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Direction générale de la production
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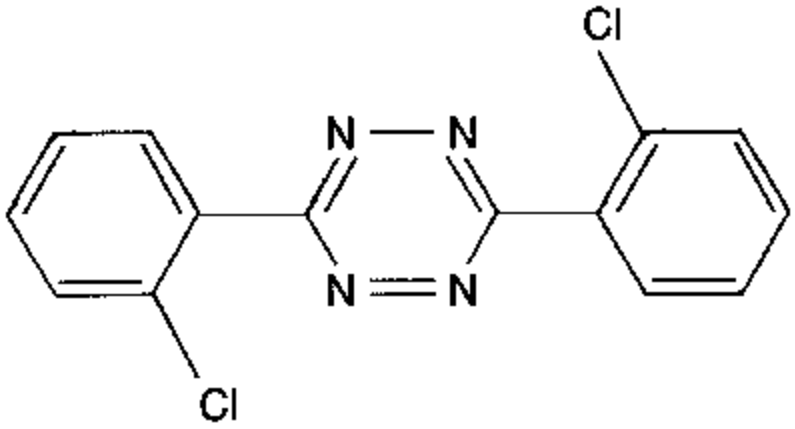
Canada

Decision Document E89-03

CLOFENTEZINE



Miticide

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FOREWORD

CLOFENTEZINE

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

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December 7, 1989

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1. SUMMARY

The purpose of this document is to provide a summary of the data reviewed and outline the regulatory action on the active ingredient clofentezine and the end-use formulation Apollo SC containing 500 g active ingredient per litre.

Agriculture Canada, with the assistance of advisors from Environment Canada, Health and Welfare Canada and the Department of Fisheries and Oceans has completed a review of the available data supporting clofentezine and Apollo SC. The data base is considered complete with respect to current regulatory data requirements.

An orchard occupational exposure study conducted with Apollo SC indicates that the margins of safety for hepatic function changes are very low but considered adequate because exposure to users is once per year. Protective clothing measures outlined on the label must be followed during mixing/loading/application (M/L/A) and clean-up operations.

Consumer dietary exposure to apples treated with Apollo SC is not a concern. Residues of clofentezine at harvest will not exceed 0.01 ppm from a single application at label rates when used from dormancy to first cover.

Clofentezine technical and its formulated product, Apollo SC are unlikely to pose an acute or chronic hazard to wildlife during use on apples. In addition, wildlife food resources and habitat should not be affected due to the low toxicity of Apollo SC to aquatic and terrestrial invertebrates, and algae. Clofentezine has been shown to be non-persistent to moderately persistent in soil under both laboratory and field conditions and non-persistent in water under laboratory conditions. Dissipation in orchard litter is fairly rapid following a single early-season application. The results of both laboratory and field studies indicated that clofentezine will not leach through soil. There is little likelihood of adverse effects on fish and fish habitats associated with the proposed use pattern for Apollo SC.

A review of agronomic and economic benefits of clofentezine centres on providing effective mite control on apples. The control of mites, such as European red mite, is particularly important to fruit growers because of the adverse effects the mites can have on yield and product quality. Apollo SC has been extensively tested in Canada and can maintain mite numbers below economically damaging levels through a full season. A desirable attribute of this product is the selective activity between plant-feeding and predatory mites. Apollo SC is expected to play

a prominent role in integrated pest management programs established in Canadian apple producing areas. As well, the availability of Apollo SC will complement the use of other registered miticides/insecticides in resistance management programs being developed for mites.

2. PESTICIDE NAME AND PROPERTIES

2.1 Pesticide Name

Common Name: clofentezine
Chemical Name: 3,6-bis(2-chlorophenyl)-1,2,4,5 tetrazine
Trade Name: Apollo SC
CAS Registry No: 74115-24-5

2.2 Physical and Chemical Properties

Empirical Formula:	C14H8Cl2N4
Molecular Weight:	303
Physical Form:	Magenta solid (technical and pure material)
Odour:	Odourless
Melting Point:	179-182°C (technical material)
Vapour Pressure:	1.3 x 10~7Pa @ 25°C
Octanol/Water partition coefficient (Kow):	1353 (log Kow = 3.1)
Solubility:	<2-130 mg/L in water <0.5 g/lOOmL in acetone 5g/lOOmL in chloroform <0.1/lOOmL in ethanol
Specific Gravity:	1.51 gm/mL (technical), 1.18 g/mL at 20° (Apollo SC)
Stability:	At temperatures below 30°C, technical is stable for at least three years.

3. DEVELOPMENT AND USE HISTORY

Clofentezine is manufactured by Schering AG (formerly FBC Limited), United Kingdom. In Canada, product development has been carried out by Nor-Am Chemical Company and United Agri-Products (formerly Pfizer Agricultural Products). Nor-Am Chemical Company of Wilmington, Delaware, United States is the registrant in Canada for both technical clofentezine and the end-use formulation, Apollo SC.

Clofentezine is currently registered for use in 25 countries, including Australia, New Zealand, France, Germany, Israel, Spain,

Switzerland and the United Kingdom. International tolerances have been established for crops such as citrus (0.5 ppm), cucumbers (1.0 ppm), currants (0.1 ppm), grapes (0.2 ppm), pome fruits (0.5 ppm), stone fruits (0.2 ppm) and strawberries (2.0 ppm). It has recently been registered in the United States on pears with a tolerance of 0.5 ppm established by the Environmental Protection Agency (EPA).

Clofentezine is a tetrazine compound showing specificity as an acaricide, and has long residual activities. It acts primarily as an ovicide but has some effects against motile stages. This compound does not appear to affect predatory mites or beneficial insect species in field experiments.

4. TOXICOLOGY

An extensive toxicology data package was submitted by the registrant, Nor-Am Chemical Co. The following data were considered in the assessment of potential human health hazards and the following status report prepared by Health and Welfare Canada was considered in our regulatory decision on clofentezine.

4.1 Summary of the Toxicological Data Base for Clofentezine

a) Acute Studies (technical):

Technical clofentezine

Oral LD_{50}:

Rat: >3200 mg/kg body weight (b.w.)
Mouse: >3200 mg/kg b.w.
Hamster: >3200 mg/kg b.w.
Dog: >2000 mg/kg b.w.

Dermal LD_{50}:

Rat: >1320 mg/kg b.w.

I.P. LD_{50}:

Rat: 800 mg/kg b.w.

