Proposed Re-evaluation Decision PRVD2013-05

Clofentezine

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Overview

Proposed Re-evaluation Decision for Clofentezine

After a thorough re-evaluation of the acaricide clofentezine, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing continued registration for the sale and use of clofentezine products in Canada.

An evaluation of available scientific information found that, under the proposed conditions of use:

- clofentezine has value in the food and crop industry and does not pose unacceptable risks to human health or the environment. As a condition of the continued registration for clofentezine uses, new risk-reduction measures must be included on the labels of clofentezine products. No additional data are required.
- The application rate of 600 mL product/hectare (300 g a.i./ha) used on apples and pears is no longer supported by the registrant and will be removed. The lower rate of 300 mL product/hectare (150 g a.i./ha) will be maintained on product labels.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment.

This proposal affects all end-use products containing clofentezine registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address any new requirements.

The regulatory approach and project plan regarding the re-evaluation of clofentezine was published in Re-evaluation Note, REV2012-06, *Re-evaluation Update: Clofentezine* on 26 September 2012.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for clofentezine and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

This consultation document is presented in two parts. This Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of clofentezine.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information on the cover page of this document).

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration[2]. The Act also requires that products have value[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at www.healthcanada.gc.ca/pmra.

Before making a re-evaluation decision on clofentezine, the PMRA will consider all comments received from the public in response to this consultation document.[4] The PMRA will then publish a Re-evaluation Decision document[5] on clofentezine, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and the PMRA's response to these comments.

For more details on the information presented in this overview, please refer to the Science Evaluation section.

What is Clofentezine?

Clofentezine is an acaricide that controls specific mite species in the egg stage and early larval stages. Clofentezine is registered to control European red mite, two-spotted spider mite and McDaniel spider mite on apples and pears, European red mite and two-spotted spider mite on peaches and nectarine and two-spotted spider mite on raspberries, strawberries and outdoor deciduous nursery stock. It is applied using ground application equipment by farmers and farm workers.

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2 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

3 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's *(a)* efficacy; *(b)* effect on host organisms in connection with which it is intended to be used; and *(c)* health, safety and environmental benefits and social and economic impact".

4 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

5 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

Health Considerations

Can Approved Uses of Clofentezine Affect Human Health?

Additional risk-reduction measures are required on clofentezine labels. Clofentezine is unlikely to affect your health when used according to the revised label directions.

Potential exposure to clofentezine may occur through the diet or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

Clofentezine is of low acute oral toxicity, and low or slight dermal toxicity. Clofentezine is minimally irritating to the eyes, and slightly irritating to the skin. Exposure to clofentezine is not expected to cause skin sensitization.

Target organs of toxicity resulting from repeated oral exposure to clofentezine were the liver and thyroid. Clofentezine administration in repeat-dose oral studies resulted in stimulation of the thyroid gland in rats (but not mice, rabbits or dogs) leading to thyroid tumors in male rats. Clofentezine was not genotoxic.

Clofentezine may induce thyroid follicular cell tumours in rats by a non genotoxic pathway which is mediated by disruption of the pituitary thyroid feedback mechanism. However, data are insufficient to confidently assess the mode of action for carcinogenesis of clofentezine in male rats. Since a threshold mode of action was not established, a quantitative cancer risk assessment was conducted.

When administered to pregnant rabbits, there was no evidence that clofentezine causes malformations, and no evidence of increased sensitivity of the young exposed to this substance.

The risk assessment protects against the above noted effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Due to the low acute toxicity of clofentezine, an acute exposure assessment was not required. An aggregate (i.e., food + water) chronic dietary exposure assessment was conducted, using residues of clofentezine per se in treated crops and drinking water as well as the sum of residues of clofentezine and the 4-hydroxyclofentezine metabolite in animal commodities. The assessment was conducted for different subpopulations representing different ages, genders and reproductive status. The cancer risk was assessed for the general population.

The aggregate chronic exposure estimates do not exceed 1.2% of the chronic reference dose for the general population and all population subgroups when using drinking water concentrations generated from water modelling and are, therefore, not of concern. The aggregate cancer exposure estimate is at about 7×10^{-7}, which is below the PMRA's level of concern for the general population (i.e., $<1 \times 10^{-6}$).

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods. Food containing a pesticide residue that is at or below the established MRL does not pose an unacceptable health risk.

MRLs for clofentezine are currently established on registered domestic and import agricultural uses and published in Health Canada's List of MRLs Regulated under the *Pest Control Products Act* on the Maximum Residue Limits for Pesticides webpage. No amendment to the current MRLs is being proposed as a result of this re-evaluation. However, as no preharvest interval (PHI) was specified on the label for use on apples, a 21-day PHI is being proposed to support the current MRL of 0.5 ppm in/on apples.

Risks in Residential and Other Non-Occupational Environments

Residential risks from the use of clofentezine on fruit trees in residential areas are not of concern.

Even though there are no domestic class registrations for clofentezine, it is possible that commercial applicators could apply clofentezine to fruit trees in residential areas. Estimates of exposure exceed the target Margin of Exposure (MOE) for adults and youth, and are therefore, not of concern. Cancer risk was also not of concern (i.e. below 1×10^{-6}).

Aggregate risk from exposure incurred as a patron of a "Pick Your Own" orchard or berry facility is not of concern.

"Pick Your Own" (PYO) facilities are considered commercial farming operations that allow public access for harvesting in large-scale fields or orchards treated with commercially labelled clofentezine products. A non-cancer aggregate PYO assessment was not required, as there were no acute toxicological endpoints identified. Estimates of cancer risk that aggregate the dermal exposure incurred during harvest and the dietary exposure from consuming fresh fruit were not of concern (i.e. below 1×10^{-6}).

Occupational Risks from Handling Clofentezine

Occupational risks to mixers/loaders and applicators are not of concern, when used according to current label directions.

Occupational risk assessments consider exposure to workers who mix, load, and apply the pesticide. Occupational risks are not of concern for agricultural scenarios based on the current use pattern, and current label mitigation.

Occupational postapplication risks are not of concern based on proposed label directions.

Postapplication occupational risk assessments consider exposure to workers entering treated sites in agriculture. Occupational postapplication risks are not of concern if proposed protective measures are followed. When the proposed mitigation measures such as lengthened restricted-entry intervals are considered, the risk estimates for postapplication workers are not of concern to the Agency.

Environmental Considerations

What Happens When Clofentezine is Introduced Into the Environment?

Clofentezine poses a potential risk to bird and mammal reproduction and saltwater arthropods, and therefore, additional risk reduction measures need to be observed.

Clofentezine, an acaricide, has very low solubility in water, a low vapour pressure and is not expected to volatilize under field conditions.

Clofentezine is non-persistent to moderately persistent in aerobic and anaerobic aquatic systems where it breaks down in a few days by chemical reaction in water (especially hydrolysis) and by biotransformation. Major transformation products are hydrazide-hydrazone, oxadiazole, 2-chlorobenzonitrile and 2-chlorobenzoic acid. These also decline relatively quickly in terrestrial and aerobic aquatic environments.

Clofentezine and its transformation products are not mobile in soils and are not expected to leach to groundwater. Clofentezine was not detected in water monitoring data from Canada and the U.S.

The use of clofentezine poses a negligible risk to terrestrial invertebrates and vascular plants but poses a reproductive risk to birds and mammals feeding on treated fields. Airblast spray drift presents a chronic risk to marine invertebrates, but this can be mitigated with spray buffer zones. Clofentezine does not present an acute or chronic risk to freshwater organisms.

Clofentezine and its transformation products, hydrazide-hydrazone, oxadiazole, 2-chlorobenzonitrile and 2-chlorobenzoic acid, do not meet any of the criteria under the Toxic Substances Management Policy to be considered as Track 1 substances and are not expected to form any further transformation products that meet all Track 1 criteria.

Value Considerations

What is the Value of Clofentezine?

Clofentezine is an ovicidal acaricide.

In Canada, there are few registered acaricides that control specific mite species at the egg stage and early larval stages. When treatment thresholds for pest mite eggs are reached an ovicide may be required. Clofentezine's uniqueness as an ovicide makes it a valuable tool in mite control and resistance management because it can be rotated with the few other acaricides that are also effective against the egg stage. Also, an early application of an ovicide may keep pest mite populations below damaging levels and reduce the need for an additional application of an acaricide. Avoiding additional acaricide applications is an effective strategy for minimizing the potential for development of pesticide resistance.

Clofentezine contributes to pesticide resistance management.

Resistance by mites to acaricides is a serious concern in orchards, berry crops and ornamentals because plant-feeding mites can adversely affect crop yield or product. Clofentezine can be rotated with the few other registered acaricides so it can help extend the useful life of these acaricides.

In Canada, the limited number of available acaricides does not allow for sufficient rotation between products with differing modes of action to reduce the risk of development of resistance. Clofentezine offers a different mode of action to control specific mite species in the egg stage and early larval stages on apples, pears, peaches, nectarines, raspberries, strawberries and outdoor deciduous nursery stock.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions are required by law to be followed.

Risk-reduction measures are being proposed to address potential risks identified in this assessment. These measures, in addition to those already identified on existing clofentezine product labels, are designed to further protect human health and the environment. The following additional key risk-reduction measures are being proposed.

Additional Key Risk-Reduction Measures

Human Health

To protect workers entering treated sites, restricted-entry intervals (REIs) are to be implemented:

- Apples, pears, peaches, nectarine – REI = 2 days (hand thinning), REI = 12 hours (all other activities);
- Raspberries – REI = 10 days (hand pruning, training, tying), REI = 12 hours (all other activities);
- Strawberries – REI = 12 hours;
- Outdoor deciduous nursery stock – REI = 12 hours.

To support the current MRL of 0.5 ppm in/on apples, a 21-day PHI is required to be added to label directions for use on apples.

To ensure no clofentezine residue uptake by secondary crops, a minimum rotational crop plant back interval (PBI) of 12 months must be observed for all crops other than those registered for use with clofentezine.

Environment

To reduce the exposure of terrestrial and aquatic habitats, additional advisory statements to protect non-target species and the use of spray buffer zones (1–5 metres) to protect aquatic life are required.

Value

The application rate of 600 mL product/hectare (300 g a.i./ha) used on apples and pears is no longer supported by the registrant and will be removed. The lower rate of 300 mL product/hectare (150 g a.i./ha) will be maintained on product labels.

What Additional Information is Being Requested?

The risks and value have been found to be acceptable when all risk-reduction measures are followed; therefore, no additional information is being requested as a result of this re-evaluation.

Next Steps

Before making a re-evaluation decision on clofentezine, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision Document, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Other Information

The test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

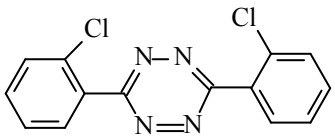
Science Evaluation

1.0 Introduction

Clofentezine is an acaricide (Resistance Management Mode of Action (MOA) Group 10A). Clofentezine acts primarily as an ovicide to control European red mite, two-spotted spider mite and McDaniel spider mite on apples and pears, European red mite and two-spotted spider mite on peaches and nectarines, and two-spotted spider mite on raspberries, strawberries and outdoor deciduous nursery stock. It is a mite growth inhibitor; the target protein responsible for the biological activity of clofentezine is unknown or uncharacterized. Following the re-evaluation announcement for clofentezine, Irvita Plant Protection N.V., the registrant of the technical grade active ingredient and primary data provider in Canada, indicated that it intended to provide continued support for all uses included on the label of the Commercial Class end-use product. There are no Domestic Class end-use products.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name	Clofentezine
Function	Acaricide
Chemical family	Tetrazine
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine
2. Chemical Abstracts Service (CAS)	3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine
CAS Registry Number	74115-24-5
Molecular formula	$C_{14}H_8Cl_2N_4$
Molecular weight	303.1
Structural formula	

Purity of the technical grade active ingredient	99.55% nominal (97.0-100.0%)
Registration number	21034

Identity of relevant impurities of human health or environmental concern
Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	1.3×10^{-7} Pa
Ultraviolet (UV)/visible spectrum	λmax = 270 nm
Solubility in water at 20°C	pH Solubility (µg/L) 5 2.52 7 <2.0
n-Octanol–water partition coefficient (log Kow)	log Kow = 4.1
Dissociation constant (pKa)	Not applicable. No dissociable functionality

2.3 Description of Registered Clofentezine Uses

Appendix I lists all clofentezine products that are registered under the authority of the *Pest Control Products Act*. Appendix II lists all uses for which clofentezine is presently registered. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of clofentezine. Also presented is whether the use was added through the PMRA Minor Use Program. While currently supported by the registrant, the data supporting the use was originally generated by a user group.

Uses of clofentezine belong to the following use-site categories: terrestrial feed and food crops, and ornamental outdoors (deciduous nursery stock).

3.0 Impact on Human and Animal Health

3.1 Toxicological Summary

An extensive toxicity data package has been submitted to the PMRA for the assessment of clofentezine, a phenyltetrazine pesticide. Overall the data are considered adequate to characterize toxicological hazards. Most of the core mammalian toxicity studies are considered to be acceptable by current standards, while the majority of the genotoxicity studies are considered to be supplementary.

Clofentezine is rapidly absorbed, reaching peak plasma concentrations after a few hours. Following absorption, tissue concentrations are generally highest in the liver and kidneys with lesser amounts detected in fat, heart, adrenals and spleen; there are some sex and species-related differences in tissue residue levels. In all species tested, clofentezine is metabolized via two separate pathways (either hydroxylation or methylthiolation), with species related differences noted in the predominant pathway of metabolism. In all species tested, elimination is nearly complete within 48 hours after administration (primarily via the faecal route).

Clofentezine is of low acute oral toxicity in mice, rats, hamsters and dogs and is of low or slight toxicity in rats exposed by the dermal route. An acute inhalation study was not identified. Clofentezine is minimally irritating to the eyes of rabbits and slightly irritating to the skin of guinea pigs. This substance is not considered to be a dermal sensitizer in guinea-pigs.

Following repeated oral exposure to clofentezine, the liver appears to be the primary target organ in all species tested (mice, rats, rabbits and dogs). Critical effects in the liver at low doses in short term oral studies included increased organ weights (all species), increased cholesterol levels (rat, dog) and increased alkaline phosphatase activity (dog). At high oral doses, there was mortality (rats), liver histopathology and increased triglyceride levels (mice, rats and dogs). Clofentezine administration also resulted in stimulation of the thyroid gland in the rat, but not mouse, rabbit or dog. In repeat dose studies, increased serum T4, iodine uptake in the thyroid, and thyroid histopathology (colloid depletion and increased incidence and severity of follicular cell enlargement) were observed in male and female rats, with effects being more pronounced in males. In specialized thyroid studies in which male rats were exposed to high oral doses of clofentezine in the diet, increased serum thyroid stimulating hormone (TSH), T4 and T3, and increased bile flow and excretion of T4 were also observed.

The mouse appears to be the least sensitive species while rat and dog have comparable sensitivities to clofentezine, based on dose selection and observed effects. Repeat-dose studies by the dermal and inhalation routes were not available.

Clofentezine was not genotoxic in *in vitro* assays or supplementary *in vivo* assays. *In vitro* assays included gene mutation studies in *S. typhimurium, B. subtilis, S. cerevisiae* and mouse lymphoma cells, and chromosomal aberration studies in Chinese hamster ovary cells. *In vivo* studies were limited to two supplementary mouse micronuclei assays, and a supplementary rat dominant lethal assay.

In a dietary carcinogenicity study in mice, decreased body weight and survival were noted, accompanied by increased heart and liver weights. In a dietary chronic toxicity/carcinogenicity study, rats had increased liver, testes and epididymal weights, and increased incidences of thyroid follicular hyperplasia in males at the LOAEL. A treatment related increase in thyroid follicular cell adenomas and carcinomas was also observed in high dose male rats.

Thyroid carcinogenesis in rodents may be induced by non genotoxic agents via direct action on the thyroid, or indirectly by alterations in thyroid hormone catabolism and excretion. The only known common pathway through which these agents act is the disruption of the pituitary thyroid feedback mechanism involving increased TSH levels. With adequate data, these agents may be considered irrelevant to human cancer risk assessment at exposure levels which do not lead to changes in thyroid hormone homeostasis.

Points considered in the weight of evidence of carcinogenicity for clofentezine include the following: a) no evidence of carcinogenicity in mice, b) treatment related thyroid tumors in male rats in an adequate study, c) no evidence of genotoxicity in in vitro studies or supplementary in vivo studies, d) hyperplastic lesions and/or adenomas in thyroid follicular cells which appear to progress to thyroid carcinomas and e) microsomal liver enzyme induction and thyroid hormonal imbalance which appear in male rats at doses which are equivalent to, or lower than those which induce thyroid tumors in this sex and species.

Clofentezine may induce thyroid follicular cell tumours in rats by a non genotoxic (threshold) pathway which is mediated by disruption of the pituitary thyroid feedback mechanism. As discussed, this mode of action may not be relevant to humans, or humans may be considerably less sensitive. However, data relating to the dose response relationship for altered homeostasis of the thyroid pituitary axis in relation to tumour induction, and in vivo genotoxicity data are considered insufficient to confidently assess the mode of action of clofentezine in rats. Further information that would support a mode of action framework include adequate in vivo genotoxicity studies, and studies containing data on increases in follicular cell size and number, changes in thyroid and pituitary hormones, correlations between the dose producing thyroid effects and cancer, and reversibility of effects with cessation of exposure. Evidence of the relevance of these changes to humans, taking into account dose and temporal responses, would be required. Information on the progression of lesions over time and structure activity relationships is also desirable.

Since data relating to the disruption of the pituitary thyroid feedback mechanism and in vivo genotoxicity data were considered insufficient to confidently assess the mode of action for carcinogenicity of clofentezine in male rats, animal tumour data are presumed to be relevant for human cancer risk assessment. A linearized low dose extrapolation (q_1*) was conducted to determine potential carcinogenic risk.

In prenatal oral developmental toxicity studies conducted in rats or rabbits, decreased mean foetal weight in rabbits and increased skeletal variations in rats and rabbits coincided with decreased body weight gains in dams exposed to clofentezine. There was no evidence of teratogenicity or increased sensitivity of the young. In the rat reproductive toxicity study, parental toxicity was based on increases in relative liver weight in males. Offspring toxicity

(decreased pup weight and altered sex ratios) was noted in the presence of parental toxicity in the second generation. No increased sensitivity of the young was evident in the rat reproduction study.

Reference doses have been derived based on the no observed adverse effect levels (NOAELs) for the most sensitive indicators of toxicity, namely histopathological effects in the thyroid and organ weight changes in the liver, testes and epididymis. These reference doses incorporate various uncertainty factors to account for extrapolation from animals to humans, as well as for variability within human populations. The toxicology endpoints used in the risk assessment of clofentezine and the results of the toxicity tests are summarized in Table 1 and 2 of Appendix III.

PCPA Hazard Consideration

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10 fold factor to take into account the completeness of the data with respect to the exposure of, and toxicity to, infants and children as well as potential pre and post natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database, no additional studies are required at this time. Data available on clofentezine include developmental toxicity studies in rats and rabbits, and a multi generation reproductive toxicity study in rats.

With respect to potential pre and post natal toxicity, there is no indication of increased susceptibility of foetuses to in-utero exposure to clofentezine. Offspring effects were confined to skeletal changes and decreased foetal weight at very high and maternally toxic doses. Similarly, there was no indication of increased susceptibility in offspring, compared to parental animals, in the rat reproductive toxicity study. An altered sex ratio, considered a serious endpoint, was observed following one mating only. However, this endpoint was seen at maternally toxic levels and at a dose well above that selected for risk assessment.

On the basis of this information, the 10 fold PCPA factor has been reduced to 1 fold.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

Data concerning the mode of action of carcinogenesis of clofentezine in the thyroid of male rats are considered insufficient. Therefore, animal tumour data are presumed to be relevant for risk assessment purposes, and a linearized low dose extrapolation (q_1*) was conducted to determine potential carcinogenic risk in humans. The product of the expected exposure and the cancer potency factor (q_1*) estimates the probability of the lifetime cancer risk. A lifetime cancer risk of 1×10^{-5} in worker populations and 1×10^{-6} in the general population is considered acceptable.

3.2.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment

3.2.1.1 Short-, Intermediate-, And Long-Term Dermal and Inhalation Endpoint(S)

For short- and intermediate-term dermal and inhalation risk assessment, the 13-week subchronic dietary study in rats was selected in the absence of appropriate route-specific studies. A NOAEL of 2.7 mg/kg bw/day was derived based on histopathological effects in the thyroid at the LOAEL of 29 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were used. A PCPA factor of 1-fold was employed for residential scenarios. The target Margin of Exposure (MOE) is 100.

For dermal and inhalation non-occupational risk assessments for the "Pick Your Own" (PYO) scenario, the endpoint selected for the short-term risk assessment was not considered to occur after a single exposure, thus was considered inappropriate for the PYO scenario. There was no other acute endpoint of concern identified and hence a non-cancer PYO assessment was not required.

3.2.1.2 Cancer Potency Factor

Data concerning the mode of action for carcinogenesis of clofentezine in the thyroid of male rats are considered insufficient to confidently establish reference doses on the basis of pre-neoplastic lesions alone. Thus, animal tumour data are presumed to be relevant for risk assessment purposes, and a unit cancer risk estimate (q_1*) of 5.56×10^{-2} $(mg/kg\ bw/day)^{-1}$ was derived based on the incidence of thyroid follicular cell adenomas and carcinomas in male rats. This cancer risk estimate is considered relevant to the occupational and non-occupational risk assessment.

3.2.1.3 Dermal Absorption

Based on a chemical-specific *in vivo* dermal absorption study, a dermal absorption factor of 30% was determined for risk assessment purposes for clofentezine.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to clofentezine through mixing, loading or applying the pesticide, and when entering a treated site to conduct activities such as scouting and/or handling treated crops.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

There is potential exposure to mixers, loaders, and applicators. The following scenarios were assessed:

- Open mixing/loading of liquids
- Airblast application (open cab) to apples, peaches, pears, nectarines, raspberries, and outdoor deciduous nursery stock
- Groundboom application (open cab) to strawberries, raspberries, and outdoor deciduous nursery stock
- Low pressure handwand (manually pressurized handgun) applications to strawberries, raspberries, and outdoor deciduous nursery stock
- High pressure handwand (mechanically pressurized handgun) applications to outdoor deciduous nursery stock
- Backpack application to outdoor deciduous nursery stock

The PMRA estimated handler exposure for mixer/loader/applicators wearing coveralls over a single layer of clothing and chemical-resistant gloves (except for applicators using groundboom equipment), which is consistent with the personal protective equipment (PPE) specified on the label. In addition, it was assumed that mixer/loader/applicators would be using groundboom or airblast equipment with an open cab.

Dermal and inhalation exposures were estimated using data from the *Pesticide Handlers Exposure Database (PHED), Version 1.1*. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment (PPE). In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing coveralls, this was estimated by incorporating a 75% clothing protection factor.

