Interdepartmental Executive Committee on Pest Management
Le Comité interministériel sur la lutte antiparasitaire

Decision Document E94-03

Imazethapyr

This Decision Document has been prepared as part of the ongoing efforts to provide a summary of the data received and to outline the regulatory action on the active ingredient imazethapyr. This document reflects input from specialists within Agriculture and Agri-Food Canada and from key departmental advisors. Based on the review of available information and in consideration of their agronomic benefits, a regulatory decision has been made to grant registration for the technical active ingredient imazethapyr and the end-use product Pursuit®.

This document is published under the authority of the Interdepartmental Executive Committee on Pest Management which represents the departments of Agriculture and Agri-Food, Health, Environment, and Natural Resources.

(publié aussi en français)

March 30, 1994

This document is published by the Submission Management and Information Division, Pest Management Regulatory Agency. For further information, please contact:

Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2250 Riverside Drive
A.L. 6606D1
Ottawa, Ontario K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca
Facsimile: (613) 736-3798
Information Service:
1-800-267-6315 or (613) 736-3799

Government of Canada Gouvernement du Canada

Canada

Table of Contents

1.0 Summary

The purpose of this document is to announce the decision that was taken on the regulatory status of the technical active ingredient imazethapyr and its end-use product Pursuit®. The document also serves as a communication tool used to provide a summary of the review of data submitted in support of the registration of these products.

Environment Canada and Health Canada assessed the risks associated with the use of Pursuit® while the performance and value of use was assessed by officials of the Plant Industry Directorate, Agriculture and Agri-Food Canada.

The risk assessments carried out by Health Canada indicated that when Pursuit® is used according to label directions, the margin of safety (MOS) for occupational exposure is considered to be acceptable. Dietary exposure to residues of imazethapyr at levels which may appear in harvested soybeans (i.e., below or equal to 0.1 ppm), will not pose any hazard to consumers.

Imazethapyr is not expected to pose an acute or chronic hazard to birds and mammals. It exhibits low toxicity to *Daphnia*, bees, earthworms and soil microorganisms. Although the product was shown to have moderate to high persistence in soil studies, field studies indicated that the chemical did not leach, which tempered the concerns around potential ground water contamination, usually associated with persistent herbicides.

In aquatic/sediment systems, photodegradation would be the only route of dissipation of imazethapyr. The active ingredient was not readily hydrolysed or biotransformed in water or sediment.

Imazethapyr is not toxic to the green algae *Selenastrum capricornutum*. Data were provided on one aquatic vascular species, the duckweed *lemna gibba*. Imazethapyr appears to be very toxic to this floating aquatic species, with a risk factor of 6.63 ($EEC/EC_{50} = 67/10.1$).

Pursuit® is highly toxic to many terrestrial plants and has the potential to indirectly impair wildlife through destruction of habitat food (plants and invertebrates that feed on them) and cover. This indirect effect could occur in instances where the active ingredient would reach non-target sites in amounts sufficient enough to cause permanent damage to the existing flora. Events such as these are more likely to occur under circumstances favouring drift or run-off. To avoid the occurrence of such events, a 15 meter unsprayed zone around important wildlife habitat (such as shelterbelts, hedgerows, wetlands, woodlots, vegetated ditchbanks and other cover on the edges of fields) along with a contra-indication for aerial application have been put on the product label.

Imazethapyr was shown to be an effective herbicide for the control of various broadleaved weeds and grass weeds in soybeans. Pursuit® can be applied either early pre-plant, pre-emergence or post-emergence to the crop. The application of Pursuit® will leave some levels of residues in the soil for the following growing season, which will result in limiting the choice of rotational crops. Crop rotational guidelines have been included on the label to address this concern.

Based on the risk factors and benefits associated with the use of imazethapyr, the decision was taken to grant this herbicide a full registration until 31 December 1995.

2.0 Pesticide Name and Properties

2.1 Pesticide name

Common name: imazethapyr

Chemical name:

CA: 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1H-imidazol-2-yl]-5-ethyl-3-pyridinecarboxylic acid

IUPAC: 5-ethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)nicotinic acid

Trade name: Pursuit®

CAS Registry No: 081335-77-5

2.2 Physical and chemical properties:

2.2.1 Technical Product

Empirical formula:	$C_{15}H_{19}N_3O_3$
Molecular Weight:	289.3
Physical form:	Solid
Colour:	Off-white to tan
Odour:	slightly pungent
Melting Point:	169-173°C
Vapour Pressure:	< 1 X 10^{-7} mm Hg @ 60°C
Octanol/water partition coefficient (K_{ow}):	11 at pH 5 31 at pH 7 16 at pH 9
Water solubility:	1415 mg/L at 25°C

Solubility in various solvents:

Solvent	**Solubility (ppm)**
Acetone	4.82
Dimethyl Sulfoxide	42.25
Heptane	0.09
Methanol	10.50
Methylene chloride	18.48
2-propanol	1.73
Toluene	0.50

Stability: Both the technical product and end-use product are stable at room temperature.

2.2.2 Formulated Product:

Product name:	Pursuit® herbicide
Guarantee:	240 g/L
Flammability:	not applicable
Storage Stability:	52 weeks @ 25ºC
	26 weeks @ 37ºC

3.0 Development and Use History

Imazethapyr is manufactured by the American Cyanamid Company. Cyanamid Canada Inc. holds the registration in Canada for both imazethapyr and Pursuit®.

Field testing with Pursuit® began in 1983 primarily in Ontario. The greatest number of trials were conducted in 1986-1989. The original submission for review was received by Agriculture and Agri-Food Canada in 1987. Imazethapyr is presently registered in Canada, the United States, Argentina, Brazil and many European countries.

4.0 Biological Properties

Imazethapyr is one in a new class of chemicals known as the imidazolinones. The imidazolinones have a very specific mode of action whereby they inhibit a single plant enzyme system that does not occur in animals. Pursuit® is absorbed through roots and foliage and is translocated in both xylem and phloem and thereby accumulates in plant growing points (meristems). The application of this herbicide, whether it be pre-plant, pre-emergence or post-emergence, has been shown to provide broad spectrum weed control without causing notable injury to the host crop soybeans. The tolerance of soybeans to imazethapyr is due to rapid degradation of the parent acid to non-toxic metabolites.