Primary Irritation:

Skin, Guinea pig: slightly irritating
Eyes, Rabbit: slightly irritating

Dermal Sensitization:

Guinea pig: low grade sensitizer

Oral LD_{50}:

Rat: >5000 mg/kg b.w.

Dermal LD_{50}:

Rat: >5000 mg/kg b.w.

Primary Irritancy:

Skin, guinea pig: mildly irritating
Skin, rabbit: slightly irritating

80 WP Formulation

Inhalation LC_{50}:

Rat: (6-hr): >1.5 mg/L of air

b) Short-term Studies

i) 90-Day Rat: A 90-day dietary feeding study in the rat, using levels of 0, 40, 400 and 4000 ppm indicated a no observable effect level (NOEL) of 40 ppm (2 mg/kg b.w./day) based on hair loss at this level and a decrease in body weight gain and food consumption, increase in liver and kidney weights, decrease in Hgb and MCH, increase in total protein, albumin, cholesterol, decrease in AST and an increase in the incidence of centrilobular hepatocyte enlargement observed at the next highest dose level of 400 ppm (20 mg/kg b.w./day).

ii) 90-Day Dog: A 90-day dietary feeding study in dogs using levels of 0, 3200, 8000 and 20000 ppm indicated a NOEL of 3200 pm (80 mg/kg b.w./day) based on an increase in relative liver weight in females at the next highest dose of 8000 ppm (240 mg/kg b.w./day). At the highest dose of 20,000 ppm (600 mg/kg b.w./day) relative thyroid as well as liver weights were increased.

iii) l-Year Dog: A one-year dietary feeding study in dogs, using levels of 0, 50, 1000 and 20000 ppm indicated a NOEL of 50 ppm (1.72 mg/kg b.w./day) based on an increase in serum cholesterol, triglycerides and liver weight observed at the next highest dose of 36 mg/kg b.w./day. At the highest

dose, there was also an increase in adrenal and thyroid weights, an increase in alkaline phosphatase and an increased incidence of enlargement of the periportal hepatocytes with cytoplasmic eosinophilia.

c) Chronic Toxicity/Oncogenicity Studies

i) Rat: In the rat study, groups of 50 male and 50 female rats were fed diets containing 0, 10, 40 or 400 ppm clofentezine for 118 weeks. Supplementary groups of 20 male and 20 female rats were fed similar diets and were sacrificed after 12 months of treatment. A no observable adverse effect level (NOAEL) of 40 ppm (2.0 mg/kg b.w./day) was demonstrated. At the highest dose (20 mg/kg b.w./day) there was a slightly increased mortality in males, a slight decrease in erythroid parameters in females, an increase in free T_4 levels in males and in cholesterol levels in females, and an increase in liver weight in males and females. Treatment-related histopathological changes at the highest dose included effects on the kidney (glomerulo-tubular nephropathy)in females, liver (centrilobular hepatocyte enlargement) in males and females, spleen (pigment deposition) in females and thyroid (agglomeration of colloid), increase in benign and malignant follicular cell tumours: (2,2,2 and 8) in males only.

ii) Mouse: In the mouse study, groups of 52 males and 52 females received diets containing 0, 50, 500 and 5000 ppm clofentezine for 105 weeks. A NOAEL of 500 ppm (54 mg/kg b.w./day) was demonstrated, based on an increased mortality (females), decreased body weight (males), increased liver weight (males and females), and an increase in the incidence of eosinophilic foci/area of hepatocytes (females) observed at the next highest level of 550 mg/kg b.w./day. At the 54 mg/kg b.w./day (mid dose) level, an increase in eosinophilic foci/area of hepatocytes was noted (3, 3, 7 and 9 in the control, low, mid and high dose groups). However, this was the only treatment-related effect noted at this level, and no trend to an increased incidence of benign or malignant liver tumours was observed. It is not considered to be of sufficient concern to lower the NOAEL to the lowest dose tested, i.e., 5 mg/kg b.w./day).

d) Reproduction

In a two-generation, two litters per generation reproduction study, groups of 30-40 male and female rats received diets containing 0, 4, 40 and 400 ppm clofentezine. No direct effects on reproduction were observed. The NOEL in this study was 40 ppm (3.47 mg/kg b.w./day) based on decreased body weight in dams, an increase in relative liver weight and an increase in the incidence of histopathological alterations in the liver of dams, and a decrease in pup and litter weights, observed at the highest level tested of 400 ppm (34.9 mg/kg b.w./day).

e) Teratology

i) Rabbit: In a rabbit teratology study, groups of 14 pregnant rabbits received daily oral doses of 0, 250, 1000 and 3000 mg/kg b.w./day from day 7 to 28 of gestation. No evidence of teratogenicity was seen. A NOEL of 1000 mg/kg b.w./day was demonstrated, based on decreased maternal weight gain and decreased foetal and litter weight observed at the highest dose tested (3000 mg/kg b.w./day).

ii) Rat: In a rat teratology study, groups of 34 pregnant rats received daily oral doses of 0, 320, 1280 or 3200 mg/kg b.w./day from day 7 to 20 of gestation. No evidence of teratogenicity was noted. A NOEL of 1280 mg/kg b.w./day was demonstrated, based on maternal toxicity (decreased body weight, liver pathology) at the highest dose of 3200 mg/kg b.w./day.

f) Mutagenicity

Point Mutation: Bacterial - Ames - negative
: Mammalian - Mouse Lymphoma - negative

Gene Conversion/Mitotic Recombination (Yeast) - negative

Chromosomal Aberration: Mouse Micronucleus - negative
Dominant Lethal: negative

g) Metabolism

Extensive metabolism studies in numerous species demonstrated that clofentezine is rapidly excreted in the feces (80%) and urine (20%) at low doses (0.1-10.0 mg/kg b.w. per day). Faecal excretion appears to be due to biliary excretion rather than lack of absorption. No sex

differences were apparent. Metabolism is qualitatively similar in all species with quantitative differences occurring between baboons and rodents. The major route of metabolism is ring-hydroxylation (in baboons) or the replacement of a chlorine atom by a methyl-thio group, followed by ring-hydroxylation (in rodents). Liver and kidneys were the only major organs to contain significant amounts of radioactivity. No increase in radioactivity was observed in thyroid tissue.