Mixer/loader/applicator exposure estimates are based on the best available data at this time. The assessment might be refined with exposure data representative of modern application equipment and engineering controls. Biological monitoring data could also further refine the assessment.

3.2.2.1.1 Occupational Exposure Non-Cancer Risk Estimates

Occupational risk estimates associated with mixing, loading, and applying clofentezine is summarized in Table 1 of Appendix IV.

Calculated MOEs exceed the target MOE, and are not of concern.

3.2.2.1.2 Occupational Exposure Cancer Risk Estimates

The cancer risk for occupational workers was determined by calculating the lifetime average daily dose (LADD) from dermal and inhalation exposure. The LADD was then compared to the q_1* to obtain cancer risk estimates. The product of the LADD and the q_1* estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-5} to 1 in 10^{-6} or less in worker populations is generally considered acceptable.

Farmer applicators were considered to be exposed 1 day per year and custom applicators were assumed to be exposed 15 days per year based on the maximum number of applications per year, and professional judgement. Additional use pattern information indicates that clofentezine is only used in apples and pears once every 3 to 4 years, and on strawberries and raspberries once every 2 years. For peaches and nectarines, clofentezine is only used on a small subset of the total peaches and nectarines grown in Canada. Since clofentezine is only used rarely in peaches and nectarines, it was assumed the frequency of application would be no greater than that of apples and pears, and that it would be unlikely that applicators would use clofentezine in peaches and nectarines more than once every 3 to 4 years. Based on this information, it was assumed that the treatment frequency would be 1 (farmer) or 15 (custom applicators) day(s) every 3 years (1 or 15 day(s)/3 years for apples, pears, peaches and nectarines, and 1 (farmer) or 15 (custom applicators) day(s) every 2 years (1 or 15 day(s)/2 years) for strawberries and raspberries. For outdoor deciduous nursery stock, it was assumed that farmers and custom applicators would apply clofentezine 1 and 15 days every year, respectively.

Lifetime cancer risk estimates associated with mixing/loading/applying clofentezine for occupational handlers wearing coveralls over a single layer of clothing and chemical-resistant gloves (except for groundboom applicators) are below PMRA's level of concern for occupational scenarios. Table 2 in Appendix IV summarizes the calculated cancer risks for mixer/loaders and applicators.

3.2.2.2 Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (for example, pruning, thinning, harvesting, or scouting). Based on the clofentezine use pattern, there is potential for short-to-intermediate term (>1 day to several weeks) postapplication exposure.

Potential exposure of postapplication workers was estimated using activity-specific transfer coefficients (TCs) and dislodgeable foliar residue (DFR) values. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard agricultural work clothing worn by adult workers. Postapplication exposure activities include harvesting, thinning, pruning, scouting and irrigating.

A chemical-specific DFR study was available for clofentezine. The study was conducted in a Rome apple orchard located in Othello, Washington. Since the dissipation of clofentezine followed first order kinetics with a high regression (i.e., R^2) value of 0.9251, it was considered appropriate to use the equation of the line from the linear regression of the natural log versus days after the last application to estimate DFR values for clofentezine. Estimated DFR values were adjusted for different application rates from those used in the study assuming a linear relationship. This study was used to estimate residues on all agricultural crops. There is uncertainty with this, as the application rate, foliage type, application equipment and crop morphology in the study may not be representative of all crops; however, it is the best data available at this time.

3.2.2.2.1 Postapplication Worker Non-Cancer Exposure and Risk Assessment

For workers entering a treated site, restricted entry intervals (REIs) are calculated to determine the minimum length of time required before people can enter after application. An REI is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures above the target MOE (i.e., > 100 for short-to-intermediate term dermal exposure).

To achieve the target MOE for postapplication workers hand thinning apples, pears, peaches, and nectarines, a 2-day REI is proposed to be added to the label. For all other crops and activities, calculated MOEs exceeded the target MOE with a 12 hour REI (Table 3 in Appendix IV).

3.2.2.2.2 Postapplication Worker Cancer Exposure and Risk Assessment

Cancer risks for postapplication workers were based on exposure to average residues for a 30 day period starting on the day of the recommended REI required to meet the target MOE, as discussed previously (Table 3 in Appendix IV), or the preharvest interval day (as specified on the registered label or proposed in this consultation document). Additional use pattern information indicates that clofentezine is only used in apples and pears once every 3 to 4 years; and on strawberries and raspberries once every 2 years. For peaches and nectarines, clofentezine is only used on a small subset of the total peaches and nectarines grown in Canada. Since clofentezine is only used rarely in peaches and nectarines, it was assumed the frequency of application would be no greater than that of apples and pears, and that it would be unlikely that postapplication workers would use clofentezine in peaches and nectarines more than once every 3 to 4 years. Based on this information, it was assumed that the treatment frequency would be 30 days every 3 years for apples, pears, peaches and nectarines, and 30 days every 2 years for strawberries and raspberries. For outdoor deciduous nursery stock, it was assumed that postapplication workers would be exposed 30 days every year.

A cancer risk less than or equal to 1×10^{-5} is considered acceptable for occupational scenarios. Occupational postapplication cancer risk for clofentezine is greater than 1×10^{-5} for the following use (Table 4 in Appendix IV), and is of concern:

- Hand pruning, training and tying of raspberries

To mitigate these risks, the proposed REI was increased as shown in Table 5 in Appendix IV. The calculated REI of 10 days for hand pruning, training and tying of raspberries is considered to be agronomically feasible. For all other activities, the calculated cancer risk was less than 1×10^{-5} and not of concern, assuming that workers were entering the treated areas on the recommended REI or preharvest interval (PHI).

3.2.3 Non-Occupational and Residential Exposure and Risk Assessment

Residential risk assessment estimates risks to the general population, including children/youths, during or after pesticide application. There are no registered domestic use products for clofentezine. However, there is potential for exposure to adults and youth through contact with transferable residues following commercial application of clofentezine on residential fruit trees.

3.2.3.1 Mixer, Loader and Applicator Exposure and Risk Assessment

As there are no domestic products registered for clofentezine, a mixer/loader/applicator assessment was not required.

3.2.3.2.1 Postapplication Non-Occupational Non-Cancer Exposure and Risk Assessment

There is potential for exposure to adults and youth through contact with transferable residues following commercial application of clofentezine on residential fruit trees. Children are not expected to use these areas for playing nor engage in the types of activities associated with these areas (for example, picking fruit). Apples were chosen as the representative crop. Short-term exposure is expected as there is only 1 application of clofentezine permitted per season.

Postapplication exposure estimates were generated on the basis of assumptions in the EPA Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments and chemical-specific DFR data.

The transfer coefficients used in the assessment are based on the ARTF data for agricultural workers. Only hand harvesting was included as this activity is considered to be the main activity that takes place in residential fruit trees and it addresses activities with lower exposure potential. Other activities associated with high exposure potential, such as thinning, are not expected to occur in residential fruit trees.

Exposure estimates for adults and youth are presented in Table 6 of Appendix IV. Calculated MOEs are greater than the target MOE for all sub-populations and are not of concern.

3.2.3.2.2 Postapplication Non-Occupational Cancer Exposure and Risk Assessment

Cancer risks for adults and youth were based on exposure to average residues for a 5 day period starting on day 0 immediately following application. It was assumed that adults and youth would be exposed to clofentezine 5 days per 3 years based on the median number of days per season that homeowners spend harvesting fruit trees from the Outdoor Residential Pesticide Use and Usage Survey and National Gardening Association Survey and additional use pattern

information that indicates that clofentezine is only used once every 3 to 4 years in apples and pears.

Cancer risk is presented in Table 7 of Appendix IV. Calculated cancer risk for adults and youth exposed to clofentezine from performing activities on fruit trees are below PMRA's level of concern (i.e., $< 1 \times 10^{-6}$).

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to clofentezine from potentially treated imported foods is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when risk exceeds 100% of the reference dose. PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Residue estimates used in the dietary risk assessment (DRA) may be conservatively based on the maximum residue limits (MRLs) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency's (CFIA's) National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (USDA PDP). Specific and empirical processing factors as well as specific information regarding percent of crops treated may also be incorporated to the greatest extent possible.

Due to low acute toxicity, an acute risk assessment was not required. An aggregate (*i.e.,* food + drinking water) chronic dietary exposure assessment as well as an aggregate cancer dietary risk assessment were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™; Version 2.14) program which incorporates consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998.

For more information on dietary risk estimates or residue chemistry information used in the dietary risk assessment, see Appendices V, VI, VII and VIII.

3.3.1 Determination of Acute Reference Dose (ARD)

Due to the low acute toxicity of clofentezine, an acute reference dose was not required.

3.3.2 Determination of Acceptable Daily Intake (ADI)

To estimate dietary risk from repeated exposure to clofentezine, the dietary chronic toxicity/carcinogenicity assay in rats was selected for risk assessment purposes. A NOAEL of 0.4 mg/kg bw/day was derived in this study based on non-neoplastic histopathology in the thyroid, and organ weight changes in the liver, testes and epididymis in males. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were used. The PCPA factor of 1-fold was applied to produce a composite assessment factor of 100.

Acceptable Daily Intake = 0.4 mg/kg bw/day ÷ 100 = 0.004 mg/kg bw/day

The ADI provides a margin of 1000 to the parental and offspring NOAEL in the 2-generation reproductive toxicity study in rats.

3.3.3 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated by using the average consumption of different foods and the average residue values on those foods. This expected intake of residues was then compared to the ADI. When the expected intake of residues is less than the ADI, then chronic dietary exposure is not of concern.

The refined chronic aggregate (food + drinking water) dietary exposure assessment was performed by using available residue monitoring data from USDA PDP. CFIA monitoring was not conducted. Anticipated residues from previous United States Environmental Protection Agency (USEPA) assessments were used for almond, meat, meat by-products and dairy products. American tolerances were used for walnut and persimmon. Supervised trial mean residue values from previous JMPR assessments were used for all other tree nuts, citrus fruits, cucumber, currant and tomato. The Codex MRL was used for dried currant and the Canadian general MRL was used for raspberry. In addition, the following inputs were used: available percent crop treated (%CT) information in Canada and in the United States; 100 %CT for all commodities for which percent crop treated information was unavailable (these include commodities imported from other countries); available information on the proportion of domestic production and import supply; experimental processing factors for orange juice and grape wine; default processing factors for all other processed commodities for which no direct monitoring data was available; and the drinking water estimated environmental concentration (EEC) obtained from modelling.

The assessment results show that the chronic exposure estimates for the general population and all population subgroups do not exceed 1.2% of the ADI and are, therefore, not of concern (Appendix V).

3.3.4 Determination of Cancer Reference Dose

Data concerning the mode of action for carcinogenesis of clofentezine in the thyroid of male rats are considered insufficient to confidently establish reference doses on the basis of pre-neoplastic lesions alone. Thus, animal tumour data are presumed to be relevant for risk assessment purposes, and a unit cancer risk estimate of 5.56×10^{-2} (mg/kg bw/day)$^{-1}$ was derived based on the incidence of thyroid follicular cell adenomas and carcinomas in male rats. This cancer risk estimate is considered relevant to dietary risk assessment.

3.3.5 Cancer Dietary Exposure and Risk Assessment

A refined cancer aggregate (food + drinking water) exposure assessment was performed for the general population using the same residues from the aggregate chronic risk assessments and applying the q_1* of 0.0556 (mg/kg bw/day)$^{-1}$. The results show that the cancer aggregate exposure estimate is about 7×10^{-7}, below the PMRA's level of concern for the general population (*i.e.,* $<1 \times 10^{-6}$) (Appendix V).

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Drinking water estimated environmental concentrations (EECs) of clofentezine were calculated using PRZM/EXAMS and LEACHM models for surface and groundwater, respectively (see modelling details below and Appendix XI). The highest surface water reservoir yearly average Level 1 EEC value of 0.000095 ppm was used in both chronic and cancer risk assessments.

Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

Estimated environmental concentrations (EECs) of clofentezine in potential drinking water sources (groundwater and surface water) were estimated using computer simulation models. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of clofentezine in groundwater were calculated using the LEACHM model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using LEACHM are based on the flux, or movement, of pesticide into shallow groundwater with time. EECs of clofentezine in surface water were calculated using the PRZM/EXAMS models, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir and a prairie dugout.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Ten initial application dates between May and July were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in the Table 1, Appendix XI. Note that the solubility was increased by 20 times for both of reservoir and dugout

runs in order to bypass the EXAMS model's restriction that concentrations not exceed the half of the solubility. These resulted in predicted EECs greater than the chemical's solubility of 2 µg /L. The limit of solubility should be considered for water exposure assessment. Where appropriate, the limit of solubility, along with the predicted EECs, is reported in Table 1, Appendix XI. The bracketed EECs could indicate additional exposure for the given application rate and scenario in less than pure water although there is considerable uncertainty in modeling of an artificially increased solubility. Details of water modelling inputs and calculations are available upon request.

3.4.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were not calculated separately. They were combined with food exposure estimates, with the EEC point estimate incorporated directly in the dietary (food + drinking water) assessments. Please refer to sections 3.3.3, 3.3.5 and 3.5 for details.

3.5 Aggregate Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Aggregate Exposure and Risk Assessment

PYO farms are those that allow the public to harvest their own fruits and vegetables. As PYO fruit and vegetable operations become more and more prevalent, the PMRA recognizes the need for a means of assessing exposure to pesticides during hand harvesting by members of the public. For the purpose of this risk assessment, PYO facilities are considered commercial farming operations that allow public access for harvesting in large-scale fields or orchards treated with commercially labelled clofentezine products.

Although there are many PYO operations involving a wide variety of produce across Canada, only a few orchard and berry crops can be eaten in an appreciable quantity during the harvest. For those PYO crops that do not represent acute, commodity-specific dietary exposure, the hand harvest exposure is covered off by the occupational postapplication exposure assessment.

The PYO assessment for clofentezine focuses on apples and strawberries. Even though it is possible that bystanders will hand harvest at PYO operations more than once per year, due to the intermittent nature of this exposure, this exposure scenario was considered to be acute in nature (i.e., 1 day).

As there is potential for a person to be exposed through contact with treated foliage as well as eating the fruits they are harvesting, both dermal and oral exposure were aggregated in the PYO cancer risk assessment.

3.5.1.1 Non-Cancer PYO Exposure Assessment

Potential exposure from PYO operations is expected to be acute in nature (i.e., one day). As there were no acute toxicological endpoints identified (see Section 3.2.1.1), a non-cancer aggregate PYO assessment was not required.

3.5.1.2 Cancer PYO Exposure and Risk Assessment

The PYO cancer risk assessment for clofentezine aggregated the dermal exposure from hand harvesting fruit, and oral exposure for consumption of fresh fruit during harvest. Since members of the public who harvest at PYO facilities may be of any age, the risk assessment was conducted for toddlers, youths, and adults. Two exposure pathways were considered: ingestion of fruit and dermal exposure through contact with fruit while harvesting. Maximum residue limits (MRLs) were used to estimate the residue of fruits consumed. The MRL is the maximum residue found in field trials, as could potentially occur in a PYO scenario. Dislodgeable foliar residue data were used to estimate the residue dislodged for dermal exposure during harvesting. Acute consumption of apples and strawberries was based on the USDA Continuing Surveys of Food Intakes by Individuals, 1994-1996, 1998.

It was assumed that the number of days spent harvesting apples and strawberries would be 1 day per 3 years for apples and 1 days per 2 years for strawberries based on additional use pattern information that indicates that clofentezine is only used on apples once every three to four years, and once every other year on strawberries.

Calculated aggregate cancer risk is presented in Table 8 of Appendix IV, and is less than PMRA's level of concern of 1×10^{-6}.

3.5.2 Aggregate Short-Term Exposure and Risk Assessment

3.5.2.1 Non-Cancer Aggregate Short-Term Exposure and Risk Assessment

Potential dermal exposure to adults and youth through contact with transferable residues following commercial application of clofentezine on residential fruit trees were aggregated with chronic dietary exposure estimates including drinking water.

The short-term aggregate exposure is presented in Table 9 of Appendix IV. Calculated aggregate MOEs are greater than the target MOE of 100.

3.5.2.2 Cancer Aggregate Short-Term Exposure and Risk Assessment

Cancer risk is presented in Table 10 of Appendix IV. Calculated cancer risk for adults and youth exposed to clofentezine from performing activities on fruit trees are below PMRA's level of concern of 1×10^{-6}.

3.6 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents from Canada and the United States were searched and reviewed for clofentezine. As of 28 March, 2012, there were no incident reports submitted to the PMRA for clofentezine.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The fate and behaviour data for clofentezine and its transformation products in terrestrial and aquatic environments are presented in Tables 6-1 and 6-2 (Appendix IX).

Clofentezine enters the terrestrial environment when it is used as an acaricide on a variety of fruit crops and outdoor nursery stock. Based on its physical properties, clofentezine has a very low solubility in water (< 2.52 µg a.i./L). It has a low vapour pressure (6.0×10^{-7} Pa at 20ºC) and is not expected to volatilize under field conditions. However, its Henry's law constant of 1.66×10^{-6} atm m^3/mole indicates that clofentezine has some potential to volatize from water but based on its rapid dissipation (hydrolysis, phototransformation and biotransformation) in standard environmental conditions in soil and water media, this is not expected to be a major route of dissipation. Phototransformation in soils is also not expected to be a major route of transformation for clofentezine (DT_{50} of 184 d).

Soil biotransformation studies, conducted under aerobic conditions in the laboratory, show that clofentzine is moderately persistent to persistent (DT_{50} 15.3-142 d). Under anaerobic conditions (flooded soil), clofentezine is more readily bound to soil and less readily transformed than under aerobic conditions. Mineralization of clofentezine residues to CO_2 proceeds rapidly in aerobic soils, but ceases when soils are flooded. Studies conducted with non-sterilized soils indicate that complete mineralization of clofentezine residues required full microbial activity but that non-biotic processes (for example, hydrolysis) may also be important in the transformation of clofentezine in soil.

Adsorption/desorption studies, soil column leaching studies, and soil TLC studies all indicate that clofentezine has low mobility or remains immobile in the soil and therefore has a low potential to leach to groundwater. In addition to the laboratory studies on mobility, leaching potential was also assessed against the leaching criteria of Cohen *et al*. (1984) and by the calculation of a groundwater ubiquity score (GUS) which both indicate that clofentezine has a low potential to leach. Under field conditions in both Canada and the United States, clofentezine remains in the upper soil horizons and is considered to be non-persistent to slightly persistent with estimated DT_{50} values (at the end of first season) ranging from 6.3 to 18.6 days. The conclusion that clofentezine is unlikely to leach is further supported by the groundwater

modelling results which do not predict any residues in groundwater (Table 1, Appendix XI). The above information all support the conclusion that clofentezine is unlikely to contaminate groundwater.

In aerobic soil biotransformation studies hydrazide-hydrazone and oxadiazole were the major transformation products formed, reaching levels of 13% and 10.8% of the applied clofentezine, respectively. These compounds were not persistent and had decreased to levels below 5% of the applied clofentezine by the end of the study. These two compounds were not detected in two other tested soils. During phototransformation in soil, the main transformation product was determined to be 2-chlorobenzonitrile (reaching a maximum of 5.5% of the amount of clofentezine applied by the end of the study).

Clofentezine can enter aquatic environments through spray drift and run-off from the application site. The hydrolysis of clofentezine is an important route of transformation in water under all environment conditions. The DT_{50} of clofentezine at 25ºC and pH 7 is 1.0 day. Major transformation products are hydrazide-hydrazone, and 2-chlorobenzontrile. The phototransformation of clofentezine in water under laboratory conditions is also a major route of dissipation with a DT_{50} of 5.7 days and 2-chlorobenzonitrile being the major transformation product formed.

Aerobic and anaerobic aquatic studies also showed that clofentezine dissipated rapidly from the water phase and partitioned into the sediment compartment where dissipation occurred more slowly. Whole system DT_{50}s ranged between 7.1 and 41.1 days. These results indicate that clofentezine is non-persistent to moderately persistent in aerobic and anaerobic aquatic systems. Among four aerobic aquatic systems tested, two systems detected hydrazide-hydrazone (in sediments only) and 2-chlorobenzoic acid (whole system) as major transformation products, but by the end of the studies the concentrations had declined to levels that would classify them as minor transformation products. The DT_{50} of hydrazide-hydrazone ranged between 12.6 and 21 days. These two compounds were also the major transformation products produced in anaerobic aquatic studies.

Based on the available information, hydrolysis, phototransformation, and biotansformation are all likely to be important processes contributing to the dissipation of clofentezine in natural waters.

Studies indicated that the bioconcentration factor (BCF) in fish varies between 230 and 430. However, clofentezine is rapidly metabolized by fish, with a clearance half-life of less than one day. Depuration of the transformation product hydrazide-hydrazone is also reported to occur rapidly in aquatic systems. Based on this information and the relatively rapid breakdown of clofentezine in natural waters, bioconcentration is unlikely to be of concern.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects

occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. EECs are presented in Tables 8-1 to 8-8 in Appendix IX. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level). Summaries of toxicity data for both terrestrial and aquatic non-target organisms to clofentezine are presented in Tables 7-1 and 7-2 in Appendix IX.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1, except for some species of beneficials where LOC = 2). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible. Data derived from monitoring studies may also be used in refining a risk assessment.

4.2.1 Risk to Terrestrial Organisms

The risk assessment of clofentezine to terrestrial organisms was based upon an evaluation of toxicity data for the following organisms:

- one earthworm species (acute and chronic exposure)
- several earthworm species (field exposure)
- one soil beneficial species (chronic exposure)
- two bee species and literature review (acute contact, acute oral and bee brood exposure)
- nine predators and parasitic arthropods (acute and field exposure)
- two bird species (acute and reproduction exposure)
- two mammal species (acute and reproduction exposure)
- several plant species (seedling emergence and vegetative vigour exposure)

Risk to Earthworms, Soil Beneficials, Bees, Predators and Parasitic Arthropods

Acute, chronic and field studies showed that clofentezine was not very toxic to earthworms. The level of concern (LOC) was not exceeded (RQ < 1; Table 5, Appendix IX), indicating that clofentezine is not expected to pose a risk to earthworms. Clofentezine is not chronically toxic to the soil beneficial arthropod *Folsomia candida*. The LOC was not exceeded (RQ < 1; Table 5, Appendix IX), indicating that clofentezine is not expected to pose a risk to soil beneficials.

Clofentezine is also not acutely toxic (contact and oral) to bee adults. The LOC was not exceeded (RQ < 1; Table 5, Appendix IX), indicating that clofentezine is not expected to pose a risk to adult bees. No data on toxicity to bee brood were available for review. However, clofentezine is not used intensively in Canada (only 5.3% of the total potential fields, between 2001 and 2009) and undergoes rapid hydrolysis in the environment with a DT_{50} of 1.1 day at pH 7 at 25˚C. Moreover, clofentezine has not been detected in field pollen samples (n=79) in France (Chauzat *et al.* 2006) and was not reported in any bee hive matrices (wax, pollen or bee samples) in an extensive pesticide residue survey in apiaries in the United States and in part of Canada (Mullin *et al*. 2010) with a level of detection of 10 ppb. Based on the expected short half-life of clofentezine in the environment, the level of residues that may be exposed to honey bee castes in hives is expected to be negligible. Also, honey bee brood are exposed to clofentezine residues mainly through feeding on contaminated bee bread, the fermented pollen and nectar brought into the hives by foraging bees. Brood is unlikely to be exposed directly to raw plant pollen and nectars. Further degradation of clofentezine residues is expected during the processing of bee bread, thus the level of exposure to brood likely is even further reduced.

