposure Database (PHED Ver 1.1, 1997) Surrogate Table. Since PHED does not contain mixer/loader scenarios for EC formulations, the liquid mixer/loader scenario from the PHED Surrogate Table was used as a conservative scenario for the EC formulation use. Table 10 summarizes HED assumptions for the commercial mixer/loader in support of groundboom application of the EC formulation. This scenario is assumed to represent the highest potential exposure of all groups handling pyridate.

Table 10. Assumptions for Handler Exposure Assessment

Factors	Quantities/Units
Mixer/Loader and Applicator body weight	70 kg
Average farm size for MINT	250 acres [1]
Mixer/loader unit exposure from PHED, (In support of Groundboom; open mixing of liquid (*surrogate for emulsifiable concentrate*), single layer of clothing with gloves). HIGH CONFIDENCE DATA	Dermal - 23 µg/lb a.i. handled[2] Inhalation - 1.2 µg/lb a.i. handled[2]

[1] Assumptions regarding acreage treated per day for mint from Personal Communication from R. Lundy, Mint Industry Research Council, 4/8/99. It is assumed that a commercial applicator could treat up to 4 farms of this size per day.
[2] Source: Pesticide Handlers Exposure Database (PHED) V1.1, Surrogate Exposure Table.

According to the 1997 Agricultural Census, the United States average farm size for brassica is no greater than 60 acres. Since the average farm size for mint is 250 acres, it is assumed that more acres of mint can be treated per day than brassica. Therefore, the exposure estimates for handlers were done only for mint. Moreover, potential exposure for the mixer/loader of the EC formulation is higher than for all other workers handling either formulation of pyridate. Therefore, the potential exposure to all other handlers of pyridate are not expected to exceed that of the mixer/loader supporting the groundboom application of the EC formulation.

All exposure calculations were done for commercial applicators. Since private applicators/handlers cannot treat as large an area in a single day, it is assumed that the commercial applicator will have higher exposure than the private applicator. Available information indicates that a commercial applicator could treat approximately 4 average-sized farms per day (Personal communication from R. Lundy of the Mint Industry Research Council to D. Vogel, 4/8/99). This assessment also assumes that one worker would complete all mixing and loading for one full day of application to over 1000 acres. Since a more typical scenario would provide for at least two mixer/loader, this assessment provides a conservative exposure assessment. Table 11 summarizes the exposure estimates for the mixer/loader supporting the groundboom application of the EC formulation.

Table 11. Handler Exposure to Pyridate

Job Function	Unit Exposure[1] (µg/lb a.i)	AR (lbs ai/Acre)	Acres/ Day	Average Dermal Daily Dose (ADD)[2] (mg/kg/day)	Average Inhalation Daily Dose (ADD)[2] (mg/kg/day)	Total Exposure (mg/kg/day)	Short/ Interm-term MOE[3]
Mixer/ Loaders - (EC)	Dermal - 23 Inhalation - 1.2	0.94	1000	6.2E-02	1.6E-02	7.7E-02	2.6E+02

MOE = NOAEL/ADD; (where NOAEL = 20 mg/kg/day, for short-term dermal and inhalation (oral equivalent))
[1] Source: Pesticide Handlers Exposure Database (PHED) V1.1, Surrogate Exposure Table.
[2] ADD = Unit exposure(ug/lb ai) x AR x Acres/Day x 1/BW x % Absorption (100% -inhalation, 20% -dermal) x 1mg/1000ug
[3] MOE =NOAEL/Total Exposure; the level of concern is for MOEs below 100

As presented in Table 11, the MOEs are 260 and greater for all handling activities. Therefore, since HED's level of concern for pyridate is for MOEs less than 100, exposure to handlers is below the level of concern.

4.3.2.b. Post-Application Exposure Assessment

Post-application exposures are expected for the proposed use. Post-application activities related to mint consist of scouting and mechanical harvesting (Personal Communication from R. Lundy (Mint Industry Research Council) to D. Vogel, 4/8/99). For brassica, post-application exposures result from scouting and cultural practices due to the fact that pyridate is mainly applied prior to head development. In both cases, there is minimal potential for post-application exposure. Therefore, since the final application can be made no less than 45 days prior to harvest, potential post-application exposure is greatest for workers performing scouting activities.

No chemical specific data are available to address post-application exposure to workers reentering areas treated with pyridate. Therefore, the exposure estimates are calculated using the following assumptions: 20 % of the highest application rate (0.94 lb ai/A) available on day 0 as dislodgeable residue, exposure duration of 8 hours/day, reentry exposure on day 0, dermal absorption (DA) factor of 20%, and a dermal transfer coefficient (TC) of 4,000 cm^2/hr. Table 12 presents the post-application exposure assessment for the scouting activity.