5.0 Regulatory Position and Rationale

Based on the results of the acute oral, dermal and inhalation toxicity studies, imazethapyr and its formulated product Pursuit® are practically non-toxic to rats and/or rabbits. A battery of subchronic and chronic toxicity tests performed on laboratory animals (rodents and non-rodents), failed to demonstrate any teratogenic, carcinogenic or mutagenic effects. Nor did it reveal any adverse effects on the reproductive potential. The data indicates that when imazethapyr is used on soybeans in accordance with label directions, residues at harvest are not considered to pose a hazard to

consumers. The supporting data also indicates that the use of Pursuit® does not present a hazard to the users.

Imazethapyr, is not expected to pose an acute or chronic hazard to birds and mammals and has low toxicity to bees, earthworms and soil microorganisms. However, imazethapyr, having the attribute of being toxic at low doses to many terrestrial vascular plants and to the only aquatic vascular species tested, has the potential of indirectly impairing wildlife through modification of their habitat. This indirect effect would be the result of changes made to the diversity and abundance of plant species around sprayed fields. This would occur when the herbicide is transported to non-target areas (through overspray, drift or run-off) in amounts sufficient enough to trigger permanent phytotoxic responses by plants. This could then ultimately result in reducing cover and depleting the food source used by wildlife and invertebrates.

This potential to affect off-target plants, combined with the moderate to high persistence of imazethapyr in both soil and water/sediment systems, has led to the inclusion of a 15 m buffer zone statement on the label. It reads as follows: "Overspray or drift to important wildlife habitats such as shelterbelts, hedgerows, wetlands, woodlots, vegetated ditchbanks and other cover on the edges of fields should be avoided. Leave a 15 m buffer zone between the last spray swath and the edge of any of these habitats." In addition, a clear statement contra-indicating aerial application will be added to the label.

It was concluded that the use of Pursuit®, while being efficacious at controlling different weeds, would not present an unacceptable risk to the user nor to the environment when used according to label instructions.

6.0 Use Summary and Benefits

6.1 Description of Market

The Canadian production of soybeans is concentrated in Southern Ontario and predominately in the three counties of Essex, Kent and Lambton[1]. Ontario production accounts for 96% of the national harvest while the remainder is in Quebec. The area seeded to soybeans has increased steadily over the last decade, going from 385 thousand hectares/year in 1982-86 to 644 thousand hectares/year in 1992. This accounts for a total net increase of 67% over eleven years[2].

The return of soybean production to the Canadian agriculture was estimated, using average price/tonne figures for the 1991-92 crop-year. Soybean production accounted for $322

[1] *Deloitte Haskins & Sells, 1982. Benefit assessment of Pursuit® in Ontario Soybean Production*

[2] *Agriculture and Agri-Food Canada, Grains and Oilseeds Branch. Fats and Oils in Canada. Annual Review 1992.*

million in Canadian farm cash receipt. Soybeans are mostly processed and sold as either soybean meal or oil.

6.2 Pest Problem

Chandler *et al*. in Stemeroff *et al*. (1988), estimated that despite weed control efforts (i.e., use of mechanical and/or chemical means of control), crop losses due to weeds could amount to approximately 9% in Canada[3].

A recent study conducted by Stemeroff *et al*. (1988), also indicated that every dollar spent on herbicide use in soybean production usually results in a $2.60 return (i.e., benefit/cost ratio of 2.6/1)[3].

6.3 Description of Proposed Use

Pursuit® is a systemic, selective herbicide for the control of various broadleaved and grass weeds in soybeans in Eastern Canada only. Efficacy trials conducted in the major use areas have shown that the product, when used at a rate of 75-100 g a.i./ha and according to label directions, will control or suppress the labelled weed species.

Pursuit® can be applied early pre-plant (up to 30 days before planting), which allows for its use in conventional, reduced tillage or no-till soybeans. It can also be used as a pre-emergence or early post-emergence treatment. A list of the accepted weed claims at these different application times is presented in Table 1. It should be noticed however, that as with most soil-applied herbicides, pre-emergence applications of Pursuit® require adequate moisture to provide acceptable weed control.

[3] *Stemeroff et al. 1988. Economics of Herbicide Use on Corn and Soybeans in Ontario. Weed Technology. Volume 2. 466-472.*

Table 1. Weed Spectrum for Pursuit® Herbicide

Weed Species	Time of Herbicide Application			
	Early Pre-Plant	**Early pre-plant to emerged weeds**	**Pre-emergence to the crop**	**Post-emergence to the crop**
barnyard grass	C	S	C	C
cocklebur	-	C	-	C
common ragweed	C	S	C	C
eastern black nightshade	S	C	S	C
green foxtail	C	C	C	C
lady's thumb	C*	-	C*	-
lamb's-quarters	C	S	C	S
large crabgrass	-	-	-	S*
old witchgrass	C*	-	C*	-
proso millet	S	S	S	S
redroot pigweed	C	C	C	C
smartweed	C*	-	C*	-
velvetleaf	C	C	C	C
wild buckwheat	-	S	-	S
wild mustard	C	C	C	C
yellow foxtail	C	C	C	C

C= controlled
S= suppressed
* = temporary registration pending submission and review of additional confirmatory efficacy data.

Pursuit® can also be tank-mixed with other herbicides to broaden the spectrum of weeds controlled. The following list outlines the accepted tank-mixtures and their respective time of application:

Tank-mix	**Application time**
Pursuit®+ glyphosate (ROUNDUP®)	Early pre-plant to emerged weeds
Pursuit®+ paraquat (GRAMOXONE®)	Early pre-plant to emerged weeds
Pursuit®+ linuron (AFOLAN®, LOROX®)	Pre-emergence

Pursuit®+ metribuzin (SENCOR®, LEXONE®) Pre-emergence

6.4 Crop Rotation Intervals

Due to the carryover potential of imazethapyr, minimum crop rotation intervals should be respected. Observance of these intervals is very important to avoid potential for injury to certain succeeding crops. Rotational crop studies conducted in Eastern Canada indicated that soybeans, field corn, spring barley and spring wheat could be planted the season following a Pursuit® application. These trials also showed that winter wheat could be planted the same season as the Pursuit® application but not earlier than 120 days after the treatment date.