While screening chemicals to control mite infection in bee hives, Atkins at the University of California reported that clofentezine was non-toxic to both adult and larval honey bees (LD_{50s} = 112.11 ug/bee larvae; more than 79 ug/bee adult respectively) (Project No 1499 report, accessed online on 29 September 2012 http://info.ucanr.org/alfseed/1989/30.pdf). Although detailed study methodology was not provided in the report, the reported LD_{50} value for adult honey bees is similar to what is reported in this current review. The reported large LD_{50} value for honey bee larvae implies that clofentezine has low or non-toxicity to honey bee larvae. This LD_{50} value was not used in the quantitative risk assessment for brood since detailed study methodology was not provided. However, this study does indicate that negligible risk is expected for honey bee larvae exposed to clofentezine.

The above information in combination with the long history of use in Canada and foreign countries and the absence of incident reports indicate that clofentezine is unlikely to pose significant risks to honey bee brood for the proposed use pattern.

A risk to predatory and parasitic arthropods was observed at the screening level but refinement of the risk assessment showed that predators and parasitic arthropods population would recover from exposure to clofentezine at a maximum rate of application in the field (250 g a.i./ha) (Tables 6, 13 and 14, Appendix IX).

Risk to Birds

Based on the screening level assessment, acute risk to birds from the use of clofentezine is not expected. However, the level of concern was exceeded for reproduction (Tables 7 and 8, Appendix IX).

To further characterize the reproductive risk for birds, the assessment was expanded to include all relevant food guilds and food items and by considering both mean and maximum residue values from the nomogram. Also, both on- and off-field exposure estimates were used. The off-field exposure takes into account the projected drift deposition at one metre downwind from the site of application.

The highest cumulative application rate of clofentezine for ground boom application (250 g a.i./ha with 1 application in strawberry and raspberry productions) and airblast application (150 g a.i./ha with 1 application in apple, pear, peach and nectarine productions) were selected for the assessment. Although the airblast application scenario represents a lower application rate than the ground boom application scenario, this type of application generates greater drift than applications with a ground boom and was thought to provide useful insight on the off-field risk. Deposition off the treated area is projected to be 6% and 74% of the application rate for applications with a ground boom (medium droplet size) and airblast application (fine droplets, early season), respectively.

Groundboom application in strawberry and raspberry production scenario for birds

Further characterization of the reproductive risk from an application of clofentezine at 250 g a.i./ha using a ground boom sprayer is presented in Table 15, Appendix IX. When considering maximum nomogram residue values, the level of concern was exceeded for all sizes of birds and most food guilds consuming contaminated items on the treated area (on-field RQ = 1.1 – 4.7). The level of concern was also exceeded when considering mean residues for small insectivores and frugivores, medium insectivores, and large herbivores (RQ = 1.1–2.6). Given that a potential for concern for reproductive effects was identified in all sizes of birds with various feeding preferences and using a range of residue concentrations, a label statement indicating that clofentezine is toxic to birds is required. The level of concern was not exceeded for birds feeding off the treated area.

The above risk quotients were calculated based on the NOEL from a reproduction study with the bobwhite quail. The NOEL represents the dose at which no effects were observed during the study and is used as a starting point for the reproductive risk assessment due to its conservative nature. For the current assessment, risk quotients were also calculated with the LOEL from the same bobwhite study in order to further explore the likelihood that adverse effects would occur in a field situation (Table 16, Appendix IX). Adverse effects observed at the LOEL under laboratory conditions included a statistically significant decrease in embryo viability at 7.82 mg a.i./kg body weight/day (or 90 ppm). The level of concern was still exceeded for small and medium sized insectivorous birds and large herbivorous birds when using an endpoint at which effects were observed under laboratory conditions. This further supports the conclusion that clofentezine could pose an on-field reproductive risk to birds.

Airblast application in apple, pear, peach and nectarine orchard scenario for birds

Further characterization of the reproductive risk from an airblast early season application of clofentezine at 150 g a.i./ha is presented in Table 17, Appendix IX. When considering maximum nomogram residues, the risk quotients exceeded the level of concern for small and medium insectivores and frugivores as well as large herbivores feeding both on and off the treated area (RQ = 1.1-2.8). When considering mean nomogram residues, the risk quotients slightly exceeded the level of concern for small and medium insectivorous birds feeding on the treated area (RQ = 1.2 – 1.6) and small insectivorous birds feeding off the treated area (RQ = 1.2).

When considering the LOEL, the risk quotients did not exceed the level of concern for the airblast scenario (Table 18, Appendix IX) since the airblast application is carried out at a lower rate than for the ground boom application scenario assessed above. Nonetheless, because a potential for concern was identified with the NOEL, the requirement for a hazard label statement is maintained.

Risk to Mammals

Based on the screening level assessment, acute risk to mammals from the use of clofentezine is not expected. However, the level of concern was exceeded for reproduction. As was the case for birds, the assessment was expanded to further characterize the reproductive risk to mammals.

The mammalian acute oral and reproductive endpoints are shown in Table 9, Appendix IX. An acute oral LD_{50} of >3200 mg a.i./kg bw was reported for mice. In a 2-generations reproductive dietary toxicity study using rats, the NOEL was determined to be 3.9 mg a.i./kg bw/day based on decreased F2 pup body weight at LD 21 (male). The LOEL from the same study was 36.1 mg a.i./kg bw/day. Screening level EDE and RQ calculations for the mammalian risk assessment are presented in Table 10, Appendix IX. The screening level assessment is based on the conservative scenario of mammals consuming food items contaminated with maximum levels of residues from the direct application of clofentezine at 250 g a.i./ha.

Groundboom application in strawberry and raspberry production scenario for mammals

Further characterization of the reproductive risk from an application of clofentezine at 250 g a.i./ha using a ground boom sprayer is presented in Table 19, Appendix IX. When considering maximum nomogram residue values, the level of concern was exceeded for all sizes of mammals (small and medium insectivores, medium and large herbivores) consuming contaminated items on the treated area (RQ = 1.6–8). The level of concern was also exceeded when considering mean residues for small insectivores as well as medium and large herbivores (RQ = 1.1–2.1). Given that a potential for concern for reproductive effects was identified in all sizes of mammals with varying feeding preferences and using a range of residue concentrations, a label statement indicating that clofentezine is toxic to mammals is required. The level of concern was not exceeded for mammals feeding off the treated area.

To further explore the potential for reproductive concern, an additional assessment was carried out using a reproductive LOEL of 36.1 mg a.i./kg bw/day (Table 20, Appendix IX). Risk quotients calculated with this endpoint were below the level of concern. However, because a wide margin separates the NOEL and LOEL (test concentrations differ by an order of

magnitude), it is unclear at which concentration between the NOEL and LOEL adverse effects would begin to occur.

Airblast application in apple, pear, peach and nectarine orchard scenario for mammals

Further characterization of the reproductive risk from an airblast application of clofentezine at 150 g a.i./ha is presented in Table 21, Appendix IX. When considering maximum nomogram residues, the level of concern was exceeded for small insectivores and medium and large herbivores feeding on the treated area (RQ = 1.1 – 2.2). When considering mean residues, the level of concern was exceeded for medium herbivores (RQ = 1.1– 1.2). The level of concern was not exceeded for mammals feeding off the treated area. Given the large difference between the NOEL and LOEL, the risk was not further explored using the LOEL.

Risk to Non-Target Terrestrial Plant

The screening level risk quotients for the maximum application rate (250 g a.i./ha) of clofentezine to plant was based on vegetative vigour endpoint (ER_{25} of > 291.96 g a.i./ha, using a ground boom equipment. The risk quotient did not exceed the level of concern (RQ <0.86) (Table 11, Appendix IX).

Transformation Products

No toxicity data were available to test the toxicity of transformation products of clofentezine to terrestrial organisms. However, no major transformation products were detected at the end of soil biotransformation and phototransformation studies (< 10% AR). Transformation products are considered not persistent and exposure expected to be limited. As such no additional studies are required at this time for further ecotoxicological review.

Endocrine Disruption

The USEPA's Endocrine Disruptor Screening Program (EDSP) is a scientific program to screen pesticides, other chemicals, and environmental contaminants to identify substances having the potential to affect the estrogen, androgen or thyroid hormone systems. Clofentezine was included in the second EDSPList. (http://epa.gov/endo /pubs/draftlist2.pdf). PMRA will consider the results of these screening tests as they become available.

4.2.2 Risks to Aquatic Organisms

The risk assessment of clofentezine to aquatic organisms was based upon an evaluation of toxicity data for the following organisms with both the technical grade active ingredient and the formulated products:

- two freshwater invertebrate species (acute and chronic exposure)
- three freshwater fish species (acute and chronic ELS exposure)
- three freshwater surrogate species for amphibians (acute and chronic ELS exposure)
- three freshwater algae species species (acute exposure)
- one saltwater invertebrate (chronic exposure)

A summary of aquatic toxicity data for clofentezine is presented in Table 4, Appendix IX. There was no toxicity data available for aquatic vascular plants. However, based on algae and terrestrial plant studies that show low toxicity, it is not anticipated that clofentezine will be toxic to aquatic vascular plants.

At the screening level assessment, risk quotients for all freshwater organisms such as invertebrates, fish, amphibian (based on surrogate species) and algae, that were tested with the end-use product (Apollo 50 SC) following acute and chronic exposures, were all below the level of concern.

No true endpoints were reported for acute tests conducted with the technical grade active ingredient. Endpoint values (EC_{50}-LC_{50}) were always greater than the maximum concentration tested, which in most cases reflected the very low limit of solubility or its maximum saturation reached during tests. For chronic exposure, the NOEC values obtained with the technical grade active ingredient always corresponded to the highest concentrations tested, except for the saltwater mysid study. Also, the duration of the chronic studies using technical grade active ingredient in flow through system, were long and are believed to be very conservative since clofentezine is known to dissipate rapidly from aquatic system. Endpoints obtained with the end-use products also reflected more accurately the actual spray treatment occurring in agricultural fields, especially for drift (Table 12, Appendix IX). As such the risk quotients reported are calculated with the end-use product rather than the technical grade active ingredient.

Refined Risk Assessment for Aquatic Organisms and Potential Risk from Drift to Saltwater Mysids

The screening level assessment indicated that aquatic saltwater mysids are at risk from exposure to clofentezine only assuming direct application to an 80 cm deep pond (Table 12, Appendix IX). A refined risk assessment was conducted to investigate the potential risk from drift and run-off, based on the highest percent drift value (6%) expected from the use of ground-boom sprayer equipment using a medium ASAE droplet size and of 74% for the airblast equipment using fine ASAE droplet size.

The refinemed risk assessment for the mysids using the ground boom scenario was below the level of concern (RQ = 0.545), but was above the LOC for the airblast scenario (RQ = 4.2) (Table 22, Appendix IX). As such, buffer zones are required to protect estuarine and marine habitats located near apple, pear, peach and nectarine orchards.

Assessment of Potential Risk from Run-Off

Since the level of concern was exceeded for the saltwater mysid (*Americamysis bahia*), the risk from exposure to run-off into a body of water directly adjacent to the application field was investigated.

The Level 1 clofentezine EECs in a 1-ha receiving water body, predicted by the PRZM-EXAMS model, are presented in (Tables 1 and 2, Appendix X). The value reported by PRZM-EXAMS

are 90th percentile concentrations determined at a number of time-frames including yearly peak, 96 hrs, 21-day, 60-day, 90-day and yearly average.

The RQ for run-off was calculated using the highest EEC in an 80-cm deep water body among different provincial sites. The time frame selected was 21 days, as it more closely represents the exposure duration of the saltwater mysid study. The Risk Quotient (RQ = 0.05) indicates that the level of concern is not exceeded for run-off (Table 23, Appendix IX).

Risk to Aquatic Organisms from Transformation Products

No studies on aquatic organism exposed to clofentezine's transformation products were submitted for risk assessment review. However, EFSA reported three acute endpoints: a 96 hr EC_{50} of 22 mg a.i./L, a 48 hr EC_{50} of 13 mg a.i./L and a 72 hr E_bC_{50} of 16 mg a.i./L for the rainbow fish, the daphnia and the algae *Pseudokirchneriella subcapitata*, respectively, exposed to the substance 2-chlorobenzonitrile.

The screening level risk quotients obtained for the three organisms (rainbow fish RQ = 0.01, daphnia RQ = 0.004 and algae RQ = 0.004) indicates that the level of concern was not exceeded when exposed to 2-chlorobenzonitrile at the highest groundboom application rate of 250 g a.i./L (3.4.2-1) (Table 12, Appendix IX).

No data were available for hydrazide-hydrazone and 2-chlorobenzoic acid. However, these transformation product dissipate relatively quickly in aerobic water/sediment systems (biotransformation and phototransformation process) and are not always present in all aquatic systems, No additional ecotoxicological studies are required.

4.2.3 Risk Mitigation

Birds and Mammals

Potential reproductive risks to birds and mammals have been identified. As such, label statements to inform the users of the potential risks are required on the product label (Appendix XII).

Saltwater Invertebrates Exposed Through Spray Drift

A risk to the saltwater mysid (*americamysis bahia*) through exposure from spray drift was identified. Spray buffer zones are required on the product label to mitigate the impact on sensitive non-target aquatic habitats (Table 1, Appendix XII).

Run-Off Label Statements

EEC in water predicted by PRZM/EXAMS and available surface water modelling indicate that clofentezine does not pose a risk from the application field. A standard run-off statement which appears on all commercial pesticide labels is required on the label.

4.2.4 Incident Reports / Additional Considerations

The availability data from the PMRA database of Health Canada and the USEPA EIIS Incident Reports (1991-2004), related to clofentezine uses; contain no injury reports and no mortality report to any terrestrial and aquatic organisms.

5.0 Value

5.1 Commercial Class Products

5.1.1 Value of Clofentezine

5.1.1.1 Clofentezine Is An Ovicidal Acaricide

Few acaricides registered in Canada are effective against mite eggs. Clofentezine is a specific acaricide which acts primarily as an ovicide. In orchards, dormant oil is the first line of defence to control European red mite but it may cause injury to trees less than 5 years of age or to susceptible cultivars. Clofentezine's uniqueness as an ovicide makes it a valuable tool in mite control because it can be rotated with the few other acaricides that are effective against mite eggs and can be used on young trees and susceptible cultivars. An early season application of an ovicide may keep pest mite populations below damaging levels and reduce the need for an additional application of an acaricide.

5.1.1.2 Clofentezine Is Important In Pesticide Resistance Management

Pesticide resistance develops very quickly in mites because many generations can occur in a single season. Repeated applications of an acaricide will quickly eliminate all susceptible mites in a population, resulting in selection of those individuals that are resistant. The more frequently a population is exposed to a pesticide, the more quickly resistance may develop. In Canada, the limited number of available acaricides does not allow for sufficient rotation between products with differing modes of action to reduce the risk of development of resistance. Clofentezine offers a different mode of action to the other registered acaricides to control specific mite species in the egg stage and early larval stages on apples, pears, peaches, nectarines, raspberries, strawberries and outdoor deciduous nursery stock. Therefore, it can be rotated with the few other registered acaricides, to extend the useful life of these acaricides. The end-use product has long residual control, up to 60 days or longer, depending on the target pest, use rate and environmental conditions. The long residual activity may reduce the need for an additional application of acaricide. Avoidance of additional acaracide applications is the most effective strategy for minimizing the potential for development of pesticide resistance. Several cases of mite resistance to clofentezine have been confirmed in Ontario orchards, therefore for resistance management purposes it is recommended that clofentezine be applied only once every two or more years.

5.2 Domestic Class Products

There are no Domestic Class products containing clofentezine registered in Canada.

6.0 Toxic Substances Management Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, clofentezine was assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Clofentezine does not meet all Track 1 and is not considered a Track 1 substance.
- Clofentezine does not form any transformation products which meet the Track 1 criteria. See Table 10, Appendix IX, for comparison with Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the list in the *Canada Gazette.* The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade clofentezine and its end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02 (PMRA Formulants Policy).

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6 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, *PMRA Formulants Policy*.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for clofentezine was adequate to define the majority of toxic effects which may result from exposure. Clofentezine is of low acute oral toxicity, low or slight dermal toxicity, is minimally irritating to the eyes and is slightly irritating to the skin. Exposure to clofentezine is not expected to cause sensitization. The primary target organs of toxicity were the thyroid and liver. Clofentezine was not teratogenic or genotoxic but did cause thyroid tumors in male rats following prolonged oral exposure. No sensitivity of the young was observed in the toxicity database.

The risk assessment protects against the observed effects by ensuring that the level of human exposure is well below the lowest dose at which these effects are observed in animal tests.

7.1.1 Occupational Risk

For mixer/loader/applicators, based on current label PPE, calculated MOEs exceed the target MOE. In addition, the calculated cancer risk is less than 1×10^{-5}. Therefore, there are no concerns for mixer/loader/applicator exposure and no mitigation measures are required.

For workers entering treated agricultural sites, acceptable MOEs are achieved with REIs of 2 days or less. However, in order to achieve a cancer risk of less than 1×10^{-5} for high contact activities in raspberries (hand pruning, training and tying), the REI needs to be extended to 10 days. These REIs are expected to be agronomically feasible.

7.1.2 Dietary Risk from Food and Drinking Water

No dietary concerns were found from chronic and cancer dietary risk assessments for the general population and all population subgroups, including infants, children, teenagers, adults and seniors.

7.1.3 Non-Occupational Risk

Residential risks from the use of clofentezine on fruit trees in residential areas are not of concern.

7.1.4 Aggregate Risk

Aggregate risk from exposure incurred as a patron of a PYO orchard or berry facility is not of concern.

7.2 Environmental Risk

The refined risk assessment showed that the use of clofentezine at the proposed application rates may pose an on-field risk to bird and mammal reproductions but will not pose a risk to freshwater organisms. A risk to saltwater invertebrates from exposure to drift has been identified.

The risk to birds and mammals can be mitigated with label statements. The risk from drift to saltwater invertebrates can be mitigated with spray buffer zones on the product label. Due to their rapid dissipation and/or absence in most terrestrial and aquatic systems, the transformation products are not expected to pose a risk to terrestrial and aquatic organisms based on proposed application rate of clofentezine.

7.3 Value

Clofentezine is a group 10A Resistance Management Mode of Action (MOA) acaricide that acts primarily as an ovicide to control European red mite, two-spotted spider mite and McDaniel spider mite on apples and pears, European red mite and two-spotted spider mite on peaches and nectarines, and two-spotted spider mite on raspberries, strawberries and outdoor deciduous nursery stock. Resistance by pest mites to acaricides is a serious concern because plant-feeding mites can adversely affect crop yield or product quality. Clofentezine offers a different mode of action to the other registered acaricides for use on apples, pears, peaches, nectarines, raspberries, strawberries, and outdoor deciduous nursery stock therefore it can be rotated with the few other registered acaricides to help extend the useful life of these acaricides. Its uniqueness as an ovicide makes it a valuable tool in mite control and resistance management. An application of an ovicide may keep pest mite populations below damaging levels and reduce the need for an additional application of an acaricide. Avoiding additional acaricide applications is an effective strategy for minimizing the potential for development of pesticide resistance.

8.0 Proposed Regulatory Decision

After a thorough re-evaluation of the acaricide clofentezine, Health Canada's PMRA, under the authority of the *Pest Control Products Act,* is proposing continued registration for the sale and use of clofentezine and associated end-use product, provided that the mitigation measures (Appendix XII) for health and environment described in this document are implemented.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Action Related to Human Health

8.1.1.1 Proposed Mitigation for Occupational Handlers

Use Precautions

In the interest of minimizing public exposure, it is proposed that the following statement be added to all labels:

"Apply only when the potential for drift to areas of human habitation or areas of human activity (for example, houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

For clarification, it is recommended that the following statements be added to the clofentezine product label:

"Not for use in greenhouses."

Restricted Entry Intervals

The recommended restricted entry intervals for all crops and activities are presented below.

Table 8.1.1.1 Recommended Restricted Entry Intervals

Crop	Activity	REI
Apples, Pears, Peaches, Nectarines	Hand Thinning	2 days
	All Other Activities	12 hours
Raspberries	Hand Pruning, Training, Tying	10 days
	All Other Activities	12 hours
Strawberries	All Activities	12 hours
Outdoor Deciduous Nursery Stock	All Activities	12 hours

8.1.1.2 Proposed Mitigation for Dietary Exposure

To support the current MRL of 0.5 ppm in/on apples, the following statement must be added to the label directions for use on apples:

"Do not harvest within 21 days after application."

To ensure no clofentezine residue uptake by unregistred secondary (rotational) crops, the following statement must be added to the label directions for use on strawberries:

"A minimum rotational crop plant back interval of 12 months must be observed for all crops other than those registered for use with clofentezine."

8.1.1.3 Residue Definition for Risk Assessment and Enforcement

The residue definition (RD) is currently expressed as clofentezine per se in plant commodities and the sum of clofententezine plus the 4-hydroxyclofentezine metabolite in animal commodities for both enforcement and dietary risk assessments. No modification to the RD is proposed in this assessment.

8.1.1.4 Maximum Residue Limits for Clofentezine in Food

In general, when the re-evaluation of a pesticide has been completed, the PMRA intends to update Canadian maximum residue limits (MRLs) and to remove MRLs that are no longer supported. The PMRA recognizes, however, that interested parties may want to retain an MRL in the absence of a Canadian registration to allow legal importation of treated commodities into Canada. The PMRA requires similar chemistry and toxicology data for such import MRLs as

those required to support Canadian food use registrations. In addition, the PMRA requires residue data that are representative of use conditions in exporting countries, in the same manner that representative residue data are required to support domestic use of the pesticide. These requirements are necessary so that the PMRA may determine whether the requested MRLs are needed and to ensure they would not result in unacceptable health risks.

Where no specific MRL is established for a pest control product under the *Pest Control Product Act*, subsection B.15.002(1) of the *Food and Drug Regulations* applies. This requires that residues do not exceed 0.1 ppm, which is considered as a General MRL for enforcement purposes. However, changes to this General MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues [Regulation B.15.002(1)]*. If and when the General MRL is revoked, a transition strategy will be established to allow permanent MRLs to be set for the concerned commodities.

Canadian MRLs have been established at 0.5 ppm on almonds, apples, and pears; 1.0 ppm on nectarines and peaches; 0.01 ppm in milk; and 0.05 ppm on all other livestock products (except liver) and published in Health Canada's List of MRLs Regulated under the *Pest Control Products Act* on the Maximum Residue Limits for Pesticides webpage. Residues in/on raspberries and strawberries are regulated under B.15.002(1) of the Food and Drugs Regulations not to exceed 0.1 ppm. The MRLs on almonds, apples, nectarines, peaches and pears were primarily established to cover residues on imported crops, based on United States field trial residue data.