h) Dermal Absorption/Penetration Study

In a rat study following a single dermal application of 4.8, 44.0 or 180 mg/kg b.w. of radio-labelled clofentezine, approximately 30% of the low and mid dose, and approximately 10% of the high dose was found in the skin of the application site, after a site wash at 10 hours post-application. Over the 10-hour exposure period less than 1.0% of the applied dose was excreted, all via the urinary route. Since the study was terminated at 10 hours and the fate of clofentezine bound to skin was not determined, a conservative estimate of systemically available clofentezine would be 30% of the dermally applied dose.

i) Summary of Pivotal Toxicological Studies

STUDY	NOEL or NOAEL mg/kg b.w./day	LOAEL mg/kg b.w./day	ADVERSE EFFECTS	SAFETY FACTORS	ADI mg/kg b.w./day
l-year dog	1.72*	36	increase in cholesterol, triglycerides, liver weight	100	0.02
chronic toxicity oncogenicity (rat)		20 2.0**	decrease in erythroid parameters, increase in free T_4 cholesterol, liver weight; non neoplastic lesions of the liver, thyroid, spleen and kidney, benign and malignant thyroid tumours (2, 2, 2, and 8).	1000	0.002
oncogenicity (mouse)	54**	550	increased mortality decreased body weight, increased liver weight, and increased incidence of eosinophilic foci in the liver.	100	0.5
reproduction (rat)	3.50*	35.0	decreased body weight, increased liver weight and liver histopathology in dams, decreased pup and litter weights.	100	0.03
Teratology:					
rabbit	1000*	3000	decreased maternal weight, decreased foetal and litter weights.	100	10
rat	1280*	3200	decrease maternal weight, liver pathology in dams.	100	128

* NOEL
** NOAEL

4.2 Conclusion

A safety factor is recommended for risk assessment based primarily on the chronic toxicity/oncogenicity study in the rat.

A NOAEL of 2 mg/kg b.w./day was demonstrated. At the highest dose (20 mg/kg b.w./day) there was a slight decrease in erythroid parameters in females, and an increase in cholesterol levels in females, and an increase in liver weights in males and females. Treatment-related histopathological changes at the highest dose included effects on the liver (centrilobular hepatocyte enlargement) in males and females, thyroid (agglomeration or colloid), increase in benign and malignant follicular cell tumours (2, 2, 2, and 8) in males and spleen (pigment deposition) in females.

With regards to the increased incidence of follicular cell tumours of the thyroid, the following considerations were made:

i) The increase is statistically significant for trend (P = 0.0023) and Fisher's Exact Test (P = 0.048) for malignant and benign tumours combined. Because follicular cell tumours of the thyroid are frequently observed, a "P" value of <0.01 should be achieved if the effect is considered to be treatment related. A positive trend test, for a commonly occurring tumour, is not considered to indicate undue concern;

ii) The historical control data is limited to two other studies. However, in one of these studies conducted concurrently with the clofentezine study, 4 malignant follicular cell thyroid tumours were observed in a treated (mid dose) group compared to 5 observed in the high dose group treated with clofentezine. Furthermore, the incidence of follicular cell tumours in the historical controls of studies conducted at FBC was higher than in the historical controls of studies conducted at other laboratories;

iii) None of the tumours in the clofentezine study were observed prior to the terminal sacrifice;

iv) No metastasis had occurred;

v) There was no treatment-related follicular cell hyperplasia noted; and

vi) Results of mutagenicity and genotoxicity tests were negative.

It is concluded that the tumour incidence data do not demonstrate that clofentezine induces the development of thyroid tumours.

5. FOOD RESIDUE STUDIES AND DIETARY EXPOSURE

5.1 ADI Assessment

The recommended ADI for clofentezine is 0.002 mg/kg b.w./day based on the use of a 1000-fold safety factor applied to the NOEL of 40 ppm (2 mg/kg b.w./day) observed in the carcinogenicity study in the rat.

5.2 Dietary Exposure

Apple metabolism data indicates that clofentezine degrades only very slowly after application. Migration of residue into the fruit is also very slow with the majority of the residues absorbed remaining in the peel. Degradation products were indistinct and numerous. The principal free metabolite, at about 4% of the total peel or fruit residue, was identified as 2-chlorobenzonitrile while the principal bound metabolite was identified as 2-chlorobenzoic acid after acid digestion. In all cases, the major extractable component was parent clofentezine.

Due to the stability of the clofentezine residues, analytical methodology has been developed to measure parent only. Due to the aromatic nature of clofentezine, analytical methodology involves extraction, partitioning, clean up, and analysis by HPLC with an internal standard using detection by UV at 268 nm. The detection limit is reported as 0.01 ppm with recoveries averaging greater than 90%. It is expected that analysis for parent clofentezine can be incorporated into general screening procedures for use by the Health Protection Branch, Health and Welfare Canada.

Canada and U.S. residue data indicate that residues of clofentezine at harvest will not exceed 0.01 ppm when a single application of up to 0.30 kg active ingredient (a.i.)/ha (maximum label rate)[l] clofentezine is used from dormancy to first cover. The theoretical daily intake (TDI) from this use on apples would not exceed 0.00001 mg/kg b.w./day and even if residues up to 0.1 ppm in apples were allowed, the TDI would not exceed 0.00013 mg/kg b.w./day.

5.3 Risk Assessment

A 1000-fold safety factor is used on the NOEL of 2 mg/kg b.w./day rather than a 100-fold because of uncertainties related to the significance of the thyroid effects. Therefore, the ADI is 0.002 mg/kg b.w./day.

Even using a residue limit of 0.10 ppm on apples, the TDI would not exceed 0.00013 mg/kg b.w./day or 7% of the ADI of 0.002 mg/kg b.w./day.

6. OCCUPATIONAL EXPOSURE

6.1 Exposure Assessment

An exposure study entitled "Exposure of Spray Operator to Clofentezine during Airblast of Apollo SC to Apple and Pear Trees" was submitted by the registrant.

a) Six workers were monitored for dermal and inhalation exposure to clofentezine (Apollo SC, a suspension concentrate) during mixing/loading and spraying for a full day. Apollo was applied to the fruit trees by airblast spraying at a rate of 0.26 lb a.i./acre or 0.3 kg a.i./ha. Workers wore cotton/polyester coveralls over their normal clothes, a baseball type cap and nitrile gloves. Open cab tractors were used. The formulation, application rate and practices were comparable to the Canadian situation. Only one application per season on apples is recommended on the Canadian label.