6.5 Pre-Harvest and Grazing Intervals

Crops that have been sprayed with imazethapyr should never be grazed nor should foliage from treated crop be fed to livestock. The residue data submitted supports a 100 day interval between Pursuit® application and harvest.

7.0 Toxicology and Occupational Exposure (Health Canada)

Evaluation

The technical material has a purity of 90-95% and all major impurities have been identified and are related to the active material. The major toxicity studies used technical material containing 91-92% purity.

7.1 Toxicology

Acute Toxicity – Technical

Acute oral toxicity studies conducted in female CF-1 mice, male and female CD strain rats and female New Zealand White rabbits with technical grade imazethapyr (91.2% purity) using 0.5% carboxy methyl cellulose as a suspending agent indicated that the test material was practically non-toxic with an acute oral LD_{50} greater than 5000 mg/kg of body weight in all three species tested. An acute toxicity study with CL 288,500 (1-hydroxyethyl derivative of imazethapyr, identified as a major plant metabolite) when administered orally by gavage to male and female CHRCD rats indicated an acute oral LD_{50} greater than 5000 mg/kg b.w.

Technical imazethapyr is virtually non-toxic to rabbits by the dermal route (LD_{50} > 2000 mg/kg b.w.). It is mildly irritating to the rabbit eye and minimally irritating to abraded rabbit skin and does not produce a sensitizing response in guinea pigs. It does not appear to be acutely toxic by the inhalation route (LC_{50} >3.27 mg/L).

Acute toxicity - Pursuit Formulated Product

Studies performed on 3 formulations with 22-23.7% imazethapyr and similar in formulation to that intended for registration showed the formulations to be virtually non-toxic via the oral route in rats and via the dermal route in rabbits, practically non-irritating to the rabbit eye and minimally irritating to rabbit skin. It is not acutely toxic by the inhalation route in rats and does not produce a sensitizing reaction in guinea pigs.

Short-Term Toxicity

Rat

A 13-week study in CD rats with the technical material (purity 92.2%) at dietary levels of 0, 1000, 5000 and 10,000 ppm indicated a no observed effect level (NOEL) at the mid-dose - 5000 ppm level (equivalent to an actual intake of 410 mg/kg b.w./day) due to an increased incidence of uterine endometrial cysts noted in the 10,000 ppm treated females (7/20, 35%) when compared to both the concurrent (0/20, 0%) and historical control incidence (0/20 - 5/20, 0% - 25%).

Dog

Administration of technical grade imazethapyr (91.2% purity) to beagle dogs for a period of 91 days at dietary levels of 0, 1000, 5000 and 10,000 ppm demonstrated a NOEL of 5000 ppm (equivalent to approximately 125 mg/kg b.w./day) based on a 30% decrease in mean total weight gain over the feeding period as recorded in the 10,000 ppm treated females.

Rabbit

A 21-day dermal study in New Zealand White Rabbits with the technical material (91% pure) at 0, 50, 200 and 1000 mg/kg b.w./day failed to indicate any signs of toxicity due to treatment. The NOEL was set at greater than or equal to 1000 mg/kg b.w./day. A 21-day dermal study in New Zealand White Rabbits with a 22% active ingredient formulation similar to the formulation intended for registration at 0, 250, 500 and 1000 mg/kg b.w./day did not show any signs of toxicity which could be attributed to the test material. The NOEL was set at greater than or equal to 1000 mg/kg b.w./day. There was no sign of dermal irritation in either of the 21-day dermal studies.

Teratogenicity

Rat

Treatment of pregnant CD(SD)BR rats orally by gavage with technical imazethapyr (91.2% purity) in corn oil at dose levels of 0, 125, 375 and 1125 mg/kg b.w./day during days 6 to 15 of gestation failed to elicit any evidence of teratogenic potential.

The NOEL for maternal toxicity was set at 375 mg/kg b.w./day based on treatment-related clinical signs, manifest at 1125 mg/kg b.w./day as excess salivation, urine-stained abdominal fur, red exudate around mouth and/or nose, alopecia, rales, ungroomed coat, red exudate around the vagina and decreased motor activity. Marginally decreased weight gain relative to the controls was also noted at the high dose level during the dosing period. With regard to embryotoxicity, a slight non-significant increase in the incidence of resorptions at 1125 mg/kg b.w./day level was primarily attributed to a single dam which resorbed 14 out of a total of 15 conceptuses.

A conservative NOEL for fetotoxicity was indicated at the mid-dose level of 375 mg/kg b.w./day based on marginal (not statistically significant) differences at 1125 mg/kg b.w./day relative to the controls. These differences were described as decreased mean fetal litter weights, slight increase in the percentage of fetuses and litters with renal pelvic cavitation (within range of historical controls) and minor delays in skeletal development expressed as a decrease in the mean number of ossification sites per litter.

Rabbit

Artificially inseminated New Zealand White rabbits treated orally by gavage with the test material (91.2% purity) at 0(vehicle, 0.75% carboxy methyl cellulose), 100, 300 and 1000 mg/kg b.w./day on days 6 through 18 of gestation indicated a NOEL for maternal toxicity at 300 mg/kg b.w./day. Treatment-related toxicity was manifest at the high-dose level as mortality, a high abortion rate, increased incidence and frequency of rabbits with feces of abnormal consistency, significantly depressed body weight gain and food intake as well as macroscopic alterations described as ulcerations in the mucosal layer of the stomach and gall bladder.

Despite the greater number of abortions at 1000 mg/kg b.w./day, there was no definitive indication of embryotoxic potential at any of the dose levels investigated. With regard to fetotoxicity, slightly decreased average fetal body weights at the high dose level could not conclusively be attributable to treatment.