8.1.2 Proposed Regulatory Action Related to Environment

To reduce the effects of clofentezine in the environment, mitigation in the form of precautionary label statements and spray buffer zones are required. Environmental mitigation statements are listed in Appendix XII (*Label Amendments for Commercial Class Products Containing Clofentezine*).

No additional data is required for continued registration.

8.1.3 Proposed Regulatory Action Related to Value

There are no regulatory actions proposed at this time for the continued registration of clofentezine.

Proposed label amendments are included in Appendix XII. These clarify the application rate reduction on apples and pears that are supported by the technical registrant (see Appendix II).

8.2 Additional Data Requirements

8.2.1 Data Requirements Related to Chemistry

No additional data is required for continued registration.

8.2.2 Data Requirements Related to Toxicology

No additional data is required for continued registration.

8.2.3 Data Requirements Related to Occupational Exposure Assessment

No additional data is required for continued registration.

8.2.4 Data Requirements Related to Food Residue Chemistry

No additional data is required for continued registration.

8.2.5 Data Requirements Related to Value

No additional data is required for continued registration.

List of Abbreviations

µg	micrograms
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
atm	atmospheres
bw	body weight
CFIA	Canadian Food Inspection Agency
cm	centimetre(s)
d	day(s)
DACO	data code
DEEM®	Dietary Exposure Evaluation Model
DER	Data Evaluation Report
DFR	dislodgeable foliar residue
DT_{50}	dissipation time to 50%
DWLOC	drinking water level of comparison
DNA	deoxyribonucleic acid
EChE	erythrocyte cholinesterase
EEC	expected environmental concentration
EP	end-use product
EXAMS	Exposure Analysis Modeling System
F_0	parental animals
F_1	first filial generation
F_2	second filial generation
g	gram(s)
GAP	good agricultural practice
GC-FPD	Gas Chromatography-Flame Photometric Detector
GC-MSD	Gas Chromatography-Mass Selective detector
GC-NPD	Gas Chromatography-Nitrogen Phosphorous Detector
ha	hectare(s)
HAP	hours after application
Hg	mercury
IPM	integrated pest management
IRED	Interim Reregistration Eligibility Decision (USEPA Document)
K_d	adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50% (a concentration causing 50% mortality in the test population
LD_{50}	lethal dose to 50% (a dose causing 50% mortality in the test population)
LEACHM	Leaching Estimation and Chemistry Model
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observed effect concentration

m	metre(s)
m^3	metre(s) cubed
mg	milligram(s)
min	minute(s)
mm	millimetre(s)
mm Hg	millimetre mercury
MOE	margin of exposure
MRL	maximum residue limit
nm	nanometre
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OC	organic carbon
OP	organophosphate
PChE	plasma cholinesterase
PCPA	*Pest Control Product Act*
PDP	Pesticide Data Program (United States data)
PHI	preharvest interval
pH	-log10 hydrogen ion concentration
PHED	Pesticide Handlers Exposure Database
pKa	-log10 acid dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppb	parts per billion
ppm	parts per million
PRVD	Proposed Re-evaluation Decision
PRZM	Pesticide Root Zone Model
PSI	pre-slaughter interval
Q_1*	cancer potency factor
RED	Reregistration Eligibility Decision
REI	restricted entry interval
ROC	residue of concern
RQ	risk quotient
TC	transfer coefficient
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
URMULE	User Requested Minor Use Label Expansion
USEPA	United States Environmental Protection Agency
USDA	United States Department of Agriculture
USFDA	United States Food and Drug Administration

Appendix I Registered Clofentezine Products as of 16 March 2012

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
21034	Technical Grade Active Ingredient	Irvita Plant Protection N.V.	ClofentezineTechnical Insecticide	Solid	99.55%
21035	Commercial	Makhteshim Agan of North America Inc.	Apollo SC Ovicidal Miticide	Suspension	500 g / L

Excluding discontinued products or products with a submission for discontinuation

Appendix II Registered Commercial Class Uses Of Clofentezine In Canada as of 16 March 2012

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i./ha)		Maximum Number of Applications per Year	Typical Number of Days Between Applications	Supported Use?[1]
				Maximum Single	Maximum Cumulative			
USC 13, 14								
Apple	European red mite (*Panonychus ulmi),* Two-spotted spider mite (*Tetranychus urticae),* McDaniel spider mite (*Tetranychus mcdanieli)*	Suspension	Ground: foliar spray	300 [150][2]	300 [150][2]	1	Not applicable	Yes
USC 14								
Pear	European red mite (*Panonychus ulmi),* Two-spotted spider mite (*Tetranychus urticae),* McDaniel spider mite (*Tetranychus mcdanieli)*	Suspension	Ground: foliar spray	300 [150][2]	300 [150][2]	1	Not applicable	Yes
Peach and nectarine	European red mite (*Panonychus ulmi),* Two-spotted spider mite (*Tetranychus urticae)*			150	150			Yes, Minor Use Program
Raspberry	Two-spotted spider mite (*Tetranychus urticae)*			250	250			
Strawberry	Two-spotted spider mite (*Tetranychus urticae)*							

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Application Rate (g a.i./ha)		Maximum Number of Applications per Year	Typical Number of Days Between Applications	Supported Use?[1]
				Maximum Single	Maximum Cumulative			
USC 27: Outdoor Ornamentals								
Outdoor deciduous nursery stock	Two-spotted spider mite (*Tetranychus urticae)*	Suspension	Ground: foliar spray	40	40	1	Not applicable	Yes, Minor Use Program

[1] Yes = use is supported by the registrant and Minor Use Program = use was registered as a User Requested Minor Use Label Expansion (URMULE).
[2] [ ] rate supported by registrant

Appendix III Toxicology Health Risk Assessment for Clofentezine

Table 1 Toxicology Endpoints For Use In Health Risk Assessment For Clofentezine

	RfD (mg/kg bw/day)	Study NOAEL (or LOAEL)	CAF[1] or Target MOE
Acute Dietary	**ARfD not required due to low acute toxicity**		
Chronic Dietary	ADI= 0.004 mg/kg bw/day	NOAEL = 0.4 mg/kg bw/day Dietary chronic toxicity/carcinogenicity study in the rat (histopathology in the thyroid, organ weight changes)	100 PCPA = 1-fold
Short-Term, Dermal, Intermediate-Term Dermal[2]		NOAEL= 2.7 mg/kg bw/day 13-week dietary study in the rat (histopathology in the thyroid)	100
Short-Term Inhalation, Intermediate-Term Inhalation[3]		NOAEL= 2.7 mg/kg bw/day 13-week dietary study in the rat (histopathology in the thyroid)	100
Carcinogenicity	Thyroid follicular cell adenomas and carcinomas were observed in male rats in a dietary chronic toxicity/carcinogenicity study Unit risk estimate (q_1*) = 5.56×10^{-2} $(mg/kg\ bw/day)^{-1}$		

[1] CAF (Composite assessment factor) refers to the total uncertainty and PCPA factors for dietary and residential risk assessment; MOE refers to the target margin of exposure for occupational assessment

[2] Since an oral NOAEL was selected, a dermal absorption factor of 30% is used in a route-to-route extrapolation.

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) is used in route-to-route extrapolation.

Table 2 Toxicology Profile for Clofentezine

Note: For studies lacking a specified PMRA #, foreign study evaluations were considered. Effects observed below are known or assumed to occur in both sexes, unless otherwise specified. Organ weight effects reflect both absolute organ weights and relative organ weights unless otherwise noted.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Metabolism/Toxicokinetic Studies			
Summary Rats achieved peak plasma concentrations 4-6 hours after dosing with clofentezine. In Beagle dogs, peak plasma residue levels were 0.06-1.6 µg/mL and occurred between 4 and 8 hr after dosing. There were no sex-related differences in distribution. In both species, plasma levels declined rapidly; plasma levels were ≤ 25% of peak levels, 18 hours after dosing. The elimination and tissue distribution of clofentezine has been determined following administration in male (♂) and female (♀) mice, rats, rabbits, dogs and baboons. In all species, faecal excretion was the predominant route of elimination. Faecal excretion after 96 hr was more prevalent in dog> rat>mouse>rabbit> baboon, with percentages of approximately 95%, 75%, 68%, 57% and 44% of the administered dose, respectively. It appears that at low doses, most of the faecal excretion is a result of biliary excretion and not due to lack of absorption. No sex-related differences were demonstrated in mice, rabbits, dogs or baboons, while male rats demonstrated higher residue levels in some tissues (heart, brain, spleen, lung and muscle), compared to females. Pre-treatment with clofentezine did not have a consistent effect on plasma or tissue residue levels. There is a dose-dependent effect on elimination of clofentezine. At high doses (10000 mg/kg bw/day) only 2% to 5% of the dose was eliminated in urine, whereas at low doses (0.1 or 10 mg/kg bw/day) 20% of the dose was eliminated in urine. This suggests that renal excretion is saturated at doses between 10 and 10000 mg/kg bw/day. In specialized studies of thyroid function, clofentezine was not detected in thyroid tissue. The two metabolic pathways of clofentezine (hydroxylation or methylthiolation) are qualitatively similar in all species tested, although there is interspecies variability in the predominant pathway of metabolism. In the baboon and cow, hydroxylation (and subsequent glucuronide conjugation) is the predominant pathway, with methylthiolation being a very minor route of metabolism. In contrast, methylthiolation was the prominent route of metabolism of clofentezine in the mouse, rat and rabbit. Liver extracts from rat, goat and cow were qualitatively similar to rat urine, and included conjugates of 3-(2'-methyl-thio-3'-hydroxyphenyl)-6-(2'-chloro-phenyl)-1,2,4,5-tetrazine and 3-, 4-, and 5-hydroxyclofentezine. PMRA # 1205363, 1205353, 1205349, 1199853, 1205354, 1205350, 1205352, 1205364, 1199850, 1205351, 1199848, 1199849, 1205355, 1199851, 1199852, 1199854, 1205357, 1205359			
Acute Toxicity Studies - Technical			
Acute Oral Toxicity CD-1 mouse 6/sex/group	Purity - 99.1%	**LD_{50} > 3200 mg/kg bw** Pitted spleens, pink staining of faeces; ↓ BWG (♀) **Low toxicity**	
Acute Oral Toxicity Swiss albino mouse 5/sex	Purity - N/S	**LD_{50} > 5200 mg/kg bw** No clinical observations.	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Acute Oral Toxicity Syrian hamster 6/sex/group	Purity - 99.1 %	**LD_{50} > 3200 mg/kg bw** No clinical observations. **Low toxicity**	
Acute Oral Toxicity CFY SD rat 6/sex/group	Purity - 99 %	**LD_{50} > 3200 mg/kg bw** ≥ 1600 mg/kg bw: ↓ BWG (♀) **Low toxicity**	
Acute Oral Toxicity Sprague-Dawley rat 5/sex	Purity - N/S	**LD_{50} > 5200 mg/kg bw** No clinical observations.	
Acute Oral Toxicity ♀ Guinea pig	Purity - N/S	**LD_{50} > 1500 mg/kg bw (♀)** No clinical signs of toxicity.	
Acute Oral Toxicity Beagle dog 1/sex/group	Purity - 98.8-99.6 %	**LD_{50} > 2000 mg/kg bw** ≥ 1000 mg/kg bw: pink staining of faeces 2000 mg/kg bw: skin reddening and some hair loss (♀)	
Acute Dermal Toxicity Sprague-Dawley rat 6/sex PMRA 1199829	Purity - 99.1 %	**LD_{50} > 1332 mg/kg bw** No clinical observations. **Slight toxicity**	
Acute Dermal Toxicity Sprague-Dawley rat #/sex - N/S	Purity - N/S	**LD_{50} > 2100 mg/kg bw** 2100 mg/kg bw: transient pink staining of the skin **Low toxicity**	
Primary Eye Irritation Study Rabbit 6 animals PMRA 1225756	Purity - 99.3%	No irritation in the cornea or iris but mild conjunctival redness and discharge (6/6) and chemosis (1/6) after 1 hr. Redness only (2/6) was observed after 1 day. Clinical signs were resolved by 48 hours post-dosing. The Maximum Irritation Score (MIS) and Maximum Average Score (MAS) were 4.3 and 0.2, respectively. **Minimally irritating**	
Primary Skin Irritation Study Guinea pig 6 ♀	Purity - 99.1 %	Very slight erythema/oedema in 2/12 sites, resolved by 2.5 days post-dosing. Slightly irritating to the skin	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Dermal Sensitization Magnusson & Kligman Maximization Test Dunkin-Hartley guinea pig 20/group PMRA 1199381	Purity - 99.8%	Scattered mild redness at 24 hr which resolved completely at 48 hrs. **Not a skin sensitizer**	
Short-Term Toxicity Studies			
13-Week Dietary Toxicity Mouse (Strain - N/S) 20/sex/dose	Purity -"technical grade" 0, 200, 1000 or 5000 ppm in diet [≈ 0, 30/35, 151/176 or 757/884 mg/kg bw/day (♂/♀)]	757/884 (♂/♀)	≥ 151/176 mg/kg bw/day: ↑ triglycerides, ↑ Ca and ↑ P levels in plasma; ↑ liver wt, centrilobular hepatocyte enlargement (♂) *[not considered adverse]* 757 mg/kg bw/day: red "stellar" crystals in urine (♂)
17-Day Gavage Toxicity Sprague-Dawley rat 5/sex/group	Purity - N/S 0, 5, 20, 80, 320 or 1280 mg/kg bw/day by gavage		≥ 20 mg/kg bw/day: ↑ liver wt (♀) *[not considered adverse]* 1280 mg/kg bw/day: pinkish-red crystalline particles in urine; ↑ liver wt (♂) **Study is supplementary due to lack of detail.**
13-Week Dietary Toxicity Sprague-Dawley rat 20/sex/group 9-Week Interim 5/sex/group 4-Week Recovery 5/sex/group PMRA 1225674, 1203193	Purity - 98-100% 0, 3000, 9000 or 27000 ppm in diet (0, 212, 632 or 1944 mg/kg bw/day)	LOAEL = 212 mg/kg bw/day	≥ 212 mg/kg bw/day: ↓ body wt, ↑ liver wt, ↑ adrenal wt, ↑ thyroid wt, ↓ Hgb, ↑ cholesterol, ↑ triglycerides, ↑ incidence of centrilobular hepatocellular hypertrophy, ↑ number of animals with hair loss 1944 mg/kg bw/day: ↑ mortality [2 deaths due to severe congestion and/or haemorrhage of the bladder and prostate at Days 6 and 90, respectively (treatment-related)] (♂)