Table 12. Worker Post-application Dermal Exposure

Exposure Scenario	Transfer Coefficient (cm^2/hr)	DFR 1 (ug/cm^2) day 0	Exposure[2] (mg/kg/day)	Short-term MOE[3]
Scouting	4,000	2.1	0.19	100

1 Surrogate DFR = application rate X % available as dislodgeable residue X 4.54E8 ug/lb X 2.47E-8 A/cm^2
2 Dermal exposure =DFR_0 (ug/cm^2) X TC (cm^2/hr) X 8 hrs/day X 0.001 mg/ug X 20% DA X 1/ BW ; BW= 70kg for adults
3 MOE = NOAEL (20 mg/kg/day)/Exposure; level of concern is for MOEs below 100

The MOE for scouts is below HED's level of concern. Therefore, potential exposure for all workers involved in post-application activities are also expected to be below the level of concern. Additionally, the label indicates that Tough® is rainfast, quickly absorbed by leaves, rapidly decomposed in soil, and has no effective pre-emergent or residual activity. Since the products do not persist in the environment, the amount of residue available for transfer is expected to be low. Therefore, post-application exposure estimates are expected to overestimate the potential exposures from the proposed uses of pyridate.

4.3.3. Restricted Entry Interval (REI)

Pyridate is in toxicity category III for acute dermal, primary dermal irritation and toxicity category IV for acute inhalation and primary ocular irritation. Based on the Worker Protection Standard (WPS), an interim REI of 12 hours is sufficient to protect workers performing re-entry activities for the proposed use of pyridate.

4.3.4. Incident Reports

There are no confirmed incident reports resulting from exposure to pyridate.

4.4 Residential Exposure

Currently, there are no registered residential uses of pyridate.

5.0 AGGREGATE EXPOSURE AND RISK ASSESSMENT/ CHARACTERIZATION

5.1 Acute Aggregate Risk

Because there are no uses of pyridate that could result in residential exposures, the acute aggregate risk assessment takes into account exposure estimates only from dietary consumption of pyridate (food and drinking water). Acute risk estimates resulting from aggregate exposure to pyridate in food and water are below HED's level of concern.

From the acute dietary (food only) risk assessment, a high-end exposure estimate was calculated for the general U.S. population and all population subgroups. The acute dietary exposure for all populations subgroups (<1% aPAD) is below HED's level of concern.

The maximum EECs of pyridate in surface and ground water are less than HED's DWLOCs for pyridate as a contribution to acute aggregate exposure (Table 13). Therefore, HED concludes with reasonable certainty that residues of pyridate in drinking water do not contribute significantly to the aggregate acute human health risk at the present time considering the present uses and uses proposed in this action.

HED bases this determination on a comparison of EECs of pyridate in surface waters and ground waters to DWLOCs for pyridate. The estimates of pyridate in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of pyridate on drinking water as a part of the aggregate acute risk assessment process.

Table 13. Summary of DWLOC Calculations - Acute Scenario

Population Subgroup[1]	Acute Scenario					
	% aPAD mg/kg/day	Food Exposure mg/kg/day	Maximum Water Exposure mg/kg/day[2]	SCI-GROW (ppb)[3]	GENEEC (ppb)	DWLOC (ppb)
U.S. Population (48 states)	<1	0.000151	0.10995	5	97	7000
Non-nursing Infants	<1	0.000278	0.10988	5	97	2000
Children 1-6 yrs. old	<1	0.000303	0.10989	5	97	2000
Females 13+ yrs. old (nursing)	<1	0.000149	0.10995	5	97	7000
Males 13-19 yrs. old	<1	0.000141	0.10994	5	97	7000

[1]Females 13+ (60 kg. body weight assumed).
[2]Maximum Water Exposure (mg/kg/day) = aPAD (mg/kg/day) - Food Exposure from DEEM (mg/kg/day)
[3]The crop producing the highest level was used.

5.2 Short- and Intermediate-Term Aggregate Risk

Since there are no residential uses or exposure scenarios, short- and intermediate-term aggregate risk assessments were not conducted.

5.3 Chronic Aggregate Risk

Because there are no uses of pyridate that could result in residential exposures, the chronic aggregate risk assessment takes into account average exposure estimates only from food and drinking water. Chronic risk estimates resulting from aggregate exposure to pyridate in food and water are below HED's level of concern. For the U.S. population and all subgroups, <1% of the cPAD is occupied by dietary (food) exposure.

The estimated average concentrations of pyridate in surface and ground water are less than HED's levels of comparison for pyridate in drinking water as a contribution to chronic aggregate exposure (Table 14). Therefore, HED concludes with reasonable certainty that residues of pyridate in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time considering the present uses and uses proposed in this action.

HED bases this determination on a comparison of estimated concentrations of pyridate in surface waters and ground waters to DWLOCs for pyridate. The estimates of pyridate in surface and ground waters are derived from water quality models that use conservative assumptions regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of pyridate on drinking water as a part of the aggregate chronic risk assessment process.