A conservative NOEL for developmental toxicity was indicated at the low dose level of 100 mg/kg b.w./day based on the slightly higher incidence of intranasals reported at the mid-dose level and the single occurrence of a malformed fetus also at the mid-dose level. Although a

strong likelihood exists that such changes were of background variability and/or congenital origin, especially in the absence of similar findings at the high-dose level - their significance may be judged to be equivocal in view of the fewer number of fetuses and litters examined at the high-dose level as a result of maternal death and abortion.

Reproduction

A two-generation (two-litter) reproduction study in Sprague Dawley rats fed the test material (91.2% purity) at dietary levels of 0, 1000, 5000 and 10,000 ppm failed to reveal any adverse effects of treatment on reproductive potential. A NOEL for non-reproductive parameters was indicated at 5000 ppm (equivalent to approximately 427 mg/kg b.w./day, actual intake) as a result of significantly decreased pup weights on day 21 of lactation in the F1a litter males and females and in the F2a litter males of the 10,000 ppm level when compared to the corresponding controls.

Long-Term Toxicity

Dog

Administration of the technical test material, (91.6% purity), to beagle dogs at dietary concentrations of 0, 1000, 5000 and 10,000 ppm for 52 weeks resulted in a No Observed Adverse Effect Level (NOAEL) of 5000 ppm (equivalent to 187 mg/kg b.w./day) based on a treatment related decrease in erythrocyte parameters in the high- and mid-dose treated females in the absence of any associated pathological changes. Macroscopic changes noted in four of six female dogs treated at the 10,000 ppm level were related to discoloration of the spleen which correlated microscopically with areas of capsular thickening characterized by fibrosis, pigmented macrophages and inflammatory cells. (Discoloration of the spleen was observed in a single female control dog but not in the low or mid-dose treated groups). A focal increase in hepato-portal fibrous tissue in two female high dose treated dogs, in the absence of similar findings in the controls was interpreted as being of questionable toxicological significance.

Mouse

Long term dosing of the technical test material (91.2% purity) to CD-1 mice at dietary levels of 0, 1000, 5000, and 10,000 ppm for up to 78 weeks indicated a NOEL for in-life parameters of 5000 ppm (equivalent to approximately 920 mg/kg b.w./day, actual intake) based on significantly decreased lymphocyte values in females after treatment at 10,000 ppm for 78 weeks and depressed weight gain in the high-dose treated mice of both sexes (13% and 24% for the males and females respectively) when compared to the corresponding controls. Treatment with the test material at levels as high as 10,000 ppm equivalent to 1% of the diet failed to reveal any strong evidence which could be suggestive of oncogenic potential.

Rat

Administration of the test material (91.2% purity) to Sprague Dawley rats for up to 24 months at dietary levels of 0, 1000, 5000 and 10,000 ppm revealed a NOEL for in-life parameters of 1000 ppm (equivalent to approximately 50 mg/kg b.w./day, actual intake) based on depressed body weight gain in the 5000 and 10,000 ppm treated female groups (4% and 6% respectively after 26 weeks; 6% and 7%, respectively after 52 weeks of treatment when compared to the controls). There was no evidence of any treatment-related neoplastic potential at dietary levels as high as 10,000 ppm.

Mutagenicity

A series of mutagenicity assays did not indicate any potential for microbial point mutation, chromosomal aberration (*in vivo* rat cytogenetics), evidence of DNA damage (rat hepatocyte) or dominant lethality in the rat. The test material under conditions of non-activation was considered positive for inducing chromosome aberrations and point mutations in CHO cells (positive evidence for induction of point mutations was questionable). The test material was, however, negative in both assays in the presence of metabolic activation and based on the results of all the mutagenicity assays performed it is unlikely that the test material would cause point mutations or chromosome aberrations *in vivo*. [It has been postulated that the addition of imazethapyr to tissue culture medium may cause effects on both the pH and the osmolality which may result in the generation of nonphysiologic conditions which in turn have the potential to cause an adverse effect on the outcome of certain *in vitro* assays].

Metabolism

Male Sprague Dawley rats administered a single oral dose of 5.7 mg/kg b.w. ^{14}C-labelled test material, eliminated 97% of the dose within 24 hours post-dosing in the urine (92%) and feces (5%). No metabolites of imazethapyr other than the unchanged parent were found in the urine. Tissue residue levels after 48 hours post-dosing were found to be negligible (<0.01 ppm).

Two male and 2 female Sprague Dawley rats were administered a single oral dose of approximately 1000 mg/kg b.w. ^{14}C-labelled test material. Of these, one male and one female rat received single oral daily doses of unlabelled material at approximately 1000 mg/kg b.w./day by gavage for 3 consecutive days prior to dosage of ^{14}C-labelled material. Both groups excreted over 97% of the administered dose within 24 hours post-dosing in the urine (87-94%) and in the feces (5-10%). The administered dose was completely eliminated in the urine and feces within 96 hours. [Although the author states that a net of about 2% of the orally administered dose is excreted as CL 288,511, the major metabolite found in soybean plants; these conclusions, under the conditions and limitations in the experimental design of the present study could **not** be substantiated].

Residue studies were conducted in lactating goats treated daily with ^{14}C-labelled test material by gelatin capsule at a dose equivalent to 0, 0.25 ppm or 1.25 ppm in the diet for 7 consecutive days. Tissue analysis failed to reveal any detectable imazethapyr associated radioactive residues (sensitivity of analytical method:
0.01 ppm in milk and 0.05 ppm in blood and other tissues).

Conclusions

A comprehensive and complete battery of mammalian toxicity studies conducted with imazethapyr has failed to demonstrate any deleterious effects on reproductive function in the rat, or reveal any potential for teratogenic activity as investigated in both a rodent and non-rodent species. Long-term studies conducted in the mouse and rat at dietary levels as high as 10,000 ppm did not reveal any evidence of treatment-related carcinogenic potential.

The most sensitive species would appear to be the rat under conditions of chronic dietary test material administration. A NOEL of 1000 ppm (49 mg/kg b.w./day, actual intake) was indicated based on depressed body weight gains at the higher dose levels.