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
13-Week Dietary Toxicity Sprague-Dawley rat (Main: 25/sex/group, 6-Week Recovery Period: 5/sex/group) PMRA 1199837, 1142403, 1199838 and 1199839	Purity - 98.8 -100% 0, 40, 400 or 4000 ppm in diet (= 0, 2.7/3.0, 32.2/29.3, 265/292 mg/kg bw/day) (♂/♀)	2.7/3.0 (♂/♀)	≥ 2.7/3.0 mg/kg bw/day: thyroid colloid depletion (♂) [*not considered adverse*] ≥ 32.2/29.3 mg/kg bw/day: ↑ liver wt, ↑ cholesterol; ↑ thyroid follicular cell size (♂); ↑ absolute spleen wt, thyroid colloid depletion (♀) 265/292 mg/kg bw/day: ↑ absolute kidney wt, ↑ relative spleen wt, ↑ relative combined testes and epididymidal wt, ↑ incidence of dull/cloudy eyes (♂); ↓ BW (8%), ↑ relative spleen wt, ↑ relative kidney wt (♀) 6-Week Recovery: ≥ 32.2 mg/kg bw/day: ↑ absolute heart wt, ↑ relative liver wt (38%) (♂) 265/292 mg/kg bw/day: ↑ relative liver wt, kidney wt (♂); ↑ relative kidney wt (♀)
9-Week Dietary Toxicity Rabbit (Strain - N/S) 6 ♀/group	Purity - N/S 0, 400, 4000 or 8000 mg/kg in diet (≈ 0, 12, 120 or 240 mg/kg bw/day)		≥ 120 mg/kg bw/day: ↑ relative liver wt (♀) ≥ 240 mg/kg bw/day: slight to moderate excess of abdominal fluid, gastric retention of food **Study is supplementary due to lack of detail and single sex used.**
17-Day Gavage Toxicity Dog (Strain - N/S) 1/sex/group	0, 125, 500 or 2000 mg/kg bw/day by gavage		≥ 125 mg/kg bw/day: red or pink colouration of faeces ≥ 2000 mg/kg bw/day: ↑ alpha GT-peptidase, ↑ LDH, ↑alpha-hydroxybutyric dehydrogenase (♂) **Study is supplementary due to lack of detail and small group size.**
4-Week Dietary Toxicity Dog (Strain - N/S) 1/sex/group	Purity - N/S 0, 200, 2000 or 20000 mg/kg in diet (≈ 0, 5, 50 or 500 mg/kg bw/day)		≥ 50 mg/kg bw/day: ↑ relative liver wt **Study is supplementary due to lack of detail and limited number of animals.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
13-Week Dietary Toxicity Beagle dog 4/sex/group PMRA 1199835	Purity - 99.7-99.9% 0, 3200, 8000 or 20000 ppm in diet (≈ 0, 80, 200 and 500 mg/kg bw/day)		≥ 80 mg/kg bw/day: ↑ ALP, ↑ liver wt 500 mg/kg bw/day: ↑ triglycerides; ↑ absolute spleen wt (♂) **Study is supplementary as several of the animals (1/sex/group) were in ill health (polyarteritis; not treatment-related).**
52-Week Dietary Toxicity Beagle dog 6/sex/dose PMRA 1203196, 1212409, 1225677	Purity - 98.2 % 0, 50, 1000 or 20000 ppm in diet (≈ 0, 1.7, 36 or 706 mg/kg bw/day)	36 (♂) 1.7 (♀)	36 mg/kg bw/day: ↑ liver wt (♀) *[not considered adverse]* 706 mg/kg bw/day: ↑ incidence of minimal enlargement of periportal hepatocytes with cytoplasmic eosinophilia (♀>♂); ↑ cholesterol, ↑ absolute liver wt, ↑ leukocytes (♂); ↑ absolute thyroid wt (♀)
Chronic Toxicity/Oncogenicity Studies			
105-Week Dietary Toxicity Swiss CD-1 mouse 52/sex/dose (no interim sacrifice) PMRA 1203211, 1203212 and 1203213	Purity - 98.7 % 0, 50, 500 or 5000 ppm in diet (≈ 0, 5.2, 54, 550 mg/kg bw/day)	54	**Non-neoplastic endpoints:** 550 mg/kg bw/day: ↓ BWG, ↑ absolute testes wt; ↓ survival (*due to amyloidosis*), ↑ absolute heart wt, ↑ absolute liver wt (♀) **No evidence of carcinogenicity**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
118-Week Dietary Toxicity Sprague-Dawley rat 50/sex/dose 52-Week Interim Sacrifice 20/sex/dose PMRA 1203200, 1203201	Purity - 98.5% 0, 10, 40 or 400 ppm in diet (♂/♀: 0, 0.4/0.6, 1.7/2.2 or 17.3/22.1 mg/kg bw/day)	0.4/2.2 (♂/♀)	**Non-neoplastic effects:** ≥ 1.7 mg/kg bw/day: ↑ absolute liver wt, ↑ absolute testes/epididymal weights, ↑ thyroid follicular cell hyperplasia (♂) 17.3/22.1 mg/kg bw/day: ↑ relative liver wt, ↑ relative adrenal wt (♂); ↑ liver wts (♀) 52-week interim sacrifice: 17.3 mg/kg bw/day: ↑ relative liver wt (♂) **Neoplastic effects:** ↑ incidence of combined adenomas and carcinomas in thyroid follicular cells in high-dose males (8/50, 16%, $p<0.05$) exceeding the upper range of historical controls (6/50, 12%), ↑ incidence of thyroid follicular cell carcinomas in high-dose males (5/50, 10%) exceeding concurrent controls (1/50, 2%) **Evidence of carcinogenicity.**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Reproductive and Developmental Toxicity Studies			
2-Generation Reproductive Dietary Toxicity Sprague-Dawley rat 30/sex/control, low and mid-dose, 40/sex/high-dose PMRA 1225684	Purity - 98.5% 0, 4, 40 or 400 ppm in diet 2 litters per generation (a and b) 74-day pre-mating treatment period F_2 generation sacrificed after 82-84 days of treatment. **[Study average intake: ≈ 0, 0.4/0.4, 3.6/3.9 or 36.1/38.5 mg/kg bw/day (♂/♀)]**	Parental: 3.6/3.9 Reproductive: 3.9 Offspring: 3.9	Parental: ≥ 3.6/3.9 mg/kg bw/day: ↑ F_2 relative liver wt (♂) *[adaptive response, not considered adverse]* 36.1/38.5 mg/kg bw/day: ↑ F_1 relative liver wt associated with minimal centrilobular hypertrophy and slight reduction in periportal fat deposition, ↓ F_2 BW (Weeks 1-6 only), ↑ F_2 relative liver wt (♂); ↓ F_1 BW, ↓ F_1 BW GD 4-21 (♀) Reproductive: 38.5 mg/kg bw/day: F_{2a} altered sex ratios Offspring: ≥ 3.9 mg/kg bw/day: ↓ F_{2a} pup BW at LD 21 (♂) *[pups may have been exposed to clofentezine via both lactation and diet and thus may have received higher intakes than those presented above]* 38.5 mg/kg bw/day: ↓ F_{2a} pup BW at LD 10, 14 and 21
Developmental Toxicity Sprague-Dawley rat 30-35 ♀/group PMRA 1225687	Purity - 99.8% 0, 320, 1280 or 3200 mg/kg bw/day by gavage on gestation days (GD) 7-20	Maternal: 1280 Developmental: 1280	Maternal: ≥ 1280 mg/kg bw/day: ↑ relative liver wt (corrected for gravid uterine wt) *[adaptive response, not considered adverse]* 3200 mg/kg bw/day: ↑ relative liver wt (corrected for gravid uterine wt), ↓ BWG during GD 7-14 and GD 14-21 Developmental: 3200 mg/kg bw/day: ↑ incidence of incomplete ossification or absence of hyoid; ↑ foetal incidence of sternebrae ossification, ↑ incidence of reduced 13th rib pair size, ↓ incidence of a reduced or absent 13th rib, ↑ foetal incidence of unilateral increased renal pelvic cavitation **No evidence of teratogenicity**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Developmental Toxicity New Zealand White rabbit 14-15 ♀/group PMRA 1203219	Purity - 98.5% 0, 250, 1000 or 3000 mg/kg bw/day by gavage GD 7-28	Maternal: 1000 Developmental: 1000	Maternal: 250 mg/kg bw/day: ↓ BWG (GD 14-18) *[transient; not considered adverse in conjunction with absence of change in BW or food consumption]* 3000 mg/kg bw/day: ↓ BWG (GD 7-28), ↓ food consumption Developmental: 3000 mg/kg bw/day: ↓ mean foetal weight, ↑ corneal opacity, ↑ foetal incidence of displaced or irregular ossification of the odontoid process, ↑ foetal incidence of irregularities affecting either one costal cartilage element or pair of elements **No evidence of teratogenicity**
Genotoxicity Studies			
In vitro gene mutation *S. typhimurium*, TA98, TA100, TA1535, TA1537 and TA1538 PMRA 1199840	Purity - 98.2 % 10 to 3300 µg/plate, with and without activation	Negative; cross-linking mutagenesis was not assessed. Precipitation at ≥ 330 µg/plate.	
In vitro gene mutation *B. subtilis*, H17 (Rec^+), M45 (Rec-)	156-2500 mg/disk (w/o activation) and 78.1-1250 mg/disk (w/ activation)	Negative.	
In vitro gene mutation *S. cerevisiae*, D7 PMRA 1199844	Purity - 98.4 % 12.5 to 200 µg/mL, with and without activation for 18 hr	Negative. **Study is supplementary due to the organism used.**	
In vitro gene mutation Mouse lymphoma assay L5178Y $TK^{+/-}$ cells PMRA 1199843	Purity - 98.4 % 2 to 128 µg/mL with activation; 15 to 128 µg/mL without activation for 4 hr	Negative.	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
In vitro chromosomal aberration Chinese Hamster Ovary assay	0.06 to 4 mg/mL with and without activation	Negative. **Study is supplementary due to lack of detail.**	
In vivo gene mutation Mouse micronucleus assay Mouse (Strain - N/S) 15/sex/group	Purity - 99.6% 0 or 8000 mg/kg in 20 mL/kg 0.5% sodium carboxymethyl-cellulose via gavage	Negative. **Study is supplementary to lack of detail.**	
In vivo gene mutation Rat (Strain - N/S) Rodent dominant lethal assay 10 Weeks 30 ♂/group, mating 2 ♀/1 ♂ for 14 days PMRA 1199842	Purity - 98.1% and 99.3 % 0, 4, 40 or 400 ppm in diet (0, 0.28, 2.81 and 27.8 mg/kg bw/day)	Negative. **Study is supplementary due to study deviation**	
Special Studies			
Palatability Studies			
Palatability Study Mouse (Strain - N/S) 5/sex/group	Purity - N/S 0, 50, 500, 5000 or 30000 ppm in diet (≈ 0, 6.5, 65, 650 or 3900 mg/kg bw/day) for 42 days	≥ 650 mg/kg bw: ↑ liver wt associated with centrilobular hepatocytomegaly (♂) 3900 mg/kg bw: ↑ liver wt (♀) Diets containing up to 30000 ppm were palatable to both sexes **Study is supplementary (non-guideline).**	
Palatability Study Rat (Strain - N/S) 5/sex/group	Purity - N/S 0, 10000, 20000 or 30000 ppm in diet (≈ 0, 500, 1000 or 1500 mg/kg bw/day) for 21 days	≥ 500 mg/kg bw/day: slight ↓ BW gain, transient ↓ food consumption; ↑ water intake (♂, first week only for ♀) Dietary intakes up to 30000 ppm clofentezine will be tolerated by rat in a 90-day study. **Study is supplementary (non-guideline).**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Palatability Study Dog (Strain - N/S) 1/sex/group	Purity - N/S 10000 ppm in diet (≈ 300 mg/kg bw/day) for 4 weeks OR 20000 or 30000 ppm in diet (≈ 600 or 900 mg/kg bw/day) for 2 weeks	900 mg/kg bw: ↓ food consumption (>33%) (♀) **Study is supplementary (non-guideline).**	
Liver Enzyme Induction Studies			
Enzyme Induction CD-1 mouse 8 Weeks 9-10 ♂/group PMRA 1199862	Purity - 99.6 % 0, 400 or 27000 mg/kg/day in diet (≈ 0, 52 or 3510 mg/kg bw/day)	52 mg/kg bw/day: ↑ cytochrome P-450, ↑ cytochrome b_5 ; *[effects considered to be marginal]* 3510 mg/kg bw/day: ↑ liver wt, ↑ cytochrome P-450, ↑ cytochrome b_5 **Study is supplementary (non-guideline).**	
Enzyme Induction CD rat 8 Weeks, with 2 Week Recovery Period 6 ♂/group PMRA 1199860	Purity - 100 % 0, 40 or 27000 ppm in diet (≈ 0, 5.2 or 1350 mg/kg bw/day)	5.2 mg/kg bw/day: no enzyme induction observed 1350 mg/kg bw/day: ↑ liver wt, ↑ aniline hydroxylase, ↑ cytochrome P-450, ↑ cytochrome b_5 Recovery: 1350 mg/kg bw/day: ↑ aniline hydroxylase, ↑ cytochrome b_5; liver wt and P-450 levels recovered to control levels **Study is supplementary (non-guideline).**	
Enzyme Induction Sprague-Dawley CD rat 2 Weeks 6 ♂/group PMRA 1199857	Purity - N/S 0, 10, 40 or 400 ppm in diet (≈ 0, 0.5, 2 or 20 mg/kg bw/day)	≥ 0.5 mg/kg bw/day: ↑ cytochrome b_5, ↓ microsomal protein concentration ≥ 2 mg/kg bw/day: ↑ cytochrome P-450 20 mg/kg bw/day: ↑ relative liver wt **Study is supplementary (non-guideline).**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Enzyme Induction Sprague-Dawley outbred albino rat 2 Weeks 10/sex/group PMRA 1205362	Purity - N/S 0, 10, 40 or 400 ppm in diet (≈ 0, 0.5, 2 or 20 mg/kg bw/day) Liver activity compared to microsomes previously prepared from rats dosed with 0.1% w/v PB in drinking water for 3 weeks	≥ 2 mg/kg bw/day: ↑ ethoxycoumarin deethylase (ECOD) (♂) 20 mg/kg bw/day: ↑ cytochrome P-450, ↑ aldrin epoxidase, ↑ ECOD, ↑ microsomal protein; ↑ liver wt, ↑ cytochrome b_5 (♂) **Study is supplementary (non-guideline).**	
Liver Function NZW rabbit 9 Weeks 6 ♀/group PMRA 1199859	Purity - 99.7-99.9% 0, 400/8000 or 4000 ppm in diet (≈ 0, 20/400 or 200 mg/kg bw/day) 400 ppm for 4 weeks, then 8000 ppm for 5 weeks Plasma cholesterol and triglycerides measured	≥ 200 mg/kg bw/day: ↑ relative liver wt 400 mg/kg bw/day: ↑ absolute liver wt, transient ↑ cholesterol and triglyceride levels Clofentezine appears to increase liver wts as an adaptive response at the dose levels tested. **Study is supplementary (non-guideline).**	
Special Thyroid Studies			
Thyroxine Half-Life Study Sprague-Dawley rat 32 ♂ PMRA 1205364	Purity - 98.8 % Single i.v. dose of [^{125}I]-thyroxine. Blood levels measured at various time points, then 0 or 30000 ppm clofentezine in diet (0 or 1500 mg/kg bw/day) for 4 weeks.	In untreated rats, the mean thyroxine half-life in blood increased from 16.7 hrs to 17.6 hrs after 1 month. In treated rats, the mean half-life of thyroxine in blood decreased from 17.05 to 16.42 hr after 1 month of treatment. There was a 9% difference in half-lives between the two groups. The study authors concluded that the difference is small and variable, but postulate that it may be significant over a longer time period. The dose level was very high, but the metabolism of thyroxine in rats was rapid. **Study is supplementary (non-guideline).**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Thyroid Uptake Study CD1 mouse Sprague-Dawley rat PMRA 1205364	Purity - 98.8 % 0 or 30000 ppm in diet (0 or 3900 mg/kg bw/day for mouse; 0 or 1500 mg/kg bw/day for rat) for 4 weeks then single i.p. dose of [^{131}I]-sodium iodide. Animals were sacrificed 6 or 24 hours post-i.p.-dosing.		Mouse: Radioactivity levels in blood were significantly decreased at 6 hr, but not 24 hr after the radiolabel administration. Radioactivity levels in thyroid were significantly increased in treated male mice, 24 hr after the administration of radiolabel. Although the magnitude of the uptake is less than in rats and is confined to males, greater uptake of iodine by the mouse thyroid was observed in the treated males relative to controls. Rat: Radioactivity levels in blood were significantly increased in treated males at 6 hr but not 24 hr after administration of radiolabel. The radioactivity level decreased in the blood of female rats at 6 hr and 24 hr. Radioactivity levels in thyroid were significantly increased in treated male and female rats at 6 hr after the radiolabel administration. Female rats also had ↑ radiolabel levels in thyroid 24 hr after administration. Clofentezine increases iodine uptake by the thyroid in the rat, with the degree of the increase appearing more pronounced in females than in males. **Study is supplementary (non-guideline).**
Thyroid Function Sprague-Dawley rat 10/sex/group 6 Weeks PMRA 1205366, 1142401	Purity - N/S 0, 400 or 30000 ppm in diet (0, 20 or 1500 mg/kg bw/day)		≥ 20 mg/kg bw/day: ↑ BW, ↑ absolute and relative liver wt, ↑ T4 (♂); ↑ DHEAS (♀) 1500 mg/kg bw/day: ↑ free T_4 index, ↑ TSH, ↑ trend incidence of thyroid follicular cell enlargement; ↑ DHEAS, ↑ progesterone, ↑ total T_3 (♂); ↓ BW, ↑ incidence of thyroid colloid depletion (♀) There is thyroid activation after administration of clofentezine at 1500 mg/kg bw/day for 6 weeks. **Study is supplementary (non-guideline).**
Biliary Excretion of T_4 Rat (Strain - N/S) 2-3 Weeks 6 ♂/dose PMRA 1142399	Purity - 99.3% 0 or 30000 ppm in diet (0 or 1500 mg/kg bw/day) for 2-3 weeks Single i.v. dose of 5 μCi of (^{125}I)-L-thyroxine, bile collected at 15 min intervals over 4 hr		1500 mg/kg bw/day: ↑ bile flow rate, ↑ biliary excretion of ^{125}I-T_4, ↑ biliary excretion of ^{125}I-T_4 glucuronide, ↑ T_4 blood clearance rate Biliary excretion of T_4 and its metabolites is one of the factors contributing to increased turnover of thyroid hormones in clofentezine-treated rats. **Study is supplementary (non-guideline).**

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Thyroid Hormone Excretion Rat (Strain - N/S) 5 Weeks 5 ♂/dose PMRA 1142399	Purity - 99.3% 0 or 30000 ppm in diet (≈ 0 or 1500 mg/kg bw/day) for 5 weeks 5 ♂/group given a single i.v. dose of 5 μCi of L-(^{125}I)-thyroxine	1500 mg/kg bw/day: ↓ urinary T_4 excretion, ↑ faecal T_4 excretion, slight ↑ overall elimination of the clofentezine dose **Study is supplementary (non-guideline).**	
Thyroid Function Rat (Strain - N/S) 4, 8 or 13 Weeks 6 ♂/group 10 ♂/group for clinical chemistry and UDPGT determinations 10 ♂/group for histopathological examination	Purity - 99.3% 0, 10, 40, 400 or 30000 ppm (0, 0.9, 3.8, 28 or 2780 mg/kg bw/day) 5 ♂/dose given a single i.v. dose of 5 μCi of L-(^{125}I)-thyroxine	28 mg/kg bw/day: ↑ liver wt, slight ↑ UDPGT 2780 mg/kg bw/day: ↓ BWG for Weeks 1 to 3, ↓ food consumption, ↑ relative liver wt , ↑ total protein/total globulin, ↑ TSH, slight ↓ T_3, marked ↑ UDPGT, ↑ severity of colloid depletion, ↑ incidence of moderate to severe follicular cell hypertrophy, slight to severe focal pituitary hypertrophy **Study is supplementary (non-guideline).**	
Thyroid Function Rat (Strain - N/S) ≥ 2 Weeks 50 ♂/group	Purity - N/S 0 or 30000 mg/kg in diet for up to 2 weeks (≈ 0 or 1500 mg/kg bw/day)	1500 mg/kg bw/day: ↓ BWG during the first 5 days of treatment, ↓ food consumption during the first 2 days. A significant reduction in total T_3 was observed after 2 days. After Day 4 and Day 7, TSH was significantly elevated while total T_3 remained significantly lower than controls. At Day 14, total T_3 levels had returned to normal and TSH levels remained elevated. T_4 levels followed T_3 values but the reductions were not statistically significant. Relative liver wt was significantly elevated after 2 days, rising further after 4 days of treatment. Liver wt remained elevated throughout the treatment period. No morphological changes were observed in thyroid after 1 or 2 days, but after 4 days proliferative stimulation of the follicular lining cells was demonstrated by mitosis. This stimulation peaked after 7 days and was still evident at Day 14. Colloid depletion, follicular cell hypertrophy and hyperplasia were seen at Day 7 and Day 14. **Study is supplementary (non-guideline).**	

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	NOAEL (mg/kg bw/day)	Results/Effects
Thyroid Function Rat (Strain - N/S) 28 Days 80 ♂/group	Purity - N/S 0, 10, 400, 3000 or 30000 ppm in diet (≈ 0, 0.6, 22.7, 169 or 1635 mg/kg bw/day)		≥ 22.7 mg/kg bw/day: ↑ liver wt after Day 14, ↑ liver UDPGT activity after Day 4, early and profound histopathological changes in the thyroid of the male rat. There was an initial increase in mitotic activity of thyroid follicular cells followed by colloid depletion, hypertrophy and hyperplasia of the follicular lining cells and an increase in thyroid wt. ≥169 mg/kg bw/day: ↑ relative thyroid wt, ↑ liver wt after Day 4 1635 mg/kg bw/day: ↓ BWG associated with slight ↓ food consumption **Study is supplementary (non-guideline).**
Thyroid Function Rat (Strain - N/S) 6 Weeks	Purity - N/S 0 or 30000 ppm in diet (≈ 0 or 1500 mg/kg bw/day)		1500 mg/kg bw/day: enlarged thyroid with follicular cell hyperplasia **Study is supplementary (non-guideline).**
Thyroid Function Electron Microscopy Study Rat (Strain - N/S) 5 ♂/group	Purity - N/S 0, 400 or 30000 ppm in diet (≈ 0, 20 or 1500 mg/kg bw/day) for an unspecified duration		No treatment-related histopathological changes in thyroid. ≥ 20 mg/kg bw/day: In anterior pituitary, hypertrophy and dilated rough endoplasmic reticulum (RER) which contained an amorphous material of medium electronic density were detected in some thyrotrophin-producing cells 1500 mg/kg bw/day: In anterior pituitary, occasional secretory granules within cisternae of RER were present in thyrotrophs, with occasional secondary lysosomes seen in these cells. It is suggested that enhanced synthesis of TSH caused accumulation of the hormone in the cisternae of RER, resulting in the formation of intracisternal secretory granules. **Study is supplementary (non-guideline).**

Appendix IV Occupational and Residential Exposure Risk Estimates for Clofentezine

Table 1 Dermal and Inhalation MOEs for Mixing/Loading and Applying Clofentezine (Non-Cancer)

Crop	Application Equipment	Max Rate	ATPD[A]	Total Exposure (µg/kg bw/day)[B]	Margin of Exposure[C]
Apples, Pears, Peaches, Nectarines	Airblast – Farmer/Custom	0.15 kg ai/ha	20 ha	7.01	385
Strawberries	Groundboom – Farmer	0.25 kg ai/ha	9 ha	0.60	4491
	Groundboom – Custom		26 ha	1.65	1633
	Low Pressure Handwand	0.5 g ai/L	150 L	0.28	9482
Raspberries	Airblast – Farmer/Custom	0.25 kg ai/ha	20 ha	11.68	231
	Groundboom – Farmer		5 ha	0.33	8084
	Groundboom – Custom		26 ha	1.65	1633
	Low Pressure Handwand	0.5 g ai/L	150 L	0.28	9482
Outdoor Deciduous Nursery Stock	Backpack	0.04 g ai/L	150 L	7.21×10^{-2}	37445
	Low Pressure Handwand			2.28×10^{-2}	118525
	High Pressure Handwand		3800 L	1.93	1402
	Airblast	0.04 kg ai/ha	20 ha	1.87	1445
	Ground – Farmer/Custom		26 ha	0.28	9717

[A] ATPD refers to area treated per day

[B] Represents the sum of dermal and inhalation exposure estimates and takes into account a 30% dermal absorption factor. Based on mixer/loader/applicators wearing coveralls over a single layer of clothing and chemical-resistant gloves (except for applicators using groundboom equipment) and an open cab.

[C] Calculated using the NOAEL of 2.7 mg/kg bw/day from the 13-week rat subchronic dietary study, target MOE of 100

Table 2 Exposure and Cancer Risk Estimates for Occupational Handlers of Clofentezine[A]

Crop	Applicaton Method	Application Rate	Area Treated per Day	Exposure Frequency (days per year)	LADD (mg/kg bw/day)[B]	Cancer Risk[C]
Apples, Pears, Peaches, Nectarines	Airblast – Farmer	0.15 kg ai/ha	7 ha	1 day/3 years	1.19×10^{-6}	7×10^{-8}
	Airblast – Custom			15 days/3 years	1.79×10^{-5}	1×10^{-6}
Strawberries	Groundboom – Farmer	0.25 kg ai/ha	9 ha	1 day/2 years	4.39×10^{-7}	2×10^{-8}
	Groundboom – Custom		26 ha	15 days/2 years	8.78×10^{-6}	5×10^{-7}
	Low Pressure Handwand – Farmer	0.5 g ai/L	150 L	1 day/2 years	2.08×10^{-7}	1×10^{-8}
	Low Pressure Handwand - Custom			15 days/2 years	3.12×10^{-6}	2×10^{-7}
Raspberries	Airblast – Farmer	0.25 kg ai/ha	7 ha	1 day/2 years	2.99×10^{-6}	2×10^{-7}
	Airblast – Custom			15 days/2 years	4.48×10^{-5}	2×10^{-6}
	Groundboom – Farmer		5 ha	1 day/2 years	2.44×10^{-7}	1×10^{-8}
	Groundboom – Custom		12 ha	15 days/2 years	8.78×10^{-6}	5×10^{-7}
	Low Pressure Handwand – Farmer	0.5 g ai/L	150 L	1 day/2 years	2.08×10^{-7}	1×10^{-8}
	Low Pressure Handwand – Custom			15 days/2 years	3.12×10^{-6}	2×10^{-7}
Outdoor Deciduous Nursery Stock	Backpack – Farmer	0.04 g ai/L	150 L	1 day/year	1.05×10^{-7}	6×10^{-9}
	Backpack – Custom			15 days/year	1.58×10^{-6}	9×10^{-8}
	Low Pressure Handwand – Farmer			1 day/year	3.33×10^{-8}	2×10^{-9}
	Low Pressure Handwand – Custom			15 days/year	5.00×10^{-7}	3×10^{-8}
	High Pressure Handwand – Farmer		3800 L	1 day/year	2.81×10^{-6}	2×10^{-7}
	High Pressure Handwand – Custom			15 days/year	4.22×10^{-5}	2×10^{-6}
	Airblast – Farmer	0.04 kg ai/ha	7 ha	1 day/year	9.56×10^{-7}	5×10^{-8}
	Airblast – Custom			15 days/year	1.43×10^{-5}	8×10^{-7}
	Groundboom – Farmer		12 ha	1 day/year	1.87×10^{-7}	1×10^{-8}
	Groundboom - Custom			15 days/year	2.81×10^{-6}	2×10^{-7}

[A] PPE is mid-level (coveralls over single layer) with open mixing/loading and open cab

[B] Calculated using the following formula:

$$\frac{\text{Absorbed Daily Dose (Dermal and Inhalation Exp Estimates) (mg/kg bw/day)} \times \text{Exp Frequency (1 or 15 days per 1,2 or 3 yrs)} \times \text{Working Duration (40 yrs)}}{\text{365 days/year} \times \text{Life Expectancy (75 yrs)}}$$

[C] Calculated using the following formula: LADD (mg/kg bw/day) × q_1* (0.0556 mg/kg bw/day)$^{-1}$

Table 3 Occupational Postapplication Exposure Estimates, MOEs, and REIs (Non-Cancer)

Crop	Activity	Max Rate (g ai/ha)	DFR (Day 0) µg/cm^2)	Transfer Co-efficient (cm^2/hr)	Dermal Exposure (mg/kg bw/day) (Day 0)[A]	Dermal MOE (Day 0)[B]	REI[C]
Apples, Pears, Peaches, Nectarines	Hand Thinning	150	0.2729	3000	0.0281	**96**	2 days
	Hand Harvest			1500	0.0140	192	12 hrs
	Hand Line Irrigation			1100	0.0103	262	12 hrs
	Hand Pruning, Scouting, Pinching, Tying, Training			500	0.0047	577	12 hrs
Raspberries	Hand Harvest, Thinning, Hand Pruning, Training, Tying	250	0.4548	1500	0.0234	115	12 hrs
	Hand Line Irrigation			1100	0.0172	157	12 hrs
	Scouting, Hand Weeding, and Other Minor Contact Activities			700	0.0109	247	12 hrs
Strawberries	Hand Harvest, Hand Pruning (pinching), Training	250	0.4548	1500	0.0234	115	12 hrs
	All Other Activities			400	0.0062	433	12 hrs
Outdoor Deciduous Nursery Stock	All Activities	40	0.0728	400	9.98×10^{-4}	2705	12 hrs

Shaded cells indicate where MOE is below the target MOE

[A] Dermal exposure (µg/kg bw/day) = $\frac{\text{DFR (µg/cm}^2\text{)} \times \text{TC (cm}^2\text{/hr)} \times \text{Duration (8 hrs/day)} \times \text{DA (30\%)}}{\text{Body Weight (70 kg)}}$

[B] Calculated using the NOAEL of 2.7 mg/kg bw/day based on the 13-week subchronic dietary study in rats

[C] Refers to restricted entry level and is the number of days or hours following application that workers can enter treated areas to perform postapplication activities, where the MOE is greater than the target MOE. Minimum REI is 12 hours.