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1 It should be noted the maximum label rate is likely to be used only under exceptional conditions. It is anticipated that a rate of 0.15 kg a.i./ha will typically be used commercially.

Dermal exposure was calculated from the dermal deposition values of clofentezine from both outside and inside patches. Hand rinses were used to assess deposition to hands protected by nitrile gloves. Clofentezine extracted from nitrile gloves represented the exposure to unprotected hands.

Most apple orchards in Canada are located in Quebec, Ontario, British Columbia and Nova Scotia. We have assumed that the average size of a Canadian apple orchard is about 20 hectares (ha). Based on the estimated daily exposure values derived from this study, exposure to clofentezine by a typical 70 kg Canadian orchard farmer treating 20 ha at the maximum application rate and

wearing short sleeves and long pants would be 1.0 mg/kg b.w./day (wearing gloves) and 1.2 mg/kg b.w./day (without gloves). This is assuming a 100% dermal penetration and absorption (Table 1). Based on a rat dermal penetration study (single application), a 30% correction factor was applied to the total exposure values (Table 1).

Table 1

Estimated Exposure (Dermal and Inhalation) to Clofentezine by Canadian Orchard Farmers (Mixing/Loading and Spraying)

	Estimated Exposure Derived from the Study (mg/kg a.i.)	Estimated Exposure To Canadian Orchard Farmers (mg/kg b.w./day)*	
		100% Absorp.	30% Absorp.
Protective Clothing			
Short Sleeves; No Gloves	14.1	1.2	0.4
Short Sleeves; Nitrile Gloves	11.2	1.0	0.3
Coveralls; Long Sleeve Shirts; Nitrile Gloves	7.2	0.6	0.2

* Based on a farmer (70 kg) wearing long pants and short sleeves and mixing, loading and spraying the maximum application rate (0.3 kg a.i./ha) to a 20 ha orchard in one day (6 kg a.i. total).

It should be emphasized that cleanup procedures which can lead to significant dermal exposure were not monitored in this study. Furthermore, the validity of using nitrile gloves as a collection medium is unknown.

6.2 Risk Assessment-Occupational Exposure

The calculations of theoretical margin of safety (MOS) for the toxicological endpoint of concern are presented in Table 2, using a NOEL of 2.0 mg/kg b.w./day as suggested in the toxicological review. This NOEL level was established from the rat chronic/ oncogenicity study.

Table 2

Clofentezine, Margin of Safety Calculations Based on Dermal Deposition and Inhalation Exposure for M/L/A Tasks

	Theoretical Margin of Safety*		
Toxicological Endpoint and Corresponding NOEL	Short Sleeves Without Gloves	Short Sleeves With Gloves	Full Protective Clothing**
reversible hepatic function change (2 mg/kg/b.w.)	5	7	10

* Use total exposure value with 30% absorption on 70-kg man
** Coveralls, long sleeved shirt and gloves

These calculated margins of safety (MOS) are very low even with protective clothing. However, several mitigating factors have to be considered.

i) The NOAEL was derived from a lifetime feeding study and was based on reversible hepatic function changes at the next highest dose level.

ii) Worker exposure will be short-term (most likely only once a season, 1 day/year) and primarily by the dermal route.

iii) The demonstrated reversibiltiy of the hepatic changes as well as the flat dose response over a very wide range of dose-levels has also to be considered as a mitigating factor.

iv) The estimated exposure values assumed a 30% dermal absorption of clofentezine. This may be a conservative estimate since the major portion of the absorbed dose was found locally in the skin (application site) after 10 hours.

These MOS's are therefore considered adequate if the following conditions are met:

i) Exposure to users will be only once per year.

ii) Protective measures will be taken to minimize exposure, i.e., a broad-brimmed hat, long-sleeved coveralls and

apron (or a non-permeable rainsuit) and suitable chemical resistant gloves to be worn during mixing/loading/application and clean-up procedures.

7. ENVIRONMENTAL CHEMISTRY AND FATE

The following review and evaluation by Environment Canada (Conservation and Protection Service, Canadian Wildlife Service) was based on the proposed use pattern on apples.

7.1 Physiochemical Properties

The vapour pressure at 25°C was extrapolated using Clapeyron-Clausius analysis and found to be 1.3×10^{-7} Pa. This result indicates that clofentezine is unlikely to dissipate in the environment by volatilization.

The octanol/water partition coefficient for clofentezine was reported to be 1353 (log Kow = 3.1). The accuracy of this value is questionable since it was based on measured concentrations of clofentezine in the aqueous phase which were well above the solubility limit in water (see Section 8.7 for further discussion).

Clofentezine was found to be essentially insoluble in water. The results of various determinations indicated that the solubility of clofentezine in water is <40 ppb.

7.2 Transformation

Clofentezine will undergo base-catalyzed hydrolysis. The half-lives for hydrolysis were reported to be approximately 4 hours at pH 9, 34 hours at pH 7 and 249 hours (10 days) at pH 5. Because of various difficulties in conducting hydrolysis studies due to the low water solubility, the accuracy of these half-lives is uncertain. However, it can be concluded from all the evidence provided that hydrolysis of clofentezine occurs fairly rapidly at environmentally relevant pH's.

Phototransformation studies indicated that clofentezine can undergo phototransformation quite readily in water, but is relatively stable to light on a soil surface.

Biotransformation studies showed that clofentezine residues will dissipate in soil by binding, by biotransformation and, most probably, by hydrolysis. Under aerobic soil conditions in the laboratory, the DT_{50} for clofentezine ranged from 4 to 8 weeks at 22°C and 9 to 14 weeks at 15°C. Under anaerobic conditions (flooded soil), clofentezine appeared to be more readily bound to soil and less readily transformed than under

aerobic conditions. Mineralization of clofentezine residues to CO_2 proceeded rapidly in aerobic soils, but ceased when soils were flooded. Studies with sterilized soils indicated that complete mineralization of clofentezine residues required full microbial activity and that non-biotic processes (e.g., hydrolysis) may be important in the transformation of clofentezine in soil. Studies conducted in the laboratory with freshly collected sediment/water samples indicated that clofentezine will partition readily into sediments and will be readily transformed. The DT_{50}'s of extractable clofentezine residues from both sediment and water in these samples were <7 days.