7.2 Food Exposure

a) Acceptable Daily Intake (ADI)

An ADI of 0.5 mg/kg b.w./day has been estimated based on a NOEL of 50 mg/kg b.w./day in a 24-month rat study and use of a 100-fold safety factor.

b) Residue Levels

Metabolism studies available indicate that the principal route of degradation of imazethapyr in plants involves hydroxylation and glucoside conjugation of the ethyl group on the pyridine ring. In soybean plants, imazethapyr appears to be readily metabolized into CL 288,511, (a hydroxyethyl analog of the parent compound), the glucoside conjugate of CL 288,511 and several unidentified metabolites. Four weeks after the application of ^{14}C-labelled imazethapyr, 88-91% of the total radioactive residues in soybean plants were extractable, of which only 0.2-1.4% were identified to be the parent compound, 8-13% CL 288,511, 36-52% the glucoside conjugate of CL 288,511 and 30-40% unidentified metabolites. The distribution of these radioactive residues is, however, very different in treated straw samples at harvest (20 weeks after the treatment). Only 67-83% of the total radioactive residues were extractable and this consisted of 37-42% metabolite CL 288,511 and 48-55% unidentified compounds. Only insignificant amounts of glucoside conjugate of CL 288,511 and no parent compound were detected in these samples.

In mature soybean seeds, the identification of metabolites was not attempted due to low concentration and low extractability (only 29-33%) of the total radioactive residues in harvested seeds. From the metabolism studies available results indicated that total radioactive residues in mature seeds are approximately 0.02 ppm (sampled 20 weeks after treatment) when soybean plants were treated at rates equivalent to 3 times the proposed application rate. These total radioactive residues would likely be comprised of the metabolite CL 288,511 and unidentified metabolites assuming that the metabolic profiles in soybean straw reflect those in the seeds. Results also indicated that the possibility of radioactive residues incorporated into oil component of the soybean seeds is very low.

Radiolabel feeding studies in the lactating goat and laying hen indicated that feeding with ^{14}C-imazethapyr at levels up to 1.25 ppm and 2.5 ppm respectively did not result in detectable total radioactive terminal residues in meat, milk, eggs or poultry products. These feeding levels are much higher than the total radioactive terminal residues detected in soybean forage (0.36-0.71 ppm 4 weeks after treatment), straw (0.24-0.34 ppm) or seeds (0.02 ppm) at 3 times the proposed rate and it is therefore not expected that the feeding of treated soybean products would result in significant residues in meat, milk, eggs or poultry products. The current label prohibits the feeding of treated forages or straw and the grazing in treated fields.

Analytical methods (M-1586 and M-1847) are available to measure only the parent compound in soybean samples. According to plant metabolism data, this method may be able to quantitate approximately 1% of the residues in young soybean plants and smaller portions, if any, of the terminal residues in whole soybean seed and straw samples taken at harvest.

Residue data generated using the method M-1586 have shown no detectable levels (<0.1 ppm) of the parent compound imazethapyr in mature soybean seeds 85-177 days after being treated at 105-280 g acid equivalent/ha. No detectable residue levels were also reported in 100-168 day straw samples and in 14-60 day plant samples. The proposed label recommended an application rate of 100 g acid equivalent/ha and a pre-harvest interval of 100 days on soybeans.

c) Dietary Risk Assessment

Since the available analytical methods would only measure a minimum and uncertain portion of the terminal residues in harvested soybean seeds, the actual residue levels in soybean oil could only be estimated from the data reported in radioactive residue studies. At 3 times the proposed application rate, approximately 0.02 ppm total terminal radioactive residues were detected in harvested seeds. The theoretical daily intake (TDI) calculated from 0.02 ppm in soybean oil would be 0.000006 mg/kg b.w./day which is approximately 0.001% of the estimated ADI. Even if a residue level of 0.1 ppm is

detected in soybean oil, the TDI would be 0.00003 mg/kg b.w./day and still less than 0.01% of the estimated ADI of 0.5 mg/kg b.w./day.

7.3 Occupational Exposure and Safety Assessment

a) Occupational Exposure

An exposure study on Imazethapyr (Pursuit®) was not submitted. Instead, the registrant submitted an exposure study conducted with imazamethabenz (Assert®), a structural analog of imazethapyr, to serve as a surrogate study. The Health Protection Branch, Health Canada, agreed to accept the surrogate study based on a similarity in the product chemistry, application equipment and crop type. Furthermore, both formulations are liquids and the application rate used in the Assert® study was higher than the maximum recommended rate for Pursuit®.

The exposure study was conducted with Saskatchewan farmers applying Assert® 300 LC with ground boom equipment. Thirteen farmers were monitored during a full day's work (4-7 hours). Their activities included mixing, loading and spraying (45-71 hectares). Dermal deposition and respiratory exposure as well as urinary metabolites were measured. The farmers used a range of application equipment (closed cab tractors versus open cab tractors, open versus closed mixing systems) and a range of protective clothing (protective gloves during mixing/loading for some loads, protective gloves during mixing/loading for all loads and protective gloves during mixing/loading and spraying). It was assumed that this mixture of protective clothing use is representative of the situation in Ontario which is the major soybean growing area.

Based on the dermal deposition and respiratory data from the Assert® study, exposure was estimated for a typical 70-kg farmer using the maximum recommended Canadian label rate for Pursuit® of 100 g active ingredient/ha and treating 120 acres (48 ha) in one day. The biological monitoring data was not used since the metabolism of the two products is different. The daily exposure estimate for a farmer using an open cab tractor and wearing long sleeves and protective gloves would be 1.72 (0.02-3.2) mg/kg b.w./day. If a combination of closed or open cab tractors and open or closed mixing systems were used (as in the Assert® study), the daily exposure estimate for a farmer wearing long sleeves and protective gloves would be 0.34 (0.003-3.2) mg/kg b.w./day. However, officials with the Ontario Ministry of Agriculture and Food estimate that less than half of Ontario soybean farmers would use closed cab tractors for spraying. The large variability in exposure values appears to be dependent on the different equipment, i.e., closed versus open tractors; different protective equipment, glove usage; and on individual worker care in handling the chemical. As no dermal absorption data were submitted for imazethapyr, 100% absorption was assumed.