Table 4 Cancer Risk for Postapplication Workers

Crop	Activity	REI or PHI[A]	LADD[B] (mg/kg bw/day)	Cancer Risk[C]
Apples, Pears, Peaches, Nectarines	Hand Thinning	2 days	2.64×10^{-4}	1×10^{-5}
	Hand Harvest	21 days	7.77×10^{-5}	4×10^{-6}
	Hand Line Irrigation	12 hrs	1.02×10^{-4}	6×10^{-6}
	Hand Pruning, Scouting, Pinching, Tying, Training	12 hrs	4.65×10^{-5}	3×10^{-6}
Raspberries	Hand Harvest	15 days	2.30×10^{-4}	1×10^{-5}
	Hand Pruning, Tying, Training	12 hrs	3.48×10^{-4}	**2×10^{-5}**
	Hand Line Irrigation	12 hrs	2.56×10^{-4}	1×10^{-5}
	Scouting, Hand Weeding	12 hrs	1.63×10^{-4}	9×10^{-6}
Strawberries	Hand Harvest	15 days	2.30×10^{-4}	1×10^{-5}
	All Other Activities	12 hrs	9.29×10^{-5}	5×10^{-6}
Outdoor Deciduous Nursery Stock	All Activities	12 hrs	2.97×10^{-5}	2×10^{-6}

Shaded cells indicate where cancer risk is greater than 1×10^{-5}

[A] Restricted entry interval refers to the day that workers can enter treated fields, based on non-cancer risk where the MOE is greater than the target MOE, as specified in Table 3 of Appendix IV. PHI refers to preharvest interval.

[B] LADD (Lifetime Average Daily Dose, mg/kg bw/day) calculated using the following formula:

$$\text{LADD: } \frac{\text{Absorbed Daily Dose (mg/kg bw/day)} \times \text{Treatment Frequency (days/yr)} \times \text{Working Durration (40 yrs/lifetime)}}{\text{365 days/yrs} \times \text{Life Expectancy (75 yrs)}}$$

Treatment Frequency = 30 days/3 yrs for apples, pears, peaches, nectarines, 30 days/ 2 yrs for raspberries and strawberries, and 30 days/yrs for outdoor deciduous nursery stock

[C] Cancer Risk, calculated using the following formula: Cancer Risk = LADD (mg/kg bw/day) × q_1* (0.0556 (mg/kg bw/day)$^{-1}$)

Table 5 Target Residue Levels to Mitigate the Cancer Risk for Postapplication Workers

Crop	Activity	TWA $TDFR_{Cancer}$ (Day 0) ($\mu g/cm^2$)[A]	$TDFR_{Cancer}$ ($\mu g/cm^2$)[B]	REI (Days)[C]
Raspberries	Hand Pruning, Training, Tying	0.3459	0.2314	10

[A] Refers to a Time-Weighted Average Target DFR_{Cancer} (Day 0) ($\mu g/cm^2$) and represents the residue level on the initial day of a 30 day consecutive period that will result in a TWA DFR value that is equivalent to the target DFR_{Cancer}.

[B] Refers to the target DFR $value_{Cancer}$ ($\mu g/cm^2$) and represents the residue level that results in a cancer risk of less than 1×10^{-5}.

[C] Refers to the restricted entry interval and is the day that workers can reenter into treated areas that will result in a cancer risk of less than 1×10^{-5}. Corresponds to the day that residues are below the TWA $TDFR_{Cancer}$ (Day 0).

Table 6 Adult and Youth Short-Term Postapplication Exposure and Risk Assessment on Residential Fruit Trees

Activity	Sub-Population	TC (cm^2/hr)[A]	Exposure Duration (hrs)	Dermal Exposure ($\mu g/kg$ bw/day)[B]	Dermal MOE[C] (Target = 100)
Apples (150 g ai/ha)					
Hand Harvesting	Adults (70 kg)	1500	0.67	1.18	2297
	Youth (39 kg)	1033		1.45	1858

[A] TC = transfer coefficient, scaled for the surface area of a youth.

[B] Exposure = DFR ($\mu g/cm^2$) × TC × Duration (hrs) × Dermal Absorption (30%)/Body weight (70 kg for adults and 39 kg for youth). A DFR value of 0.2729 $\mu g/cm^2$ was used.

[C] Based on an oral NOAEL of 2.7 mg/kg bw/day.

Table 7 Adult and Youth Cancer Exposure and Risk Estimates from Residential Postapplication Exposure on Fruit Trees

Activity	Sub-population	Transfer Co-efficient[A] (cm^2/hr)	Exposure Frequency (days/yrs)	Duration of Exposure (yrs)	Absorbed Daily Dose[B] (mg/kg bw/day)	LADD[C] (mg/kg bw/day)	Cancer Risk[D]
Apples (150 g ai/ha)							
Hand Harvesting	Adults	1500	5 days/3 yrs	63	2.23×10^{-3}	8.54×10^{-6}	5×10^{-7}
	Youth	1033	5 days/3 yrs	6	2.75×10^{-3}	1.00×10^{-6}	

[A] TC = transfer co-efficient. Based on ARTF TCs for apples and scaled for surface area of youths
[B] Absorbed Daily Dose expressed in mg/kg bw/day. Calculated using the following formula: 5-day TWA DFR (0.5167 µg/cm^2) × TC (cm^2/hr) × Duration (0.67 hrs) × Dermal Absorption (30%)/Body Weight (70 kg adult, and 39 kg youth)
[C] Lifetime Average Daily Dose expressed in mg/kg bw/day, calculated using the following formula: LADD = (Absorbed Daily Dose * Exposure Frequency (5 days/3 yrs) * Exposure Duration (6 yrs for youth, and 63 yrs for adults)/ (365 days/year * Life Expectancy (75 yrs)
[D] Cancer risk calculated using the following formula: Cancer risk = LADD * q_1* (0.0556 (mg/kg bw/day)$^{-1}$)

Table 8 Cancer Exposure and Risk Estimates from PYO Operations

Sub-Population	DFR (µg/cm^2)	TC (cm^2/hr)	Dermal Exposure (mg/kg bw/day)[A]	Dietary Exposure (mg/kg bw/day)[B]	Absorbed Daily Dose (ADD) (mg/kg bw/day)[C]	LADD (mg/kg bw/day)[D]	Cancer Risk[E]
Apples (150 g ai/ha)							
Adults (19+)	0.1522	1500	1.96×10^{-3}	1.98×10^{-3}	3.94×10^{-3}	3.02×10^{-6}	3×10^{-7}
Youth (10-18 yrs)		1034	2.42×10^{-3}	3.52×10^{-3}	5.95×10^{-3}	5.79×10^{-7}	
Children (1-9 yrs)		534	3.25×10^{-3}	7.07×10^{-3}	1.03×10^{-2}	1.01×10^{-6}	
Strawberries (250 g ai/ha)							
Adults (19+)	0.2997	1500	3.85×10^{-3}	2.39×10^{-4}	4.09×10^{-3}	4.71×10^{-6}	4×10^{-7}
Youth (10-18 yrs)		1034	4.77×10^{-3}	4.26×10^{-4}	5.19×10^{-3}	7.59×10^{-7}	
Children (1-9 yrs)		534	6.40×10^{-3}	9.07×10^{-4}	7.31×10^{-3}	1.07×10^{-6}	

[A] Dermal Exposure expressed in mg/kg/bw/day, calculated using the following formula: DFR (µg/cm^2) (0.2997 µg/cm^2 for strawberries & 0.1522 µg/cm^2 for apples) × TC (cm^2/hr) × Duration (2 hrs) × DA (30%)/Body Weight (70 kg adult, 39 kg youth, and 15 kg toddler). The DFR value is for the preharvest interval day of 15 days for strawberries and 21 days for apples.
[B] Dietary Exposure was calculated using the following formula: Dietary Exposure (µg/kg bw/day) = (MRL (0.5 µg/g for apples and 0.1 µg/g for strawberries) × Consumption (g/day))/Body Weight (Adults 70 kg, Youth 39 kg and Children 15 kg).
[C] Absorbed Daily Dose (mg/kg bw/day) was calculated by summing dermal and dietary exposure. Absorbed Daily Dose = Dermal Exposure (mg/kg bw/day) + Dietary Exposure (mg/kg bw/day)
[D] Lifetime Average Daily Dose expressed in mg/kg bw/day, calculated using the following formula: LADD = (ADD * Exposure Frequency (1/3 yrs for apples & 1/2 yrs for strawberries) * Exposure Duration (8 yrs for children and youth, and 63 yrs for adults) / (365 days/year * Life Expectancy (75 yrs))
[E] Cancer Risk calculated using the following formula: Cancer Risk = LADD * q_1* (0.0556 (mg/kg bw/day)$^{-1}$)

Table 9 Aggregate Residential Short-Term Exposure and Risk Assessment

Sub-Population	Dermal Exposure (mg/kg bw/day)[A]	Dietary Exposure (mg/kg bw/day)[B]	Total Exposure (mg/kg bw/day)[C]	Aggregate MOE[D]
Apples (150 g ai/ha)				
Adults (70 kg)	1.18×10^{-3}	1.00×10^{-5}	1.19×10^{-3}	2278
Youth (39 kg)	1.45×10^{-3}	1.80×10^{-5}	1.47×10^{-3}	1836

[A] Dermal Exposure = DFR (µg/cm^2) × TC × Duration (0.67 hrs) × Dermal Absorption (30%)/Body Weight (70 kg for adults and 39 kg for youth). A DFR value of 0.2729 µg/cm^2 was used.
[B] Dietary Exposure based on chronic exposure estimates and includes drinking water.
[C] Total exposure is the sum of dermal and dietary exposure estimates. Total Exposure (mg/kg bw/day) = Dermal Exposure (mg/kg bw/day) + Dietary Exposure (mg/kg bw/day)
[D] Based on the oral NOAEL of 2.7 mg/kg bw/day, target MOE of 100.

Table 10 Cancer Aggregate Short-Term Exposure and Risk Assessment from Residential Postapplication Exposure on Fruit Trees

Sub-Population	TC (cm^2/hr)[A]	Exposure Frequency (days/year)	Dermal Exposure Estimates (mg/kg bw/day)[B]	Dietary Exposure Estimates (mg/kg bw/day)[C]	Absorbed Daily Dose (ADD) (mg/kg bw/day)[D]	LADD (mg/kg bw/day)[E]	Cancer Risk[F]
Apples (150 g ai/ha)							
Adults	1500	5 days/3 years	1.11×10^{-3}	1.00×10^{-5}	1.12×10^{-3}	4.31×10^{-6}	3×10^{-7}
Youth	1033	5 days/3 years	1.38×10^{-3}	1.80×10^{-5}	1.39×10^{-3}	5.09×10^{-6}	

[A] TC = transfer coefficient. Based on the ARTF TC for hand harvesting fruit trees and scaled for body weight and surface area of youths
[B] Dermal Exposure Estimates expressed in mg/kg bw/day, calculated using the following formula: 5-day time-weighted average DFR (0.2583 µg/cm^2) × TC (cm^2/hr) × Duration (0.67 hr) × Dermal Absorption (30%)/Body Weight (70 kg adult, and 39 kg youth)
[C] Dietary Exposure Estimates based on chronic dietary estimates including drinking water
[D] Absorbed Daily Dose, expressed in mg/kg bw/day, was calculated by summing dermal and dietary exposure. Absorbed Daily Dose = Dermal Exposure (mg/kg bw/day) + Dietary Exposure (mg/kg bw/day)
[E] Lifetime Average Daily Dose expressed in mg/kg bw/day, calculated using the following formula: LADD = (ADD × Exposure Frequency (5 days/3 yrs) × Exposure Duration (6 yrs for youth, and 63 yrs for adults) / (365 days/year * Life Expectancy (75 yrs))
[F] Cancer risk calculated using the following formula: Cancer risk = LADD × q_1 (0.0556 (mg/kg bw/day)$^{-1}$)

Appendix V Dietary Exposure and Risk Estimates for Clofentezine

Table 1 Dietary Exposure and Risk Estimates of Clofentezine

Population Subgroup	Refined							
	Chronic Dietary[1]				Cancer Dietary[2]			
	Food Only		Food + Water		Food Only		Food + Water	
	Exposure (mg/kg/day)	%ADI	Exposure (mg/kg/day)	%ADI	Exposure (mg/kg/day)	Lifetime Risk	Exposure (mg/kg/day)	Lifetime Risk
General Population	0.000011	0.3	0.000013	0.3	0.000011	6.3E-07	0.000013	7.4E-07
All Infants (<1 year old)	0.000023	0.6	0.000030	0.7				
Children 1-2 years old	0.000046	1.2	0.000049	1.2				
Children 3-5 years old	0.000033	0.8	0.000036	0.9				
Children 6-12 yrs old	0.000017	0.4	0.000019	0.5				
Youth 13-19 yrs old	0.000009	0.2	0.000010	0.3				
Adults 20-49 yrs old	0.000007	0.2	0.000009	0.2				
Adults 50+ years old	0.000008	0.2	0.000010	0.3				
Females 13-49 years old	0.000007	0.2	0.000009	0.2				

[1]Acceptable Daily Intake (ADI) of 0.004 mg/kg bw/day applies to the general population and all population subgroups.

[2]q_1* of 0.0556 (mg/kg bw/day)$^{-1}$ applies to the general population.

Note: An acute risk assessment was not required.

Appendix VI Food Residue Chemistry Summary

1.1 Metabolism

The nature of the residue in plant and animal commodities is adequately understood based on acceptable metabolism studies in apple (foliage and fruit), lemon (foliage), peach (fruit), grapes, lactating cows, lactating goats and laying hens, as well as several comparative studies between laboratory animals and livestock. Clofentezine was ^{14}C labelled on both carbon atoms of the tetrazine ring.

Animals – Metabolism studies in animals showed that most of the radioactivity associated with clofentezine was rapidly excreted in the feces and urine. Comparative metabolism studies (rat, mouse, rabbit, calf, dog, baboon, cow, and goat) between laboratory animals and livestock have demonstrated that clofentezine metabolism is qualitatively similar in all species. The major routes of metabolism are ring-hydroxylation and/or replacement of a chlorine atom by a methylthio group followed by ring-hydroxylation. Liver was the major target organ and the major part of the residue was oftentimes constituted of the 4-hydroxyclofentezine (4-OH clofentezine) metabolite. However, in one study performed on a goat and a calf, the metabolites in liver were identified as a mixture of hydroxylated clofentezine isomers, mainly 3-OH and 4-OH clofentezine with a small amount of 5-OH clofentezine. The parent clofentezine was never detected in ruminant matrices, except in one study, where it accounted for 8% of the total radioactive residue (TRR) in calf liver. In contrast to ruminants, the parent compound was by far identified as the dominant compound in all poultry tissues.

Plants – Metabolism studies in plants showed that the metabolic pattern was similar in all tested plants, with the parent clofentezine being the major compound of the extractable residues (55-87% of the TRR) in fruit or leaf samples collected 25 to 103 days after application. Bound residues accounted for up to a further 40% of the total radioactivity (in apples). However, it has been shown that this bound residue is not bioavailable. All other compounds identified accounted for less than 10% of the recovered radioactivity. The most significant of these was 2-chlorobenzonitrile. This compound results from the cleavage of the tetrazine ring and can be further oxidised to 2-chlorobenzamide, 2-chlorobenzyl alcohol and 2-chlorobenzoic acid. This degradation pathway is specific to plants, since no metabolites resulting from the cleavage of the parent compound were found in the rat metabolism study, where mainly hydroxyclofentezine metabolites were identified. Residues in plants were mostly found as a surface residue.

Proposed metabolic pathways for clofentezine in plants and animals are shown in Fig.1 and Fig.2, respectively.

Figure 1 Proposed metabolic pathway for clofentezine in plants

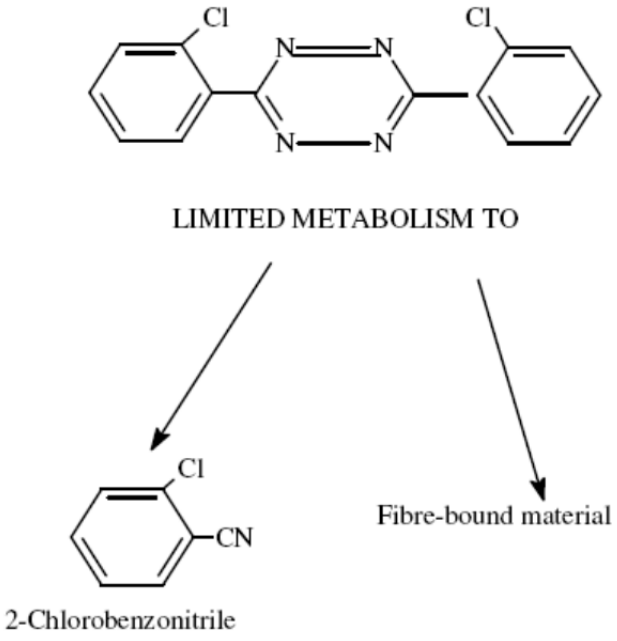
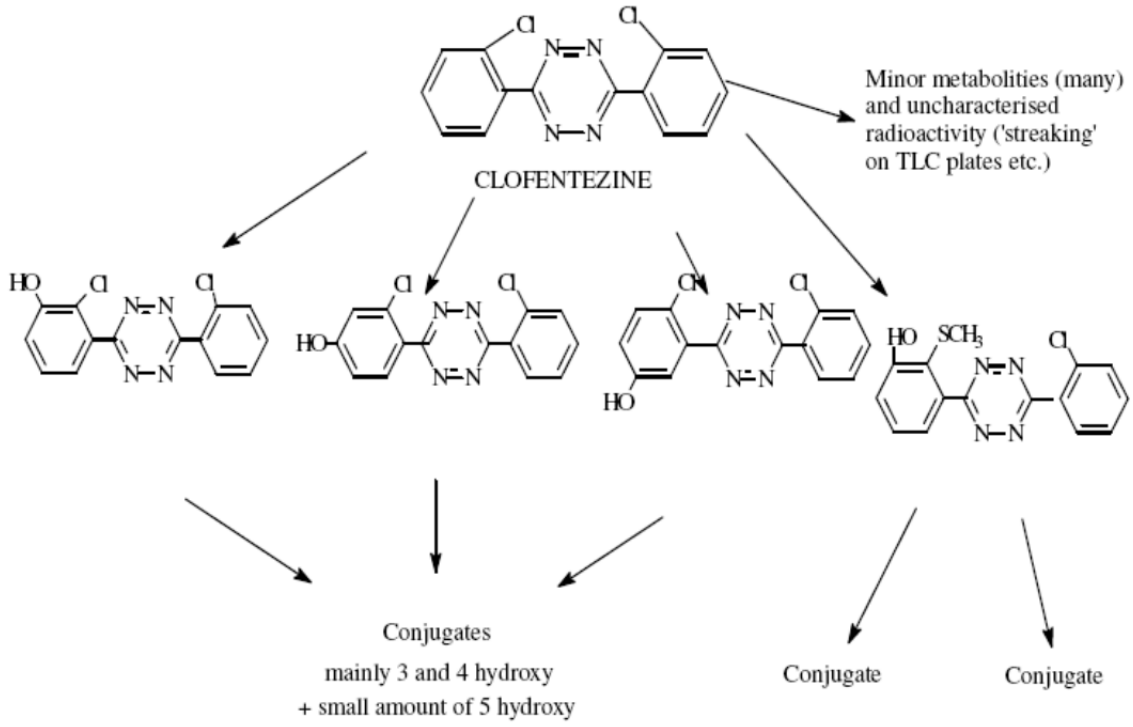


Figure 2 Proposed metabolic pathway for clofentezine in animals



1.1.1 Plant metabolism

Apple

– Three apple trees were placed in a sheltered position outdoors. Two of the trees were treated with ^{14}C-clofententezine (formulated as 35% WP) on the leaves, petioles, twigs and flowers. This treatment reportedly corresponded to an application rate of 0.5 kg ai/ha. Complete treated areas of twigs and leaves were excised at 10, 25, 50 and 100 days post application. The samples were rinsed with dichloromethane (DCM), then homogenised and extracted with DCM followed by methanol. The remaining fibre was dried at 40°C for 16 hours. Methanol extracts were analyzed by LSC and TLC. Fibre samples were combusted and quantitated by LSC. Analysis results showed that even after 100 days the majority of radiolabel (67.1% TRR) was recovered from the foliage surface. The proportion of fibre bound radiolabel showed a steady increase with time up to 17% TRR after 100 days. The majority of radiolabel was recovered as unchanged clofentezine (81.9% TRR after 10 days; 86.8% after 25 days; 78.4% after 50 days; 65.9% after 100 days). Small amounts of label co-chromatographed with the marker compound dihydroclofentezine (NC 22505). No other single metabolite accounting for more than 1% of the recovered radioactivity was observed.

– The metabolism of clofentezine was also studied in apple fruit, using ^{14}C labelled clofentezine formulated as 50% WP and diluted to 0.03% ai (recommended field rate) and 0.76% ai (25x exaggerated rate to aid metabolite identification) prior to application. Five trees were selected for treatment 1 (0.03% ai) and treatment 2 (0.76% ai). A 100 µL treatment was applied dropwise (2 µL/drop) evenly over the surface of the fruit. Apples harvested at maturity (75 days postapplication) were separated into peel and flesh. Peel samples were washed with DCM, the residue extracted by macerating 3 times with DCM/acetone followed by 3 further extractions with acetone/water. Flesh samples were extracted with DCM/acetone followed by acetone/water. Residues were characterized by both TLC and HPLC and confirmed by mass spectrometry. At day zero 107% of the applied radiolabel was recovered one hour after treatment 1. Unchanged clofentezine accounted for 97% of the mean recovered radiolabel after treatment 1 and corresponded to a mean residue of 0.858 ppm. According to the authors of the report, the loss of clofentezine derived residues coupled with growth dilution resulted in very low total residue in apples harvested at maturity. Apples at the two treatment levels of 0.03% and 0.76% ai contained only 14.2 and 11.5% respectively of the applied radiolabel, corresponding to 0.031 and 1 ppm clofentezine equivalents. In treatment 1, only the peel DCM wash of apples harvested at maturity contained an extractable residue >0.01 ppm (*i.e.,* 0.012 ppm, 37.1% of recovered radiolabel). Further analysis showed this fraction to consist primarily of unchanged clofentezine (0.011 ppm, 33% TRR). All other extracts contained ≤0.004 ppm. The peel fibre however contained 38.4% of the recovered label or 0.012 ppm. In treatment 2, the distribution of labelled residue was found to be different; a significantly lower percentage (8.8% vs. 38.4%) of the recovered label was fibre bound and a concomitantly higher level of extractable residue was observed in the peel DCM wash (72.4% vs. 37.1%). The extracts from peel with DCM and DCM/acetone and from flesh with DCM/acetone accounted for 90% of the recovered radioactivity. Chromatographic separation of these extracts yielded a major peak and 2-3 minor peaks. The major peak in each case was confirmed as clofentezine by mass spectrometry and accounted for 81.8% (0.81 ppm) of the recovered label. The minor peaks accounted for approximately 10% of the recovered label. At least nine minor compounds were separated. 2-Chlorobenzonitrile was the principal component contributing 4% of the total recovered label (0.035 ppm). The second most prevalent

compound represented only 0.9% of the recovered label and was unidentified. Hydrobromic acid digestion released 71.1% of the fibre bound label. The principal components of the HBr extracts were 2-chlorobenzoic acid and at least 4 unidentified compounds (total <0.03 ppm equivalents). About 29% of the fibre bound residue remained unextracted.