In biotransformation studies no transformation products were observed that were both major and persistent. However, in aqueous phototransformation studies conducted under sterile conditions, the transformation product, 2-chlorobenzonitrile, was observed to accumulate, accounting for 75% of the recovered radioactivity by the end of a 31-day sunlight exposure period. In dark controls, this transformation product also accumulated over the study period, but accounted for a maximum concentration of only 6% by the end of the study. On a soil surface treated with 14C-clofentezine, 2-chlorobenzonitrile accounted for 5.5% of the applied radioactivity after exposure sunlight over a period of 31 days. In hydrolysis studies, 2-chlorobenzonitrile was observed in samples taken at approximately 1.5 half-lives for clofentezine hydrolysis and accounted for approximately 6% of the recovered radioactivity. In non-sterile, aerobic soil samples and in sediment/water microcosms incubated in the dark, 2-chlorobenzonitrile was not observed, which may indicate that the compound is rapidly biodegraded, strongly adsorbed, or formed only in undetectable quantities.

Further information was provided to show the probable fate of 2-chlorobenzonitrile in the environment. The transformation of similar compounds, bromoxynil and dichlobenil, in which nitrite groups are hydrolyzed to corresponding amides and then further hydrolyzed to the acid and then CO2, suggests a similar route for 2-chlorobenzonitrile. Because of (1) the low potential for mobility of clofentezine; (2) the potential for 2-chlorobenzonitrile to hydrolyze; and, (3) 2-chlorobenzonitrile was not observed in soil, further studies are not required at this time.

7.3 Environmental Dissipation

Under field conditions in both Canada and the United Kingdom, clofentezine was seen to be non-persistent to moderately persistent in soil, with DT_{50}'s ranging between 19 and 73 days. In soil surface litter in a B.C. orchard, clofentezine

appeared to be non-persistent following an early season application. However, some additional information concerning experimental design was necessary to substantiate these observations and to define the scope of the submitted information.

The results indicate the clofentezine should dissipate fairly rapidly in orchard litter following the proposed single early-season applications.

The results of both laboratory and field studies indicated that clofentezine will not leach through soil.

8. ENVIRONMENTAL TOXICOLOGY

The submitted studies indicated that clofentezine is of low toxicity to earthworms, soil microorganisms, honey bees, and indicator species of fish and aquatic invertebrates. Clofentezine was stimulatory to algae at low concentrations, possibly by acting as a source of nitrogen. No algal growth inhibition was observed.

The bioconcentration factor for clofentezine in bluegill sunfish was reported to be 430. The depuration of residues from the fish was rapid with 88% being eliminated after three days from the cessation of exposure.

The submitted information indicated that clofentezine would not be directly toxic to the following beneficial predators and parasites, some of which are important in integrated pest management in orchards: Tyhlodromus occidentalis, Phytoseilus persimilis. The safety of clofentezine to Typhlodromus pyri was also shown, however, there was some evidence which suggested a low level of mortality in eggs and nymphs of this predator for seven days after being sprayed with solution containing 300 ppm clofentezine under field conditions.

8.1 Wild Birds

The acute toxicity of clofentezine to birds is low. No mortalities occurred when adult bobwhite quail were given an oral dose of 7500 mg a.i./kg b.w. Exposure of birds in orchards through ingestion of food contaminated with clofentezine is also unlikely to cause mortality. When fed levels of up to 20000 mg clofentezine/kg diet for five days, there was no mortality among 10-day-old bobwhite quail, and 10-day-old mallard ducks.

Clofentezine is reported to be a highly effective bird repellent at 10-1000 g/ha. This level is considerably below that being acutely toxic to birds, and should provide an additional MOS to avian species. However, no data are available to support this.

Effects on avian reproduction have not been studied, nor have any field studies on birds been done. Given the very low acute toxicity of clofentezine to birds, and its rapid metabolism, the need for avian reproduction studies and major field assessment of impacts on birds seems unwarranted.

8.2 Wild Mammals

Clofentezine technical is not highly toxic to laboratory rats, mice, hamsters, guinea pigs or dogs. Acute oral LD_{50} values range from 1500 mg a.i./kg for the guinea pig to 3200 mg a.i./kg for the rat, mouse and hamster. Similarly, the formulated product, Apollo SC, is also of low toxicity, the acute oral LD_{50} for the rat being greater than 2100 mg a.i./kg.

Using the technical product, the acute intraperitoneal LD_{50} for the rat is 800 mg a.i./kg.

A stable aerosol of Apollo SC could not be made, thus inhalational toxicity was not calculated for the formulated product. Inhalation of the formulated product is not expected to be a major route of exposure to wildlife.

Studies on the metabolism of clofentezine have shown that it is extensively metabolized and rapidly eliminated by rats, rabbits, dogs, mice and baboons. Clearance is almost complete within two days.

No field studies on wild mammals have been done. Mammals could be exposed either dermally or through their food. At levels of exposure expected following application of Apollo SC to apple orchards, wild mammals should be at little risk, and field studies are not justified at this time.

8.3 Amphibians and Reptiles

No data are available to evaluate the risk to amphibians and reptiles.

8.4 Aquatic Invertebrates

Due to the low solubility of technical clofentezine (i.e., 35 ug/L), difficulties were encountered in obtaining LCs0 values in aquatic toxicity studies. In a study using Daphnia magna, 100 mg a.i./L were added to the test vessel, but the clofentezine remained in suspension; the actual dissolved concentration was less than 0.14 mg a.i./L. At this concentration, mortalities did not exceed those of the control. A study using the more soluble, formulated product,

Apollo SC, however, showed that there were no toxic effects, measured as immobilization, on Daphnia magna at concentrations as high as 100 mg a.i./L. The concentration of the test solution decreased by 50% during the 48 hour duration of the test due to hydrolysis, however concentrations still far exceeded that which would occur assuming a direct over spray of a shallow body of water (i.e., 0.0S mg a.i./L).

8.5 Terrestrial Invertebrates

The formulated product (50% WP) is of low toxicity to worker honey bees, Apis mellifera. The contact LD_{50} was greater than 1500 mg a.i./L, and the oral LD_{50} was greater than 20 ug/bee.

One and six months after a field application of 372 g a.i./ha of the 50% WP, no effect on numbers of earthworms was detected.

When clofentezine technical was applied at 1.0 and 10.0 kg a.i./ha, no effect on ammonification was observed on either sandy loam or clay soils. Nitrification was slightly reduced in soils unamended with lucerne and slightly stimulated in amended soils (i.e., organic nitrogen added). These effects, however, were not significant.