Limitations in study design (i.e., lack of exposure monitoring during cleanup and repair and lack of adequate recovery or storage stability data for the hand exposure data) could lead to an underestimate of exposure.

b) Safety Assessment

The safety data base for imazethapyr and the formulation Pursuit® indicates that Pursuit® does not present an acute toxicity hazard to users. There is also no indication of potential teratogenic, reproductive or carcinogenic hazards.

The occupational risk assessment is therefore based on general toxic effects observed after repeat oral exposure to imazethapyr. The lowest NOEL for systemic adverse effects was 49 mg/kg b.w./day found in the 24-month rat feeding study based on depressed body weight gains. This NOEL was used for the purpose of calculating MOS for users. The theoretical margins of safety for a typical 70 kg farmer are presented in the following table.

Margins of Safety for Farmer[1] using Pursuit®

Scenario	**Margin of Safety[2]**
open cab tractor, protective gloves, long sleeves (n=2)	28.5 (15-2450)
combination of closed and open cab tractors, protective gloves in an inconsistent manner, long sleeves (n=12)	144 (15-16333)

[1] *Based on exposure estimates from Assert® exposure study and assuming a 70 kg farmer applying Pursuit® at the maximum recommended label rate to 48 hectares in one day.*

[2] *Based on a NOEL of 49 mg/kg b.w./day for depressed body weight gains in the 24-month rat study.*

While the open cab tractor is a more typical scenario since less than half of Ontario farmers are assumed to have closed cab tractors, there are obvious limitations to conducting a safety assessment based on only two workers. However, the MOS calculated for the combination scenario (10 closed cab, 2 open cab and a mixture of closed and open mixing systems) is likely larger than that based on the exposure to a typical soybean farmer in Ontario who would use an open cab tractor and an open mixing system. Furthermore, limitations in the study design of the exposure study are likely to

lead to an underestimate of exposure, and consequently somewhat of an overestimate of safety.

However, taking into consideration all the other factors affecting this safety assessment, the Health Protection Branch, Health Canada, considers the MOS to be acceptable even for the open cab tractor scenario.

The factors considered are the following:

1) 100% dermal absorption has been assumed, a likely overestimate

2) the NOEL for which the safety assessment is based is from a chronic 24-month feeding study and occupational exposure is intermittent (one application/season), short-term and mostly dermal

3) short-term, repeat exposure dermal studies in rabbits have not revealed any toxicity at doses up to 1000 mg/kg b.w./day

4) the MOS based on the larger sample size for the exposure study, albeit with mostly closed cab tractors, is considerably higher than that calculated based on 2 workers using open cabs.

8.0 Environmental Aspects (Environment Canada)

8.1 Summary

Environment Canada's review of imazethapyr, is with reference to the proposed use as a pre-emergence or as a post-emergence spray to control broadleaf weeds and grasses in soybean.

In terrestrial systems, imazethapyr would be persistent: it would not readily volatilize, photodegrade or biotransform. Laboratory studies indicated that it has low adsorption to soils and was highly mobile. Field studies, however, indicated that the chemical did not leach. It has low toxicity to bees, earthworms, and soil microorganisms.

In aquatic/sediment systems, photodegradation would be the only route of dissipation of imazethapyr. The chemical was not readily hydrolyzed or biotransformed in water or sediment. It has low toxicity to *Daphnia*.

The concern about this herbicide is its high persistence in soil and water/sediment, and its potential mobility in soils. However, the results of the field studies have provided some assurance that, at the proposed application rate of 0.10 kg a.i./ha, the chemical would not

contaminate groundwater through leaching. Aerial application, however, could contaminate water bodies where the herbicide could persist in water and sediment.

Imazethapyr is not expected to pose an acute and chronic hazard to birds and mammals. However imazethapyr is toxic to many terrestrial vascular plants and has, therefore, the potential to indirectly impair wildlife through destruction of habitat (food and cover) or reduction of invertebrates that live on plants. Imazethapyr is not toxic to the green algae *Selenastrum capricornutum*. Information provided on the toxicity to *lemna gibba* demonstrated that imazethapyr is highly toxic to this floating aquatic vascular species. Mitigation measures are required for the full registration (i.e., no aerial spray and a 15 meter buffer zone around aquatic and terrestrial areas important to wildlife).

8.2 Environmental Chemistry and Fate

Physicochemical characteristics

a) Vapour pressure

The vapour pressure of imazethapyr determined by the gas saturation method was less than 1×10^{-7} mm Hg (torr) (1.3×10^{-5} Pa) at 60ºC. This vapour pressure indicated that the herbicide would not be volatile if applied to soil or plant surfaces. Volatilization would not be a route of dissipation of the herbicide in the environment.

b) Octanol-water partition coefficient

The octanol-water partition coefficient (K_{ow}) values were calculated to be 11 at pH 5, 31 at pH 7 and 16 at pH 9. These low K_{ow} values suggested that the herbicide has a low potential to bioaccumulate in animal fat or aquatic biota.

c) Water solubility

The water solubility of imazethapyr was high (1415 mg/L in distilled water and 3685 mg/L in water buffered at pH 3.9, both at 25/C). Considering the very high water solubility and the low vapour pressure of this herbicide, Henry's Law Constant (air/water distribution ratio) was calculated to be 2.7×10^{-11} $atm.m^3$ mol^{-1} indicating a high potential for the chemical to remain in water rather than volatilize into the air.

d) Dissociation constant

Imazethapyr is an acid (pKa of 3.9).

Transformation

a) Hydrolysis

Laboratory data indicated that hydrolysis would not be a major route of dissipation of this herbicide in the environment. No degradation was observed in treated pond water or buffered water by day 30. By this time, 99% of the applied radioactivity was still present as the parent chemical.

b) Phototransformation

Results of tests in aqueous media, indicated that phototransformation has the potential to be a major route of dissipation of this herbicide in the aquatic environment. When exposed to simulated sunlight, the chemical phototransformed in distilled and in buffered water. DT_{50}'s were as follows: 45.8 h in distilled water; 43.5 h, 49.8 h and 56.8 h in water buffered at pH 5, 7 and 9, respectively.