– The nature of the fibre bound residues of clofentezine in apples was further investigated following application of ^{14}C-clofentezine formulated as a 50 SC to apples at field rates of 0.06 kg ai/L and 0.48 kg ai/L in South Africa. The high application rate was used to assist in the identification of both extractable metabolites and bound residues. The apple trees were grown and treated outside in an orchard and the fruits harvested 25 and 64 days after application. The apples were separated into peel and flesh samples for the residue determination. The total radioactive residues in apples at the lower application rate ranged from 0.08-0.224 ppm clofentezine equivalents (20.9-42.4% of applied radioactivity). In all cases the majority of the recovered residue was found in the peel (90-96%). Bound residues from samples treated at the lower application rate were largely restricted to the peel fraction and accounted for 4.5-11.3% of the recovered radioactivity (0.009-0.010 ppm). This proportion was dependent upon apple variety and increased with time. Bound radioactivity was effectively released by 16 hours base hydrolysis and partially solubilised by enzymatic treatment with pectinase and cellulase. Analysis showed that the insoluble residue consisted of unchanged clofentezine (approximately 50% of the fibre bound residue) and breakdown products (2-chlorobenzoic acid and 2-chlorobenzyl alcohol) which had become incorporated into peel components.

Grapes

The metabolism of ^{14}C-clofentezine (50 SC formulation: 500 g ai/L) was investigated in grapes grown under glasshouse conditions in the UK. The formulation was applied in droplets directly to the surface of grape berries at rates corresponding to a normal field rate (NFR) of 0.01% (0.078 mg ai/ml) and a 10 × NFR of 0.1% (0.634 mg ai/ml) at two different growth stages of development to obtain two separate post treatment intervals (day 24/25 and 45/46) at harvest. Results indicate that the major part of the extractable radioactivity was in the grape surface wash. The quantities of fibre bound residues increased with time after treatment. At day 0 after treatment with the 0.01% and 0.1% formulations, 1.05 and 8.30 ppm (equivalent to 99.7% and 99.9% of the extracted radioactivity), were removed from the grape surface, respectively. At 24 days after treatment this residue had decreased to 0.38 and 2.49 ppm (97.3% and 98.3% of the radioactivity), respectively. At day 45 after application the total fibre bound radioactivity increased to 23% and 11.5% (equivalent to 0.03 and 0.05 ppm), respectively.

Characterisation of the radioactivity found at these stages confirmed that by far the majority of the residue was present as parent clofentezine with 76.9% and 85.5% of the extracted radioactivity 24 days after treatment with 0.01% and 0.1% formulations, respectively. This is equivalent to a total residue of 0.3 and 2.15 ppm. At the same treatment rate and analysis time, the remaining residue was made up predominantly of 2-chlorobenzonitrile (0.04 ppm, 9.61% of extracted radioactivity and 0.18 ppm, 7.13% of extracted radioactivity) and polar compounds comprising 2-chlorobenzoic acid, 2-chlorobenzamide and 2-chlorobenzyl alcohol (1.39% of extracted radioactivity, 0.005 ppm for the low dosage and 0.76% of extracted radioactivity, 0.02 ppm in the case of high dosage). At 45 days after treatment with the same treatment rate, the quantities of clofentezine present were significantly lower, due to a lower overall residue and also the incorporation of radioactivity into fibre bound residue. At this point the extractable

radioactivity comprised (for low and high dosage rates respectively): clofentezine (55.4% and 69.2% or 0.06 and 0.31 ppm), 2-chlorobenzonitrile (5.11% and 7.34% or 0.006 and 0.033 ppm) and polar compounds (3.79% and 2.63%, 0.004 and 0.012 ppm). The remaining radioactivity was present as fibre bound residue. Analysis of the fibre bound material by solubilisation under harsh hydrolytic conditions indicated that, as in the case of apples, it was partially degradable to 2-chlorobenzoic acid. Application of a residue method detecting the parent compound demonstrated that the method accounted for the majority of the clofentezine in the samples.

Lemon

The metabolism of ^{14}C-3,6-tetrazine labelled clofentezine formulated as a 50 WP on lemon foliage was studied over a period of 103 days. Clofentezine was applied as a wettable powder at a field application rate of 0.03% (equivalent to 0.3 kg ai/ha) on trees. Semi-mature leaves were treated each with 350 µL of formulation to simulate treatment in the field where a "runoff" method is used. Samples were taken 0, 10, 25, 54 and 103 days after treatment. There was a steady decline in the radioactivity isolated from the leaves, falling to 26.8% of the applied dose at day 103. The majority of the recovered activity remained associated with the leaf surface. After 103 days, only 13% of the recovered and extracted activity had penetrated the leaf tissue. Chromatographic analysis showed that the majority of radioactivity still associated with the leaves from a DCM wash of the foliage (surface wash) remained as unchanged clofentezine (77% at day 103). At least 20 breakdown products were observed, the largest of which was 2-chlorobenzonitrile (6.8% of TRR at day 103), the principle photodegradation product of clofentezine. Dissipation of this volatile metabolite from the leaf surface probably accounted for the loss of radioactivity with time. No other single metabolite accounted for more than 2.1% of the total recovered activity. Only 2.4% of the total radioactive residue at final harvest was associated with fibre bound residues.

Peach

– The metabolism of ^{14}C-clofentezine (formulated as 50 SC) was studied in immature peach fruit (at fruit set) grown under glasshouse conditions in the UK. Treatments were made at 0.01% and 0.1% 62 days prior to harvest. A separate application of 0.01% was made to leaves of peach trees adjoining untreated fruits. Immediately following the treatments of fruits with 0.01% and 0.1% spray concentrations, 87.7% and 96.1% of TRR were identified as parent compound, respectively. Of the recovered total radioactive residue at 62 days (0.047 ppm clofentezine equivalents) at normal field treatment rate, the surface wash contained 74.9% (0.036 ppm) of the total recovered radioactivity as clofentezine and 8.4% (0.004 ppm) as 2-chlorobenzonitrile. The fibre bound residue was negligible (< 0.005 ppm). No other metabolites were observed. At the exaggerated field treatment rate, a total residue of 0.70 ppm clofentezine equivalents was recovered. Analysis showed that 90.9% (0.633 ppm) of the recovered radioactivity was present as clofentezine, 5.4% (0.038 ppm) as 2-chlorobenzonitrile and only 0.6% (0.004 ppm) as fibre bound residue. Negligible translocation of residue from foliar applications was observed to peach leaves and to developing untreated fruit (0.0005 ppm). The majority of the radioactivity on the surface of these treated leaves remained as unchanged clofentezine. A separate extraction using the residue method for parent clofentezine accounted for 91.4% of the total residue.

1.1.2 Animal metabolism

Rat, goat and calf – Clofentezine radiolabelled at the two carbons of the tetrazine ring was used to dose rats, a goat and a calf.

– Six rats were dosed orally at 20 mg ^{14}C clofentezine/kg bw with three rats sacrificed at 16 and three at 48 hours. The rat liver contained total residues of 1-9 ppm clofentezine equivalents at 16 hours after dosing and 0.58-0.87 ppm after 48 hours. Methanol extraction recovered 32-69% of the radiolabelled residues present at 16 hours and 15-28% at 48 hours. TLC indicated higher levels of parent clofentezine at 16 hours than at 48 hours. Hydrolysis of unextracred residues with hydrobromic acid (HBr) *i.e*., conversion of unextracted residues to *ortho*-chlorobenzoic acid (OCBA) followed by ether extraction allowed recovery of a further 11-29% (16 hours) and 28-33% (48 hours) of the liver radiocarbon, 83-88% and 65-94% of which (respectively) were found to be OCBA on TLC. Total recovery was therefore 76-88% and 65-77% of the original liver radiocarbon for the 16 and 48 hours samples, respectively, the total recovery being calculated as % methanol extract + 2 × % HBr/ether extract × % HBr/ether extract found to be OCBA on TLC.

– The goat was dosed orally twice a day for two days. Each dose contained 2.5 mg ^{14}C clofentezine/kg bw. The goat was sacrificed 19 hours after the final dose. The goat liver contained 1.45 ppm clofentezine equivalents. About 50% of the radiocarbon was extractable with methanol. Hydrolysis with HBr gave a further 23.2% of the radiocarbon, 76.9% of which was found to be OCBA. Total recovery was therefore 85.6% of the original radiocarbon.

– The calf received a single oral dose of 5.1 mg ^{14}C clofentezine/kg bw and was sacrificed after 12 hours. The calf liver contained 1.51 ppm clofentezine equivalents. Eighty percent of the available radiocarbon was extracted with methanol. Of this fraction, parent clofentezine accounted for only 8% of the total and hydroxylated clofentezine conjugates accounted for 43%. Hydrolysis with HBr yielded a further 12% of the original residue, 96% of which was OCBA. The total residue accounted for in the liver of the calf was therefore 103%.

In each case the extracted residues had a chromatographic profile which was qualitatively similar to that found in rat urine, with conjugates of 3-, 4- and 5-hydroxylated clofentezine and a 3-(methylthiohydroxyphenyl)-6-(2'-chlorophenyl)-1,2,4,5-tetrazine (*a.k.a.* 2-SMe-3-OH clofentezine) isomer. The unextracted residues could be converted almost quantitatively to *ortho*-chlorobenzoic acid by hydrobromic acid reflux, suggesting that the overall clofentezine moiety was still present in the residue. No qualitative difference was found in the metabolic fate of clofentezine in rat, goat and calf.

Rat, mouse, rabbit, calf, dog and baboon – A comparative study of the metabolism of clofentezine in mammals was conducted in rat, mouse, rabbit, calf, dog and baboon. In all species, the major route of excretion for clofentezine was in the feces. Urinary excretion levels varied from 1-2% TRR in dog to 19-27% TRR in mouse to 35% TRR in rabbit. It is concluded that urinary excretion of clofentezine metabolites appears to be favoured in rodents. The rate of excretion is similar in all species with most of the dose being eliminated in the first 48 hours. The metabolism was qualitatively similar, with hydroxylation and replacement of chlorine with a methylthio group being the two major pathways, usually followed by conjugation. Many minor metabolites were formed in all species. Quantitative interspecies differences were apparent, most

notably the fact that in the calf and the baboon hydroxylation and subsequent conjugation were the most prominent pathways, with methylthiolation being a very minor route of metabolism. The latter pathway was apparently more prominent in rodents – especially the rat - and the rabbit and also present in the dog.

Goat – A lactating goat was fed a single oral dose of 22 ppm (22 mg in 1 kg pomace) ^{14}C labelled clofentezine. Blood and milk samples were taken for 72 hours and then the animal was sacrificed and tissues samples taken for analysis. Blood plasma residues peaked about 5.5 hours after dosing with residue levels reaching 0.04 ppm. Residues in the milk were highest after 24 hours, reaching 0.049 ppm. At 72 hours both plasma and milk residues were <0.001 ppm. At sacrifice (72 hours), liver and eyes contained 0.03 ppm, kidney and adrenals contained 0.01 ppm, and all other tissues sampled contained <0.01 ppm residues. Analysis of excreta indicated that 17.9% and 8% of the dose were excreted in the urine and feces, respectively, in the first 24 hours after dosing. Excretion was virtually complete after 72 h.

– A lactating goat was dosed with ^{14}C-clofentezine at the exaggerated rate of 2.2 mg/kg bw/day for 7 consecutive days to ensure quantifiable residues in milk. Milk samples were collected twice per day and several urine samples were also obtained and analysed. Residues in milk reached a plateau level of approximately 0.2 mg/L on the third day of dosing. A total of 93% of the residue in milk was extractable with methanol. Of the extractable residue, 83.5% consisted of hydroxyclofentezine isomers with 4-OH clofentezine being the largest single component. A fraction of 16.5% did not respond to enzyme hydrolysis and is believed not to be a conjugate of hydroxyclofentezine. The residue in milk was mostly hydroxyclofentezine complexed with endogenous material. There was no evidence for the presence of significant residues of 2-SMe-3-OH clofentezine. The major urinary metabolite was identified as 4-OH clofentezine, both free and conjugated.

Cow – A lactating cow was orally dosed with ^{14}C-clofentezine daily for five days at a rate of 0.27 mg/kg bw/day. According to the authors of the report the dose corresponded to 22 ppm in apple pomace used as feed. Residues in milk were monitored for five days and the cow was sacrificed for tissue analysis 18 hours after the last dose. Residues of ^{14}C-clofentenzine equivalent in milk reached a plateau level of approximately 0.007 mg/L on the second day with only minor variations in concentration on subsequent days. Residues were highest in bile (1.09 ppm), intestinal tract (0.02-0.23 ppm) and liver (0.09 ppm).

Goat and cow – A lactating goat and a lactating cow were dosed orally with ^{14}C-clofentezine (labelled at both carbon atoms of the tetrazine ring) at 2.2 mg/kg bw/day for a period of 3 days. Whole milk samples were analysed using radiospectrometric, TLC and HPLC techniques. Milk residues plateaued (3 days) at 0.17 and 0.20 ppm for goat and cow respectively. About 98.7% of the ^{14}C total terminal residues in cow's milk were extracted into methanol with only 1.3% associated with the protein pellet. In cow's milk, a single compound (75% of the total ^{14}C extracted) was isolated and identified as 4-hydroxyclofentezine. 4-Hydroxyclofentezine was also the major metabolite isolated from goat's milk. Liver tissues from the cow study contained total ^{14}C residues of 0.76 ppm while other tissues contained 0.36 ppm (kidney), 0.016 ppm (muscle), 0.26 ppm (renal fat) and 0.02 ppm (subcutaneous fat). About 60% of the total liver residues were extractable and 4-hydroxyclofentezine was identified as the only metabolite.

Poultry – The metabolic fate of clofentezine was investigated in laying hens dosed for three consecutive days at a rate of 17 mg ^{14}C-clofentezine/kg bw/day. The highest radioactive residues were found in fat (3.04 ppm), skin (0.87 ppm) and liver (0.70 ppm). In contrast to ruminants, the parent compound was by far identified as the dominant compound in all hen tissues, accounting for 34-89% of the TRR with lower amounts of 4-OH and 3-OH clofentezine (6-30% TRR). It should be noted that poultry is not exposed to clofentezine residues based on the current uses.

1.1.3 Residue Definition

The main residues in fruit crops were the parent clofentezine and the metabolite 2-chlorobenzonitrile. However, the levels of 2-chlorobenzonitrile found were < 0.05 ppm, which was approximately a tenth of those of the parent residue. Other metabolites identified were present only at low levels and these metabolites were not considered to be of toxicological significance. Therefore, only the parent compound is included in the residue definition for plant matrices.

The metabolism data submitted for clofentezine in animal products showed that the vast majority of the residue in cattle and goat tissues is 4-OH clofentezine. However, poultry studies showed more significant quantities of parent clofentezine, in addition to 3-OH and 4-OH clofentezine.

Therefore, based on metabolism studies, the RD in plant commodities is expressed as clofentezine *per se*. The RD in animal commodities is expressed as the combined residue of clofentezine and the metabolite 4-hydroxy-clofentezine (3-(2-chloro-4-hydroxyphenyl)-6-(2-chlorophenyl)-1,2,4,5-tetrazine). These RDs are used for both enforcement and dietary risk assessment purposes.

1.2 Analytical Methods

Adequate single analyte analytical methods have been developed for the determination of clofentezine residues in plant commodities and for the determination of clofentezine and its metabolite 4-hydroxyclofentezine in animal commodities. The methods rely on HPLC with UV detection, HPLC with PDA (photodiode array) detection and GC with MS (mass selective) or EC (electron capture) detection. Some of those analytical methods have been successfully validated for enforcement purposes and are listed in the USEPA index of residue analytical methods (RAM). The limits of quantitation (LOQ) are reported to be in the range 0.01-0.05 ppm with acceptable recoveries. Multiresidue methods in USFDA's pesticide analytical methods (PAM)-Volume I Appendix I were found to be inadequate for enforcement (due to poor recoveries) and clofentezine is not listed in the CFIA's Volume 7: Multiresidue Analytical Method Manual. Details from the individual study reports and reviews are summarized below.

1.2.1 Supervised Residue Trial Analytical Methodology

As unchanged clofentezine residues have been identified as the principal component of terminal residues in plants, analytical methods for plants have been developed to measure parent only. For residues in animal tissues and fluids different analytical methods were developed to permit quantitation of parent compound and its major metabolites containing the non-substituted 2-chlorophenyl common moiety (*i.e.*, 4-OH clofentezine in cattle and goat tissues; parent, 3-OH, and 4-OH clofentezine in poultry tissues). The total metabolite residues are measured as 2-chlorobenzoic acid.

Plant matrices

Method# R29 – *Analytical Method for Residues of NC 21314 in Apples and Pears (Improved Method)*: Apple samples were extracted with acetone. After dilution with water and partition of clofentezine into hexane, concentrated extracts were cleaned up through a silica Sep-Pak cartridge. Quantitation was effected via normal phase HPLC with detection by UV absorption at 268 nm and comparison with 2-naphthol, added as an internal standard. Recoveries from apple samples fortified with 0.01 to 1.0 ppm were in the range 82.7-98.3%. The limit of detection (LOD) was reported as 0.01 ppm.

Method# R111 – *Analytical Method for Residues of Clofentezine in Miscellaneous Fruit Crops*: This method is essentially the same as Method# R29. The internal standard was changed to N-2-(2-propyl)phenylbenzamide (NPPBA). Detection limit is reported as 0.01 ppm with recoveries of 75-107% for spike levels of 0.01-0.20 ppm on apples, pears, grapes, peaches and strawberries.

Method# R94 – *Analytical Method for Residues of Clofentezine in Apples (2nd Edition)*: Apart from some minor changes in the volume of extraction solvents in the initial stages and substitution of 2-naphthol by N-2-(2-propyl)phenylbenzamide (NPPBA) as internal standard, this procedure is the same as Method# R29.

Method# R74 – *Investigation of potential interferences by other pesticides during the determination of clofentezine residues in apples*: The objective of this study was to test whether any of a series of 40 standard pesticides recommended for use on apples caused problems of interference with the determination of clofentezine by Method# R94. Subsamples of minced control samples were fortified with the standard pesticides at concentrations reflecting their respective American tolerances. None of the standard pesticides tested gave a peak which interfered with clofentezine or the internal standard NPPBA. Volck oil added at 10 ppm gave an apparent clofentezine residue at the limit of determination (0.01 ppm).

Method# Cb=R4 – *Analytical Method for NC 21314 in Animal Diet*: Samples of laboratory animal chow were extracted by shaking with acetone, the resultant solution was analysed by HPLC on a reverse phase Partisil column. Quantitation was made with an UV detector set at 268 nm and comparison to an internal standard, p-terphenyl. There were no co-extractive peaks in the submitted chromatograms which might interfere with the analyte peak. The method was linear over the concentration range used (400-700 ppm) and recoveries averaged 101.8±1.9% (range 99-106%; n=24).

Method# J/02/92 from NOR-AM Chemical Company with modification for determination of clofentezine in strawberry and raspberry: Berry samples were homogenized and extracted with acetone. After centrifugation, the supernatant was partitioned with hexane and concentrated. The extraction was cleaned up using silica solid-phase extraction cartridges and eluted with 20% ethyl acetate/hexane, and the solvent was exchanged into 50% methanol/water with a nitrogen evaporator. The cleaned sample was analyzed using HPLC with an UV detector at the wavelength of 268 nm. The minimum detection level (MDL) and the minimum quantifiable level (MQL) were reported to be 0.02 and 0.05 ppm, respectively.

Residue analysis of clofentezine in strawberries and apples: Clofentezine residue determination in strawberries and apples was performed according to a modified DFG multiresidue method S19. Residues were extracted with acetone/water (2:1), cleaned-up by partitioning into cyclohexane/ethyl acetate (1:1) followed by gel-permeation chromatography, and analysed by HPLC/PDA. No interferences were observed. LOQ: 0.02 ppm for apple and strawberry.

Animal matrices

Method# R72 – *Analytical Method for Residues of Clofentezine and Metabolites in Animal Tissues and Milk*: This method is reported to measure parent and total metabolite residues in animal tissues and milk by formation of 2-chlorobenzoic acid (2-CBA) from the non-substituted 2-chlorophenyl moiety that is retained in each identified metabolite structure. Samples are hydrolyzed by refluxing with HBr and cleaned-up by partition into diethyl-ether followed by a back partition between alkali and ether. The 2-CBA residues are methylated (diazomethane) and quantitated by GC-ECD on comparison to an external standard of 2-chlorobenzoate (ECB). The 2-CBA residues are expressed in terms of equivalent clofentezine through multiplication by the molecular weight ratio 303/156 = 1.936. The detection limit was ≤0.02 ppm 2-CBA or 0.05 ppm clofentezine equivalents. Recoveries from samples of tissue, organ and milk homogenates fortified with 2-CBA at 0.1-3.0 ppm (liver), 0.1-1.0 ppm (kidney), 0.03-0.3 ppm (muscle), 0.025-0.1 ppm (fat) and 0.05-0.5 ppm (milk) were found to be in the acceptable range (≥70%). However, data were required to confirm the extent of conversion of parent clofentezine to 2-CBA.

Method# R72 2nd Edition – *Analytical Method for Residues of Clofentezine and Metabolites in Animal Tissues and Milk (Second Edition)*: This method is identical to Method# R72 with modifications for improved cleanup (ion exchange cartridge column) and the use of capillary GC for determination of residues. Lower limits of determination for milk and tissues (liver, fat and muscle) were 0.01 and 0.05 ppm respectively. Recoveries for milk spiked at 0.01-0.1 ppm averaged 83.6±9.5% and recoveries for tissues spiked at 0.05-0.20 ppm averaged 83.9±10.5%.

Method# R72 3rd Edition – *Analytical method for the determination of residues of Clofentezine and 4-hydroxy-Clofentezine in animal tissues by gas chromatography*: This method is essentially the same as Method# R72 except that the final determination is by GC with mass selective detection operating in the selected ion mode. The lower limit of determination was 0.05 ppm for both compounds and for all tissues (muscle, liver and kidney). Recoveries averaged 87±12% (4-hydroxyclofentezine) and 97±14% (clofentezine) for tissues spiked at 0.05 and 0.25 ppm.

Method# R182 – *Clofentezine: Analytical Method for the Determination of Clofentezine Metabolites in Animal Tissues and Milk by High Performance Liquid Chromatography*: see 2nd Edition below.

Method# R182 2nd Edition – *Clofentezine: Analytical Method for the Determination of Residues of 4-hydroxyclofentezine in Milk and Animal Fat by HPLC*: Milk samples were mixed with acetone and extracted with hexane to remove fat followed by an enzyme hydrolysis (snail digestive juice). After acidification, the metabolite was extracted into hexane/ethyl acetate for analysis by HPLC and UV detection at 301 nm. The LOD was 0.004 ppm and recoveries of 4-hydroxyclofentezine at 0.01 and 0.05 ppm spike levels averaged 76.4±6%.

Method# R54 – *Analytical Method for the Determination of NC 21314 Residues in Animal Tissues and Milk (Preliminary Edition)*: see 2nd Edition below.