Several studies were done on the effects of the formulated products, (SC, 50% WP and 80% WP), on beneficial predators and parasites in orchards in Australia, New Zealand and England. These populations are important biological control agents, and are used in integrated pest management programs.

The two-spotted mite predator Typhlodromus occidentalis, the spider mite predator Phytoseiulus persimilis, and a whitefly parasite Encarsia formosa suffered little damage relative to pest mite populations which were significantly reduced. The European red mite predators Typhlodromus pyri and Agistemus longisetus, also were favoured over the pest mite population, although one study showed there is some evidence that clofentezine is toxic to young T. pyri (i.e., nymph, larva and egg). This acaricide shows potential for use in integrated pest management programs.

8.6 Wildlife Habitat Considerations

As with studies on aquatic invertebrates (see above), difficulties were encountered in toxicity tests due to the low solubility of the technical material. In a study on the effect of technical clofentezine on the growth of a green alga, Scenedesmus pannonicus, the no-observable-effect-concentration was estimated to be 32 ug

a.i./L nominally, although the actual concentration at the start of the experiment was an order of magnitude less than expected, i.e., 2.3-3.3 ug/L. At concentrations above the water solubility of the compound, growth was affected.

A study on the toxicity of Apollo SC to the green alga Selenastrum capricornutum indicated that algal growth was stimulated at the higher concentrations tested (16 and 50 mg a.i/L). An EC_{50} was not calculated as no effects were observed at low concentrations. This indicator species suggests that algae should not be affected should the formulated product enter an aquatic system.

No studies are available to evaluate the effects of clofentezine or Apollo SC on aquatic vascular plants or terrestrial plants. However, phytotoxic effects were looked for during field trials on the effects of formulated clofentezine on predatory mite populations. No phytotoxicity to apple trees was observed. Also, no toxicity to bush lima bean, Phaseolus lunatus, was observed during tests on the toxicity of Apollo SC to two-spotted and carmine spider mites.

The above data suggests little impact on wildlife habitat from the use of Apollo SC in apple orchards.

8.7 Bioaccumulation

Bioaccumulation was studied using bluegill sunfish, Lepomis macrochirus, in a dynamic system. Fish were exposed to approximately 0.018 mg a.i./L at 22°C for 28 days. A plateau was reached after three days, and the bioaccumulation factor was estimated to be 430. Clearance half-life was less than one day.

Bioaccumulation can be predicted from correlations using the physicochemical characteristics of the pesticide such as its n-octanol:water partition coefficient (Kow) and its water solubility. Clofentezine has a log Kow of 3.1 and a water solubility of approximately 35 ug/L. Based on the correlation using Kow developed by Veith et al. (1979), the bioaccumulation factor for fish is predicted to be 86. Similarly, using the correlation developed by Kenaga and Goring (1978), based on water solubility, the bioaccumulation factor is predicted to be 4000. The discrepancy in predictions may be due to the reported value of Kow. As reported above this value is suspect. Based on the results of the bioaccumulation study discussed above, and the low water solubility of clofentezine, the log n-octanol:water partition coefficient would be expected to be about an order of magnitude higher than reported.

Clofentezine is rapidly metabolized by mammals and fish, with a clearance half-life of less than one day. Mammals are unlikely to bioaccumulate residues of clofentezine to levels causing effects.

9. EFFECTS ON AOUATIC RESOURCES

The following assessment of the potential effects of Apollo SC on fish, fish habitat and the quality of fisheries resources used as food was prepared by the Department of Fisheries and Oceans.

9.1 Fish

Determination of the acute toxicity of clofentezine to fish was confounded by the fact that the LC_{50} values for this compound exceeded its water solubility. For example, the 96-h LC_{50} for rainbow trout (Salmo gairdneri) was reported to be >100 mg/L (maximum nominal test concentration) at 13-15°C, under test conditions in which the mean concentration of total clofentezine (both dissolved and suspended) was measured at <26 mg/L and the mean concentration of dissolved clofentezine was measured at <0.040 mg/L. In another test, on bluegill sunfish (Lepomis machrochirus), the 96-h LC_{50} value was 0.25 mg clofentezine/L; this concentration represented the maximum solubility of clofentezine, using the chemical solubilizer Tween 80 to maximize the concentration of the test chemical in water, and resulted in 20% mortality.

No chronic-exposure toxicity testing was undertaken using clofentezine or Apollo SC on fish, although there was no observed effect of clofentezine exposure on the growth of L. machrochirus during the 28-day duration of the biocencentration test.

Clofentezine, at a mean exposure concentration of 0.018 mg/L, was concentrated in L. machrochirus, with the whole-fish concentration reaching a plateau (7.77 mg clofentezine/kg fish tissue) by the third day of exposure and representing a bioconcentration factor of 432. The clearance half-life was less than 1 day.

9.2 Fish Habitat

As with the toxicity testing of clofentezine on fish, testing of this compound on p~æhnia maqna (a representative fish-food species) was complicated by its low water-solubility. Using neither solvents nor solubilizers, the 48-h EC_{50} was estimated to be greater than the maximum water-solubility of clofentezine (0.10 mg/L, confirmed by measurement in exposure water). By contrast, the 48-h EC50 value for clofentezine, when applied as the much more water-soluble Apollo SC

formulation to D. magna, was >100 mg a.i./L (also confirmed by measurement).

No chronic-exposure toxicity testing of clofentezine on aquatic invertebrates was undertaken.

Although an EC_{50} was not determined, clofentezine did not inhibit the growth of the green alga, Scenedescmus pannonicus, at concentrations up to those representing the maximum solubility of the chemical in water. In tests where attempts had been made to enhance the water-solubility of clofentezine, using dimethyl sulfoxide as a solubilizer, a slight negative effect upon growth yield was observed; however, no morphological abnormalities were observed at any time throughout the incubation period.

At very high concentrations of clofentezine (approaching 50 mg/L), the end-use formulation, Apollo 50 SC, produced a growth-stimulation effect upon the green alga, Selenastrum capricornutum. A reduction in algal cell size accompanied this growth stimulation. No toxicity testing was conducted on aquatic macrophytes.

9.3 Movement into and Transformation in Aquatic Environments

Based upon its proposed, limited use as a ground-applied miticide in orchards, clofentezine is not expected to reach high concentrations in aquatic environments. Low persistence of clofentezine in soil (half-life <22 days) was shown to occur, predominantly due to transformation resulting from aerobic microbial metabolism and, although no soil adsorption studies were conducted, clofentezine and its transformation products were demonstrated to be relatively non-mobile in all soils tested. Because of these characteristics

and also because of its very low water-solubility, movement of clofentezine into aquatic systems is likely to occur only via soil erosion or as a result of the accidental over spraying of water.