Results of tests on sandy loam soil indicated that photodegradation on the soil surface would not be a major route of dissipation of imazethapyr in the terrestrial environment. When treated soil was exposed to simulated sunlight continuously for 28 days, there was only 13% transformation of the chemical. DT_{50} was extrapolated to be 126 days.

c) Biotransformation

Biotransformation studies showed that imazethapyr was persistent in soils. Under aerobic soil conditions (22/C) in the laboratory, imazethapyr did not readily biotransform (DT_{50} 29-37 months).

Laboratory studies indicated that imazethapyr did not transform to any degree in soil under anaerobic conditions. Therefore anaerobic transformation in soil would not be a likely route of dissipation of the chemical in the environment. After two months of anaerobic incubation, about 94% of the parent compound still remained in the system. Biotransformation will not be a major route of dissipation of the chemical in both aerobic and anaerobic soils.

Studies in the laboratory showed that imazethapyr was persistent (<1% decrease after a month) in natural pond water under aerobic conditions. Laboratory data also showed that imazethapyr was persistent in an aquatic anaerobic (water/sediment) system. Only about 3-5% of the applied active ingredient was transformed after eight months. Biotransformation is thus not an important mode of dissipation of the chemical in the aquatic environment under both aerobic and anaerobic conditions.

Mobility (laboratory data)

a) Adsorption/desorption

Adsorption/desorption studies with four soil types showed that imazethapyr had low K_{oc} values (19.8 -83.9) which suggested that little adsorption would be expected for any of the soils. There was no correlation between the organic matter content of the soils and the K_{oc} values. The small adsorption (K_{oc}) values and the high amount of the chemical that could desorb from soils (52 - 69% of adsorbed radioactivity) indicated that imazethapyr has very high mobility and consequently a high potential to leach.

b) Soil thin layer chromatography

The mobility of radiolabeled imazethapyr was determined in eight different soil types by thin layer chromatography (TLC). The results indicated that imazethapyr was in mobility class 4 or 5 (high mobility) for all soils except a silt loam from Wisconsin where the mobility was with class 3 compounds (moderate mobility).

Field dissipation

Field soil dissipation studies

Field studies conducted in Ontario indicated that imazethapyr may be of moderate to high persistence in silt loam soils (DT_{50}'s ranged from about 2-8 months). About 21-26% of the applied imazethapyr could be carried over when the herbicide was applied pre-emergence but no herbicide was detected at the end of the second season (September). Post-emergence application resulted in no carry-over; however, the high variability in the data did not provide a good indication of the behaviour of the herbicide in soil when applied post-emergence. Field studies conducted in the U.S. also indicated that imazethapyr applied pre- or post-emergence was of moderate to high persistence in silt loam and loam soils (DT_{50}'s ranged from 2-10 months) and the results also indicated that carryover in U.S. soils could potentially be high as well.

Although, laboratory data on imazethapyr suggest that there is a high potential for the herbicide to leach and thus contaminate groundwater, leaching of the herbicide under field conditions was slight. In all the field studies most of the herbicide was found in the 0-7.5 cm soil layer. However, towards the end of the first season, varying levels of the herbicide were detected in the 7.5-15 cm layer: 0-14% of day 0 concentration in the pre-emergence studies, 0-21% in the post-emergence studies. The herbicide was not detected in the 15-22.5 cm soil layer.

8.3 Environmental Toxicology

a) Wild birds

Wild birds are most likely to be exposed to imazethapyr by direct overspray or spray drift, or by consumption of sprayed vegetation or consumption of contaminated prey. Since Pursuit® can be applied post-emergence and it takes as long as 2-4 weeks to kill susceptible plants, residues may be consumed for some time by birds. Southwestern Ontario is a zone with a rich bird population, some of the species in decline due largely to agriculture, urbanization and industry. Three species are classified as endangered, the Kirtland's Warbler, Peregrine Falcon and Piping Plover; two species are threatened, the Henslow's Sparrow and Loggerhead Shrike.

Acute oral and dietary toxicity studies with imazethapyr as well as the avian reproduction study indicated a low toxicity to the Bobwhite Quail and Mallard Duck. The data from the LD_{50} and LC_{50} studies indicate that imazethapyr was not toxic to Bobwhite Quail and Mallard Duck. In both species the acute LD_{50} of the technical product exceeded 2150 mg ai/kg b.w. No mortality was reported. The 8-day dietary studies exceeded 5000 mg ai/kg b.w. Two mortalities for the Bobwhite Quail and one mortality for the Mallard Duck were reported but they did not seem to have been related to the product. The two avian reproduction studies carried out with the technical product did not show any evidence of maternal toxicity (weight loss, food consumption, number of eggs laid), nor any biologically significant differences in the number of fertile embryos and survival of chicks for both the Mallard Duck and the Bobwhite Quail.

Risk factors (ratio of expected exposure over the level causing toxicity) estimated for wild birds are 5.21×10^{-5} and 2.65×10^{-3} if the product is used at the recommended label rate of 0.10 kg ai/ha.

b) Wild mammals

Mammals could be exposed to imazethapyr through direct overspray or spray drift or through consumption of contaminated vegetation in soybean fields or adjacent margins. Since Pursuit® can be applied post-emergence and it takes as long as 2-4 weeks to kill susceptible plants, residues may be consumed for some time by mammals. Some mammals could be exposed by ingestion of earthworms or insects, and carnivores could be exposed by ingestion of small herbivores. However since Pursuit® does not bioaccumulate toxicity is not likely to be enhanced through the food web.

Photodegradation in water is very rapid (DT_{50} = 2 days) but hydrolysis occurs slowly. Some animals living around aquatic habitats near fields cultivated with soybeans could be exposed to some quantity of Pursuit® through leaching or run-off.

In grainfield habitats, adjacent fencerows and woodlots in Southern Ontario (Mixed-Wood Plain Ecozone), 26 species of mammals can be found, among them the rare Eastern Mole, the Grey Fox and the Southern Flying Squirrel. In aquatic environments 19 mammal species have been inventoried.