Table 14. Summary of DWLOC Calculations - Chronic (Non-Cancer) Scenario

Population Subgroup[1]	Chronic (Non-Cancer) Scenario					
	cPAD mg/kg/day	Food Exposure mg/kg/day	Maximum Water Exposure mg/kg/day[2]	SCI-GROW (ppb)[3]	GENEEC (ppb)[4]	DWLOC (ppb)
U.S. Population (48 states)	<1	0.000048	0.19985	5	25	3900
Non-nursing Infants	<1	0.000121	0.19985	5	25	1100
Children 1-6 yrs	<1	0.000114	0.19985	5	25	1100
Females 13+ (nursing)	<1	0.000046	0.19985	5	25	3900
Males 13-19 yrs.	<1	0.000057	0.19985	5	25	3900

[1]Population subgroups chosen were U.S. population (70 kg. body weight assumed), the infant/child subgroup with the highest food exposure (10 kg. body weight assumed), the female subgroup with the highest food exposure (60 kg. body weight assumed), and the male subgroup with the highest food exposure (70 kg. body weight assumed).
[2]Maximum Water Exposure (mg/kg/day) = cPAD (mg/kg/day) - Food Exposure from DEEM (mg/kg/day)
[3]The crop producing the highest level was used.
[4]HED policy specifies that the 56-day GENEEC value be divided by 3 to obtain a value for chronic risk assessment calculations.

6.0 DEFICIENCIES / DATA NEEDS

6.1. Toxicology

- The FQPA SFC recommended that a developmental neurotoxicity study be conducted.

6.2. Chemistry

- A revised Section F
-

6.3. Occupational Exposure

- None

7.0 REFERENCES

7.1. Toxicology

HED DOC. NO.: 013793
Subject: ***PYRIDATE*** - Report of the FQPA Safety Factor Committee
From: Brenda Tarplee
To: Melba Morrow
Dated: October 15, 1999
MRID(s):

HED DOC. NO.: 013299
Subject: REPORT OF THE HAZARD & FQPA COMMITTEE FOR EXPEDITE ACTIONS Section 18: PYRIDATE (PC Code 128834) For Use in Montana on Mint
Dated: April 5, 1999
MRID(s):

7.2. Chemistry

DP Barcode(s): D228354
Subject: PP# 6F04754. Pyridate (i.e. TOUGH®) in/on Brassica Head and Stem Subgroup and Collards. **Evaluation of Residue Data and Analytical Methods.**
From: George F. Kramer
To: Jim Tompkins/Tobi Colvin-Snyder
Dated: 20-SEP-1999
MRID(s): MRID#s 440562-01 & -

DP Barcode(s): D259325
Subject: PP# 9E06025. Pyridate (i.e. TOUGH®) in/on Mint. **Evaluation of Residue Data and Analytical Methods.**
From: George F. Kramer
To: Jim Tompkins/Tobi Colvin-Snyder
Dated: 20-SEP-1999
MRID(s): 448712-01

DP Barcode(s): D259289
Subject: Pyridate - Acute and Chronic Dietary Exposure Analyses.
From: Jennifer E. Rowell
To: George F. Kramer
Dated: 23-NOV-1999
MRID(s):

Attachment: IRLS sheets

cc: PP# 6F04754 & 9E06025, Melba Morrow (RAB1), George F. Kramer (RAB1), D. Vogel (RAB1)
RDI: K. Whitby (1/24/00); Branch (1/19/00); Team (1/11/00); Chemists (10/28/99)
G.F. Kramer:806T:CM#2:(703)305-5079:7509C:RAB1

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name:	Common Name:	X Proposed tolerance □ Reevaluated tolerance □ Other	Date:
O-(6-chloro-3-phenyl-4-pyridazinyl)-S-octyl-carbonothioate	pyridate		09/14/99

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number: 9E06025 DP Barcode: D259325 Other Identifier:
Residue definition:	Reviewer/Branch: G.F. Kramer
	Residue definition: parent + its metabolite 6-chloro-3-phenyl-pyridazine-4-ol, and conjugates of that metabolite, all expressed as pyridate

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		mint, tops (leaves and stems)	0.03
		mint oil	0.03

Limits for Canada	Limits for Mexico
X No Limits □ No Limits for the crops requested	X No Limits (for these crops) □ No Limits for the crops requested
Residue definition:	Residue definition:

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions:.
F. Ives 8/15/99

Rev. 1998

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name:	Common Name:	X Proposed tolerance □ Reevaluated tolerance □ Other	Date:
O-(6-chloro-3-phenyl-4-pyridazinyl)-S-octyl-carbonothioate	pyridate		09/14/99

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above □ No Codex proposal step 6 or above for the crops requested	Petition Number: 6F04754 DP Barcode: D228354 Other Identifier:
Residue definition:	Reviewer/Branch: G.F. Kramer
	Residue definition: parent + its metabolite 6-chloro-3-phenyl-pyridazine-4-ol, and conjugates of that metabolite, all expressed as pyridate

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Brassica head and stem subgroup	0.03
		Collards	0.03

Limits for Canada	Limits for Mexico
X No Limits □ No Limits for the crops requested	**X** No Limits (for these crops) □ No Limits for the crops requested
Residue definition:	Residue definition:

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions:.
F. Ives 9/15/99

Rev. 1998