Calculation of the environmental concentration expected from the direct over spray of a 15 cm depth of water (typical of small streams) at the maximum proposed rate of application, indicated a potential concentration of 0.2 mg clofentezine/L in the receiving water. This value lies below the LC_{50} values determined for fish and fish-food species and above the estimated solubility of clofentezine in water.

Dissipation of clofentezine from aquatic environments was not investigated under field conditions. Laboratory microcosm studies, however, using [^{14}C]-clofentezine, showed that direct introduction of clofentezine to water resulted in a rapid partitioning of the compound from the water column into

sediment. One week after application (1.0 kg a.i./L equivalent), up to 72% of the recoverable 14C was detected in the sediment as a mixture of parent and transformation products. These studies indicated that the half-life for parent clofentezine, in water/sediment, was up to 7 days, but that the sediment-bound transformation products remained in the sediment for an undetermined length of time. A similar half-life (8 days), for clofentezine in water, was observed during the Selenastrum capricornutum toxicity testing.

10. ENVIRONMENTAL IMPACT ASSESSMENT

Clofentezine has been shown to be non-persistent to moderately persistent in soil under both laboratory and field conditions, and non-persistent in water under laboratory conditions. Clofentezine should dissipate fairly rapidly in orchard litter following single early-season applications. The vapour pressure determination indicates that clofentezine is unlikely to dissipate in the environment by volatilization. Clofentezine is not expected to leach significantly in soil.

Clofentezine technical and its formulated product, Apollo SC, are unlikely to pose an acute or chronic hazard to wildlife from the proposed use pattern on apples. In addition, wildlife food resources and habitat should not be affected due to the low toxicity of Apollo SC to aquatic and terrestrial invertebrates, and algae. Data were not available to evaluate effects on aquatic and terrestrial vascular plants. No data were available to evaluate the effects on reptiles and amphibians, however, due to the low toxicity to fish and aquatic invertebrates, studies on the toxicity of Apollo SC to these groups of animals are unwarranted at this time.

The results of environmental toxicology studies on a variety of non-target indicator species, coupled with the results of environmental chemistry and fate studies, would suggest that clofentezine is unlikely to pose a threat to non-target organisms. The low toxicity of clofentezine to beneficial mites and insects was demonstrated for several indicator species, thus, the compound has the potential to be of use in integrated pest management programs.

The low water solubility, low soil mobility, high soil/sediment adsorption-affinity and short half-life of clofentezine in water and sediment, in addition to its rapid depuration rate in fish and its low acute toxicity to aquatic biota indicate that minimal aquatic impact is expected from the proposed ground-application of Apollo SC.

These conclusions are based, however, upon data generated only through laboratory studies and laboratory/field soil studies and

are supported by a predicted maximum environmental concentration which has been estimated from the label application rate of Apollo SC to typical fish habitat. No data from field aquatic studies were available to confirm the fate, persistence and effects of clofentezine in aquatic ecosystems.

11. AGRONOMIC BENEFITS

11.1 Description of Proposed Uses

Apollo SC is proposed for use on apples as a specific ovicidal miticide with activity against European red mite (*Panonychus ulmi*), two-spotted spider mite (*Tetranychus urticae*) and McDaniel spider mite (*Tetranychus McDaniel*). The recommended timing for a single application is from delayed dormant through first cover with optimum results likely to be achieved with treatment at petal fall before mites hatch. Application would be by ground equipment using dilute or concentrate sprays at a rate of 300-600 mL Apollo SC/hectare in water volumes ranging from 475 to 3800 litres.

11.2 Description of Market

Apple production in Canada is centred in Quebec, Ontario, British Columbia, Nova Scotia and New Brunswick with the total acreage approximating 35,000 ha (86,000 acres). The farm-gate value of apple production is estimated at $137 million. Although Canada has a substantial apple industry providing both fresh and processed products nationally and internationally, $100 million worth of apple products are imported into Canada annually.

11.3 Pest Problem

A wide range of insect and mite pests offset apple production in all fruit growing regions in Canada. Four phytophagous mite species, European red mite, two-spotted spider mite, apple rust mite and McDaniel spider mite, are considered to be the important pests. In most regions, at least 0.5 to 1.5 miticide applications are utilized annually to reduce populations or to maintain them at acceptable levels. Frequency of applications varies widely among regions and is highly dependent on the type and use of different pesticides required for other pest problems. The sophistication of established integrated mite control programs also affects the frequency of applications. Both factors relate primarily to programs established to conserve and monitor populations of mite predators which help limit plant-feeding mite populations.

The control of mites is seen as particularly important to apple growers because of the adverse effects mites may have on yield and product quality. Quantifying mite feeding damage to apple trees is very complex, with effects varying with apple variety, tree vigour, population levels over time, climate and crop load.

Phytophagous mites are generally considered to be induced pests, being almost completely regulated by natural enemies in the wild. In commercial orchards without predators, miticides are often necessary because the pesticides needed to manage other key pests reduce the natural enemy complexes. In general, all pesticides and application rates recommended in apple pest control programs are selected to conserve predators or are evaluated to determine the degree of impact. Decisions to utilize other pesticides and rates which may ultimately lead to severe mite increases are taken because extensive direct fruit loss would occur if these other pests are left untreated.

11.4 Available Control Methods

In most commercial orchards, both phytophagous mites and predators are routinely monitored to ensure that the populations do not reach unacceptable levels. Each apple producing region in Canada utilizes interventions such as miticides differently because dissimilar key pests and other crop management strategies dictate use of other pesticides which impact on mite predators.

In those apple producing regions which rely upon more extensive use of miticides, rapid evolution of miticide-resistant biotypes has occurred. Currently available miticides in Canada for mite control on apples include: dormant oils, dicofol (Kelthane) formetanate hydrochloride (Carzol), chinomethionate (Morestan), propargite (Omite), and fenbutatin oxide (Torque). Viable mite control programs, if needed, require proper alternation of miticides in order to minimize the possibility of pesticide resistance development. This is important, even, in areas with reasonably stable pest management programs because the entire pest complex on apple is constantly changing. For example, the introduction of a new pest or the development of resistance to a key pesticide necessitates the use of a novel pesticide which may dramatically alter the natural enemy complex.