Both imazethapyr and Pursuit® are practically non-toxic to mammals. LD_{50}s for rats, rabbits and mice were greater than 5000 mg ai/kg b.w. A NOEL of 100 mg ai/kg b.w. was determined for the teratology study on rabbits. This number is very conservative and was chosen mainly because of a low sample size due to a high mortality of females and pups at 300 mg ai/kg b.w. Risk factors estimated for wild mammals are between 0.204 (for the Meadow Vole) and 9.8×10^{-3} mg a.i./kg. b.w. Given that the scenario is based on the maximum label rate at day 0 application, this is a worst-case scenario. Risk factors calculated with the LD_{50}s are between 2.7×10^{-5} to 1.7×10^{-3} mg ai/kg b.w.

c) Amphibians and reptiles

No data were available to evaluate the risk to amphibians and reptiles from the use of imazethapyr. These organisms could be exposed by direct dermal exposure from spray drift or by ingestion of contaminated invertebrates.

d) Soil microbial systems

Results of laboratory studies indicated that imazethapyr had no adverse effects on numbers of soil microorganisms, growth rates of microbial populations, mineralization of organic substrates, nitrogen cycling, sulfur oxidation, soil enzymes (dehydrogenase and phosphatase) or normal soil respiratory processes.

e) Terrestrial invertebrates

Results of toxicity tests based on topical application, showed that imazethapyr (100 ：g a.i./bee) was non-toxic to bees. The acute toxicity of imazethapyr to the earthworm *Eisenia foetida* was determined in an artificial soil under laboratory conditions and involved treatments with imazethapyr at a range of concentration from 0.2-15.7 mg/L (equivalent to application rates of 0.1 to 10 kg a.i./ha). The results indicated that imazethapyr was of low toxicity to earthworms in soil and did not have any effect on worm weight. Therefore, the chemical should not present significant hazard to earthworms.

f) Aquatic invertebrates

Acute toxicity of imazethapyr to *Daphnia magna* is low (48-h $LC_{50} > 1000$ mg/L). Results of chronic toxicity tests indicated that survival, growth and reproduction of *Daphnia magna* at all of the herbicide test concentrations were not statistically different

from the controls. The maximum acceptable toxicant concentration (MATC) for *D. magna* was estimated to be >15 mg/L.

g) Wildlife habitat considerations

Wildlife living in the vicinity of cultivated fields could be affected by a shortage of food invertebrates due to a reduction of macrophytes on which invertebrates subsist, or reduction of seeds and cover through damage and destruction of plants. When used at the recommended application rate, imazethapyr is not expected to pose an acute risk to aquatic or terrestrial invertebrates.

Imazethapyr has the potential to contaminate non-target areas via run-off or wash-off. Both laboratory and field studies indicate that imazethapyr will be persistent in soil. Its only major route of dissipation is through photodegradation in water (but not on soil surfaces).

The toxicity of the algal growth inhibition test performed with technical imazethapyr indicated a low risk factor of 1.67×10^{-3} to the green algal species *Selenastrum capricornutum*.

Data on vascular plants were submitted to assess the toxicity of the herbicide to a number of weed and crop species from several families. As for animals, data on known species allow an extrapolation of the results to non-target organisms. The purpose of the plant assessment is to estimate potential impacts on wildlife habitats. The data used come from the plant screening performed in the greenhouse by the company during product development. A very conservative scenario is adopted that 10% of the amount of pesticide applied will reach non-target environments via spray drift (=0.010 kg ai/ha); a level of 25% detrimental effect (EC_{25}) for terrestrial plants is considered permanent damage by EPA.

Data submitted on terrestrial plants showed that imazethapyr is toxic to many species (30% if applied post-emergence and 53.8% pre-emergence) and from several families (58.8 and 82.4%), at 10% recommended label rate. Furthermore toxicity could not always be predicted for a whole family i.e. species within some families responded differently to the product. In a worst case scenario, if overspray occurred at the recommended label rate, 90% of the plant species would be irreversibly damaged (i.e. 90% of the species have an $EC_{25} < 0.10$kg ai/ha).

A toxicity study was performed with *Lemna gibba* as part of the requirement for testing aquatic vascular species. Imazethapyr appears to be very toxic to this floating aquatic species, with an EC_{50} of 10.1 ：g/L. The expected environmental concentration at the recommended label rate, calculated in 15 cm of water is 67 ：g/L, conveying a high risk ($EEC/EC_{50} = 67/10.1 = 6.63$) to the aquatic vascular indicator species. No other study

has been provided with other aquatic species, submergent or emergent species. In the absence of information on more species, the risk scenario has to be calculated on the currently known effect on *Lemna*.

The extent of soybean growth in Southwestern Ontario is also an area inhabited by several endangered and threatened species. Habitats important to wildlife that are in close vicinity with cropland include hedgerows, shelterbelts, woodlots, vegetated ditchbanks, wetlands and other cover on the edge of fields. In the light of the high toxicity levels demonstrated by the data provided on terrestrial and aquatic species, the following mitigation measure should be established:

1. A strict contraindication on aerial delivery, clearly identified on the label,

2. A buffer zone statement on the label to protect not only wetlands and bodies of water, but equally, terrestrial non-target habitats that are used by wildlife associated with farmland. It should read, "OVERSPRAY OR DRIFT TO IMPORTANT WILDLIFE HABITATS SUCH AS SHELTERBELTS, HEDGEROWS, WETLANDS, WOODLOTS, VEGETATED DITCHBANKS AND OTHER COVER ON THE EDGES OF FIELDS SHOULD BE AVOIDED. LEAVE A 15 METER BUFFER ZONE BETWEEN THE LAST SPRAY SWATH AND THE EDGE OF ANY OF THESE HABITATS."

Please direct any inquiries regarding this document to:

Pest Management Regulatory Agency
Health Canada
2250 Riverside Drive
A.L. 6606D1
Ottawa, Ontario
K1A 0K9

Information Service: 1-800-267-6315
(In Canada only)