11.5 Efficacy Trials and Yield/Quality Effects Including Phytoxicity

Apollo SC was evaluated extensively by Agriculture Canada Research Branch scientists, provincial agricultural

authorities and company representatives in all apple growing areas of Canada from 1985-1988. Unlike most currently registered actives with miticidal activity, clofentezine has been shown to act primarily as an ovicide and thus application is made earlier in the growing season when adult mite populations may be at lower levels.

In the efficacy trials conducted in Canada, the degree of mite control was determined in comparison to untreated plots or plots treated with alternative products. The range of rates and timings (up to first cover) proposed by the manufacturer have been tested.

In general terms, the results from these trials showed acceptable levels of mite control. The level and duration of control (i.e., maintaining population

levels below economic treatment levels[2]) varied among regions and seasons and was dependent upon treatment timing, and pest and predator population levels. For purposes of this section, only one example of typical results achieved with Apollo against European red mite on apple is presented in Table 3.

Table 3 Effects on European red mite (ERM) and a predatory mite, Typhlodromus occidentalis after a single treatment with clofentezine (Apollo SC) at 350 g/ha applied when eggs of the first summer generation began to hatch (June 5)*.

	Apollo SC			Check (No Treatment)		
Sample Date	Avg. ERM Per Leaf		Predatory Mites Per 50 Leaves	Avg. ERM Per Leaf		Predatory Mites Per 50 Leaves
	Active	Eggs		Active	Eggs	
June 2 (Pre-Spray)	2.6	64.3	8.7	1.6	43.5	10.0
June 15	4.2	50.3	18.0	16.6	30.6	7.3
June 23	3.9	53.9	20.0	28.7	43.7	11.3
June 29	1.7	29.0	22.7	26.1	118.2	10.7
July 13	1.4	43.6	34.0	32.3	175.7	20.7
July 31	7.7	125.9	97.3	39.5	114.7	89.3

* Economic treatment level for this apple block was 15 active ERM per leaf.

Two notable features are evident from the data presented in Table 3. Seasonal mite control was achieved, with the damaging stages of European red mite kept to low levels; likely through a combination of the effects of clofentezine on eggs laid by successive generations and predatory mites. In contrast, levels of European red mite in the untreated plots remained at levels above the economic threshold level for most of the growing season even when fairly high predator population levels were present. The apparent lack of effect on

predatory mites is a second important feature of this active which was demonstrated often in this and other field experiments.

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2 Economic treatment levels which have been established for mite species, such as European red mite on apple, vary from region to region in Canada. Factors such as stage of apple development, variety and strain of apple, seasonal climate and production needs influence acceptable population levels of mites.

Further published performance results for Apollo SC (clofentezine) are found in Pesticide Research Reports[3] published from 1981 to 1988. Apollo SC has been tested on most of the major varieties of apple with no signs of crop injury being reported by investigators.

11.6 Special Product Features

An important, but yet unexplained feature of clofentezine (Apollo SC) is the apparent lack of effect on eggs and young stages of mite predators, such as Typhlodromus occidentalis. This predator is an important component of the mite integrated pest management (IPM) programs established in British Columbia orchards since the late 1960's. Other predatory mites such as Phytoseiulus persimilis, Agistemus longisetus, Typhlodromus pyri, Zetzellia mali (Ewing) have been shown to tolerate clofentezine treatments in field experiments. Although, one study suggests some toxicity to early stages of Typhlodromus pyri, the overall assessment of clofentezine selectivity indicates that this product should prove useful in integrated pest management strategies in all Canadian apple producing regions.

12. REGULATORY POSITION

Based on the review of all available data, full registration under the authority of the Pest Control Products Act has been granted to clofentezine technical (Reg. No. 21034) and the end-use product, Apollo SC (Reg. No. 21035). There are no current outstanding data requirements which would be needed to support the currently acceptable use pattern on apples. Several cautionary label statements and limitations are highlighted below:

1. Users must follow all handling, use directions and clean-up procedures noted on the label. Wear a broad-brimmed hat, long-sleeved coveralls and apron (or a non-permeable rainsuit) and suitable chemical resistant gloves during mixing, loading, application and clean-up to minimize exposure.
2. Do not make more than one application of Apollo SC per season.

3. Do not apply after first cover (provided first cover is not more than 14 days after petal fall).

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3 Compiled by the Expert Committee on Pesticide Use in Agriculture. Address: Research Program Service, Scientific Information Retrieval Section, Research Branch, Agriculture Canada, Ottawa, Ontario, K1A OC6.

Appendix 1. Glossary of Terms and Abbreviations

ADI - allowable daily intake; the amount of chemical (mg/kg) which may be ingested daily for a lifetime without appreciable risk.

Bioconcentration Factor - At equilibrium, bioconcentration is characterized by the bioconcentration factor, KB; the ratio between the concentration in biota, CB, and the concentration in water, Cw, such that: $K_B = C_B/C_W$.

(from: Connell, D.W., 1988, Bioaccumulation behaviour of persistent organic chemicals with aquatic organisms. Rev. Env. Cont. Tox. 102: 117-154).

DT_{50} - the time for 50% disappearance of a chemical, for example, in soil.

EC_{50} - the concentration of a chemical which will be fatal to 50% of the population.

Exposure Assessment - the determination or estimation (qualitative or quantitative) of the magnitude, frequency and route of exposure.

Environmental Fate - the destiny of a chemical after release into the environment; involves temporal and spatial considerations of transport, transfer, storage and transformation.

LC_{50} - the Lethal Concentration 50% value expressed as parts per million (ppm). It is an estimate of the concentration of a pesticide in water that it takes to kill 50% of the test fish. The LC_{50} value in air is used in connection with the poisoning of mammals by inhalation.

LD_{50} - the statistical estimate of a Lethal Dose which, when administered, will kill 50% of the test animals under stated conditions. It is the accepted method of recording the relative toxicity of a pesticide and is expressed in milligrams of dose per kilogram of body weight of the test animal.

M/L/A - refers to mixing, loading, application procedures.

Octanol/Water Partition Coefficient (log K_{ow}) - a value which serves to indicate the likelihood of a chemical's uptake and accumulation in biological organisms.

TDI - theoretical daily intake; calculated by combining information on daily per capita consumption of specific food commodities (produced by Statistics Canada and Nutrition Canada) and the proposed maximum residue limits for each food.