Method# R54 2nd Edition – *Analytical Method for the Determination of Free Clofentezine Residues in Animal Tissues and Milk by High Performance Liquid Chromatography*: The method can be used for the analysis of free clofentezine in muscle, liver, kidney, renal fat, subcutaneous fat tissues and whole milk. Tissues were extracted with DCM/methanol while milk was extracted with hexane/diethyl ether after first breaking the milk fat globule membrane with potassium oxalate/ethanol. Extracts were cleaned up using hexane/acetonitrile and silica Sep-Pak cartridge. Eluates were analysed using HPLC with UV detection of clofentezine at 268 nm. LOD and LOQ were 0.002 and 0.01 ppm (respectively) for all samples. Average recoveries for samples spiked at 0.01-0.40 ppm (6 levels) were >70% in all tissues and in the milk.

Method# R54 3rd Edition – *Clofentezine: Analytical Method for the Determination of Residues of Free Clofentezine in Milk and Animal Fat by HPLC*: Milk Samples were extracted with ether/hexane, the organic layer washed with water (aqueous layer discarded) and evaporated to dryness. The residue was dissolved in hexane and clofentezine partitioned into acetonitrile and back extracted into hexane. The evaporated extract was cleaned up on a silica Sep-Pak cartridge and analyzed at 268 nm using HPLC-UV. Recoveries at 0.01 and 0.05 ppm averaged 91.5±10%.

Method# R143 – *Residues of Clofentezine and Metabolites in the Tissues and Eggs of Laying Hens Following a 28-day Feeding Study in the UK, 1986*: This method is essentially the same as Method# R72. Tissues (liver, kidney, muscle, abdominal fat, skin and subcutaneous fat) and eggs were spiked with clofentezine and 2-CBA at levels of 0.05-1.0 ppm (5 levels); recoveries averaged 95±18%. The method has an LOQ of 0.05 ppm clofentezine equivalents.

1.2.2 Enforcement Analytical Methodology

An enforcement analytical methodology has not been explicitly identified in the clofentezine residue chemistry database. However, single analyte HPLC/UV methods are listed in the USEPA's index of Residue Analytical Methods (RAM), pending compilation in PAM Vol. II: i) Nor-Am Method J-91R-01 (RAM# J/02/92) is a modification of the method referenced in §1.2.1 as Method# R111 which measures clofentezine in apples, pears, grapes, peaches and strawberries; the method has an estimated LOQ of 0.01 ppm; ii) AgrEvo USA Co. Method J-95R-02 measures clofentezine in raw apples with an LOQ of 0.005 ppm; iii) Schering Ag Method identified in USEPA RAM as RES/89/50 is the method referenced in §1.2.1 as Method# R54 3rd Edition which measures free clofentezine in milk with an estimated LOQ of 0.01 ppm;

iv) Nor-Am Method identified in USEPA RAM as RES/89/49 is the method referenced in §1.2.1 as Method# R182 2nd Edition which measures 4-hydroxyclofentezine with an LOQ of 0.01 ppm. Pesticide analytical method (PAM)-Volume I multiresidue methods are not acceptable for tolerance enforcement due to poor recoveries. Clofentezine is not listed in the CFIA's Volume 7: Multiresidue Analytical Method Manual.

1.2.3 Independent Laboratory Validation (ILV)

There are no ILV data on file. However, analytical methods listed in the USFDA's PAM Vol. II (see §1.2.2) are considered as having undergone an adequate inter-laboratory validation. In addition, the following method validation studies have been submitted to and reviewed by the 2007 JMPR:

Animal matrices

Validation of an analytical method for the determination of clofentezine and metabolites in animal tissue: Independent Laboratory Validation: This report validates the method which was developed based on Method# R72 (Resid/85/32) and Method# R143 (Resid/87/30). Clofentezine residues in minced tissues or whole milk are hydrolysed to 2-chlorobenzoic acid by addition of hydrobromic acid, cleaned up by partition into diethyl ether/hexane and back-partition between alkali and ether. The extracts are then concentrated and cleaned up by anion-exchange chromatography. 2-chlorobenzoic acid is derivatised using N-methyl-N-trimethylsilyltrifluroacetamide (MSTFA) and determined within 24 hours by GC-MSD. LOQ: 0.01 ppm for eggs and milk, 0.02 ppm for fat and meat and 0.05 ppm for liver.

Independent validation of an analytical method for the determination of clofentezine and its metabolites in animal tissues: This report includes the confirmation of the method developed and validated based on modifications to Method# R72 (Resid/85/32) and Method# R143 (Resid/87/30). LOQ: 0.01 ppm for eggs and milk, 0.02 ppm for muscle and fat and 0.05 ppm for liver and kidney.

Plant matrices

Independent laboratory validation for the determination of clofentezine residues in strawberries and apples based on the DFG-S19 multiresidue enforcement methods: This method (see §1.2.1) was independently validated in strawberries and apples. The method is based on the DFG multiresidue method S19. Residues were extracted with acetone/water (2:1), cleaned-up by partitioning into cyclohexane/ethyl acetate (1:1) followed by gel-permeation chromatography, and analysed by HPLC-UV. No interferences were observed. LOQ: 0.02 ppm for apple and strawberry.

Independent laboratory validation of an analytical method for determination of residues of clofentezine in miscellaneous fruit crops: This report validates and confirms Method# R111. In the validation experiments, a slightly changed mobile phase allowed better separation of interfering peaks near to the clofentezine retention time. Clofentezine residues are extracted with acetone, cleaned up by silica Sep-Pak cartridge and determined with HPLC-DAD (Diode Array Detection). LOQ: 0.01 ppm for apple, pear, grape, peach and strawberry.

In addition, the following studies have been submitted to and reviewed by the USEPA:

Validation of an Analytical Method for Residues of Clofentezine in Fruit (Western Red Delicious Apples), USA, 1995.

Validation of an Analytical Method for Residues of Clofentezine in Fruit (Western Red Delicious Apples), USA, 1995: Amended Report.

Independent Laboratory Confirmation of AgrEvo Residue Method for Clofentezine in Apples According to PR Notice 88-5 Guidelines.

1.2.4 Multi-Residue Analytical Method (MRM) Evaluation

The following tests of multiresidue methods were submitted to and evaluated by the PMRA.

Behaviour of Clofentezine and its Metabolites through EPA Multiresidue Protocols I and III: None of the compounds tested (clofentezine, 3-, 4- and 5-hydroxyclofentezine) was quantifiable in fortified soybean (protocol I) or beet samples (protocol III) using the EPA multiresidue methodology. This was attributed to thermal degradation during GLC. As an alternative, the authors suggested HPLC analysis as described in the H&W Analytical Methodology Manual for carbendazim determination. However, the applicant study report concluded that recoveries were also poor due to "lack of elution through Florisil", and even then eluates contained large amounts of coextractives that completely overwhelmed analyte peaks.

Clofentezine through the EPA Multiresidue Protocols I and III: Clofentezine residues determination was screened through PAM Vol. I multi-residue protocols I and III with apples as the substrate. Residues of clofentezine were extracted with acetonitrile or acetone followed by liquid-liquid partitioning, Florisil column clean-up and gas chromatographic determination with electron capture detection. At high column temperatures, decomposition of clofentezine during gas chromatographic analysis was observed and this is believed to contribute significantly to the low recoveries observed (15-50% at fortification levels of 0.05-0.5 ppm). It was thus concluded that PAM Vol. I multiresidue protocols I and III may be used for qualitative detection of clofentezine but not for quantitative analysis.

1.3 Food Residues

1.3.1 Storage Stability

1.3.1.1 Storage Stability of Working Solutions in Analytical Methodology

Tests on storage stability of working solutions of clofentezine and 4-hydroxyclofentezine were not found in the clofentezine residue chemistry database. These tests will be required for any future submission of residue data.

1.3.1.2 Freezer Storage Stability

Previously reviewed data on file have shown that clofentezine residues are stable in frozen conditions in apples for up to 1 year, in peaches for up to 2 years and in almond for 1 year. Based on these data, the PMRA concluded that residues of clofentezine were stable in the remaining registered crops for up to 1 year of frozen storage. Parent clofentezine was found to be relatively unstable in products of animal origin, but the total residue (*i.e.,* all metabolites containing the 2-chlorobenzoyl moiety) was stable for at least 15 months.

Apples – Apples were fortified with 10 µg of ^{14}C-clofentezine by pipetting a standard solution onto the surface of the fruit. The fortified samples were stored at -18°C and analyzed at 0, 1, 3, 6, 12, 18 and 24 months post-treatment. Residues were extracted initially by DCM surface rinse followed by maceration of the whole fruit with a DCM/methanol mixture and subsequent clean-up through a Sep-Pak silica cartridge. Radioactivity in final extracts and remaining solids was determined by LSC or combustion/LSC and characterized by HPLC. The results showed an increase in the fibre bound residues, with a corresponding decrease in the extractable residues as storage intervals became longer. The pattern shown in the HPLC analysis suggested that some 75% of the extractable residue consisted of unchanged clofentezine after 18 months storage. Beyond 18 months it was difficult to predict the stability of these residues. These results suggest that significant breakdown of clofentezine residues is likely (*i.e.,* >25%). In addition, the breakdown products at 18 months have not been identified *i.e.,* 75% is clofentezine, 4% an early eluting hydrolysis product, the remaining 21% is unidentified. Thus, clofentezine residues in apples stored at -18°C should be stable for not more than 12 months (86% of the nominal residue still present).

Peaches – Peaches were treated with clofentezine at 0.02 and 1.0 ppm and stored at -15°C for 24 months. Samples were analysed for clofentezine at 3, 6, 12, 18 and 24 months post-treatment. Clofentezine was found to be relatively stable in peaches under freezer conditions for up to 2 years. Degradation of clofentezine followed first order kinetics with half-life values of 9.7 and 4.5 years for samples spiked at 0.02 and 1.0 ppm, respectively.

Almonds – Samples of hull were fortified at 0.02 ppm or 2.0 ppm with clofentezine. Samples of nutmeat were fortified at 0.02 or 0.2 ppm. These samples were stored in a freezer at -15°C and analysed at 3, 6, 12 and 24 months post-treatment. The USEPA evaluation of the data determined that clofentezine was essentially stable in almond hulls for over 2 years and fairly stable in almond nutmeat for 1 year.

Animal tissues and milk – Samples of lean meat (muscle), liver and peritoneal fat were fortified with approximately 1 ppm clofentezine; whole milk was fortified with approximately 0.26 ppm. The samples were stored frozen at -20°C. At intervals of 0, 1, 3 and 6 months, samples were removed for analysis of parent compound only. At intervals of 6, 12 and 15 months, total clofentezine-derived residues were determined by derivation (via refluxing with HBr) to 2-chlorobenzoic acid (2-CBA). The acid hydrolysis effectively splits the tetrazine ring of clofentezine and derivatives non-symmetrically, with only one of the two tetrazine carbon atoms becoming part of a 2-CBA molecule, the hydrolysis proceeding on a 1:1 mole ratio basis. Only half of the ^{14}C-carbons from the hydrolysed residues in this study will be incorporated into 2-CBA molecules. Therefore, total residues were derived from the method by multiplication of the activity recovered as 2-CBA by a factor of two. After 6 months storage, the mean percentage of

parent had fallen to 38.3% (muscle), 71.7% (liver), 50.5% (peritoneal fat), and 50.1% (milk). It appeared that clofentezine residues are quite unstable on storage for as short a period as 1 month. However, results obtained by using the total residue method showed that 92% of the original radioactivity in muscle, 101% in liver, 94% in fat, and approximately 84% in milk was accounted for after 15 months storage. It is concluded that parent clofentezine is relatively unstable in products of animal origin, but the total residue (*i.e.,* all metabolites containing the 2-chlorobenzoyl moiety) is stable for at least 15 months.

1.3.2 Crop Residues

1.3.2.1 Supervised Residue Trial Studies

Clofentezine is currently registered in Canada for use on apples, nectarines, peaches, pears, raspberries and strawberries. MRLs have been established on almonds, apples, nectarines, peaches and pears, primarily to cover residues on imported commodities, on the basis of field trial residue data mostly from the United States and other countries worldwide. Clofentezine residues on raspberries and strawberries are regulated under the General MRL (0.1 ppm).

Supervised residue trial data on file for apples, peaches/nectarines, pears, raspberries and strawberries were previously reviewed and deemed adequate to support the currently established MRLs. Residue data are also on file for plums, apricots and cherries as well as grapes and persimmon. The data were previously reviewed by the USEPA.

Supervised residue trial data on citrus fruits were submitted to and reviewed by the 2007 JMPR. The Meeting noted that the residue data for orange, lemon, tangerine and mandarin were from similar populations (*i.e.,* the data passed the statistical test for homogeneity of variance) and can be combined. Mean residues in ranked order in whole citrus fruits were: 0.06, 0.07, 0.08(3), 0.09(4), 0.10(2), 0.12, 0.14, 0.15(2), 0.17, 0.18(2), and 0.24 ppm (n=19). [Note: n is the number of trials; the mean was calculated for each trial; the number in brackets represents the frequency of the preceding mean value]. A similar situation was found for residues in flesh and the ranked order of concentrations in flesh was: <0.01, 0.01, 0.02 (5), 0.03(3) and 0.17 ppm (n=11). The meeting estimated an MRL for citrus fruits and a supervised trial mean residue (STMR) value for flesh of 0.5 and 0.02 ppm, respectively. The meeting also estimated an STMR value for clofentezine in whole citrus fruits of 0.10 ppm.

Supervised residue trial data on tomatoes were submitted to and reviewed by the 2007 JMPR. The Meeting noted that, based on the Mann-Whitney test, the residues from France, Germany and the Netherlands were from similar populations and could be combined. Mean residues in ranked order from these countries were: <0.05(3), 0.05, 0.06(2), 0.09(2), 0.10, 0.11(2), 0.12, 0.16 and 0.18 ppm (n=14). The Meeting estimated an MRL and an STMR value for clofentezine in tomatoes of 0.5 and 0.09 ppm, respectively.

Supervised residue trial data on tree nuts conducted in the United States were submitted to and reviewed by the 2007 JMPR. Homogeneity tests indicated that the residue data for walnut and almond were from similar populations and could be combined. Mean residues in ranked order on tree nuts were: <0.01(9), <0.02(11), <0.05(13), 0.10(3), 0.20(2), and 0.30(4) ppm (n=42). The meeting estimated an MRL and an STMR value for clofentezine in tree nuts of 0.5 and 0.05 ppm, respectively.

Supervised residue trial data on blackcurrants conducted in the UK are on file. The data were not reviewed by the PMRA. Residue data from supervised trials conducted on blackcurrants in France were reviewed by the 2007 JMPR. Mean residues in ranked order were: <0.04(3) and 0.09 ppm (n=4). The Meeting agreed to extrapolate from blackcurrants to red and white currants and estimated an MRL and an STMR value for clofentezine in currants of 0.2 and 0.04 ppm, respectively.

Supervised residue data on file for cucumbers conducted in Holland, Greece, the UK and Cyprus were not reviewed by the PMRA. Residue trial data on cucumbers conducted in France, Greece and Switzerland were submitted to and reviewed by the 2007 JMPR. Mean residues in ranked order were: 0.07, 0.12(2), 0.13, 0.14 and 0.16 ppm (n=6). The meeting estimated an MRL and an STMR value for clofentezine in cucumber of 0.5 and 0.125 ppm, respectively.

Supervised residue trial data on melons were submitted to and reviewed by the 2007 JMPR. Mean residues in ranked order were: <0.001, 0.03(2), <0.05(4), 0.05 and 0.06 ppm (n=9). The residues in all pulp samples were below the LOQ (n=9). The Meeting estimated an MRL of 0.1 ppm. Taking into account that the parent compound practically did not translocate in plants, the Meeting estimated an STMR value of 0 ppm for clofentezine in melons.

1.3.2.2 Residue Decline Study

Apart from decline studies conducted concurrently with supervised residue trials, formal residue decline studies in crops treated with clofentezine are on file for apples, grapes, peaches, pears, and plums. The studies were previously reviewed by the PMRA and deemed adequate to support a PHI of 21 days for peaches, nectarines and pears, and a PHI of 15 days for raspberries and strawberries.

There is no PHI specified for apples on the label. A residue decline study conducted on apples grown in Canada indicates that clofentezine degradation in/on apples follows first order kinetics with a half-life of 8 days. Clofentezine was applied at a nominal rate of 0.28 kg ai/ha (maximum registered rate is 0.30 kg ai/ha) and mature apples were harvested 1, 3, 7, 14, 28 and 48 days after application. The residue declined from 1.16 ppm at 1-day PHI to 0.02-0.04 ppm at 48-day PHI. Graphical interpolation gives a residue of 0.22 ppm at 21-day PHI. As a Canadian MRL of 0.5 ppm has been established on apples, a 21-day PHI appears to be adequate. Similarly, a Codex MRL of 0.5 ppm has been established on pome fruits (JMPR 1987) on the basis of a 21-day PHI. Thus, a 21-day PHI is being proposed as a label amendement for clofentezine use on apples.

A number of other studies, which were submitted to and reviewed by the 2007 JMPR and/or USEPA, are being requested for confirmatory purposes.

1.3.2.3 Confined Crop Rotation Trial Study

As per DIR98-02, apples and pears (pome fruits), peaches and nectarines (stone fruits) and raspberries (berries group crop) belong to the group of crops for which rotational crop studies will not be required. However, a rotational crop study is required due to the registered use of clofentezine on strawberries. There is currently no confined crop rotation data on file. The lack of this data (*i.e.,* uptake of clofentezine into a rotational small grain, a leafy vegetable, and a

root/tuber crop) is considered a deficiency in the residue chemistry database for clofentezine. Until an acceptable study (or adequate rationale) is submitted, a plant back interval of at least 12 months has to be observed. This measure is proposed as an amendment to be added to the label directions for clofentezine use on strawberries.

1.3.2.4 Field Crop Rotation Trial Study

The need for a field crop rotation trial study and/or rotational crop restrictions will be determined following the review of the outstanding confined crop rotation trial study. Until an acceptable study (or adequate rationale) is submitted, a plant back interval of at least 12 months has to be observed. This measure is proposed as an amendment to be added to the label directions for clofentezine use on strawberries.

1.3.2.5 Processed Food/Feed

A study on the fate of ^{14}C-clofentezine residues during aqueous hydrolysis under simulated conditions of pasteurisation, baking/brewing/boiling, and sterilisation has been submitted to and reviewed by the 2007 JMPR. The study was performed at pH 4, 5 and 6, and at temperatures of 90°C, 100°C and 120°C, respectively, for between 20 and 60 minutes. Clofentezine was shown to be hydrolytically stable at pH 4 with no degradation occurring after 20 minutes at 90°C. At pH 5, clofentezine degraded by about 10% to form one known hydrolysis product, characterised as 2-chlorobenzoyl (2-chlorobenzylidene) hydrazide. This fraction accounted for 12.4% of the applied radioactivity at the end of the incubation period. At pH 6, clofentezine degraded completely to three known metabolites, characterised as 2-chlorobenzoyl (2-chlorobenzylidene) hydrazide, 2-chlorobenzonitrile and 2-chlorobenzamide. These compounds represented 77.6%, 4.9% and 17.0% of the applied radioactivity after 20 minutes at 120°C, respectively. Thus, under mild hydrolytic conditions the RD in processed plant commodities can still be expressed as parent clofentezine. However, under drastic hydrolytic conditions (for example, sterilisation), the RD would have to include the hydrolytic degradation products, if these are found to be of toxicological concern.

Among registered crops, apples can be processed into juice, sauce, dried apple or pomace; peaches and pears into juice or dried fruits; raspberries and strawberries into juice.

Apples:

– Apples treated with clofentezine 80WP at a rate of 0.03% (1.12 kg ai/ha) 14 days before harvest were processed into canned apple juice and sauce, fresh cider and wet and dry pomace. Samples were analysed by a modified Method# R29 for parent clofentezine with an LOD of 0.05 ppm for apple pomace and 0.01 ppm for all other matrices. A mean residue of 1.29 ppm was found in raw apples at harvest. Mean residues of <0.01, 0.02, 0.01, 7.34 and 19.5 ppm were found in fresh cider, apple juice, apple sauce, wet pomace and dry pomace, respectively. These represent processing factors of <0.008, 0.016, 0.008, 5.69 and 15.1, respectively.

– Apples received early (107-, 149- and 158-day PHI) or late (21-, 40- and 45-day PHI) season applications of clofentezine 50SC at rates of 0.28 and 0.56 kg ai/ha. The apples were processed into fresh apple juice, mash and wet and dry pomace and analysed by Method# R94 (slightly

modified Method# R29) for parent clofentezine. Given the proposed PHI of 21 days for the application of clofentezine on apples, results of applications at 40-, 45-, 107-, 149 and 158-day PHI are not relevant for the estimation of processing factors. Only the single late application at 21-day PHI at 0.28 and 0.56 kg ai/ha is of interest. Mean residues of samples treated at lower rate (0.28 kg ai/ha) were at or close to the detection limit in raw apples (0.01 ppm) and in juice (0.02 ppm) and at 0.55 and 0.86 ppm in wet and dry pomace, respectively. At higher rate (0.56 kg ai/ha), a residue of 0.19 ppm was found in raw apples at harvest. Mean residues in processed commodities were 0.02 ppm in juice, 0.27 ppm in mash, 1.1 ppm in wet pomace and 2.2 ppm in dry pomace. These represent processing factors of 0.11, 1.4, 5.79 and 11.6, respectively. These processing factors are more representative of the Canadian use pattern than those reported in the study above.

Peaches, pears, raspberries, strawberries:

– No processing studies were submitted to the PMRA for peaches, pears, raspberries and strawberries. However, processing studies for strawberries along with oranges, apples and grapes have been submitted to and reviewed by the 2007 JMPR. The obtained processing factors are summarized in the table below:

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors [a]	Median or best estimate
Orange	Flesh	0.06, < 0.08(3), 0.08(2), 0.09, < 0.10, 0.13, < 0.14(5), 0.14, 0.16, < 0.17, 0.17(3), 0.19, < 0.20(4), 0.20(4), 0.22(3), < 0.25(4), 0.25(4), 0.26, < 0.33(5), 0.33(2), 0.43, < 0.50(2), 0.50, 0.94	0.20
	Peel	2.00, 2.07, 2.13, 2.15, 2.43, 2.44(2), 2.50(2), 2.63, 2.67, 2.69, 2.71, 2.75, 2.86, 2.88, 2.90, 3.00(2), 3.20(2), 3.22(2), 3.25(2), 3.40, 3.43(2), 3.50(4), 3.56, 3.57, 3.67(5), 3.71, 3.78, 3.83(2), 4.00(4), 4.08, 4.17, 4.22, 4.40, 4.62, 6.70	3.43
	Juice	< 0.08, < 0.11, < 0.14, 0.14, < 0.17(3), < 0.20, < 0.25(2), < 0.33(2)	0.14
	Oil	86.7, 120	103
	Wet peel	<1.25, <1.70	<1.25
	Dried peel	1.25, 2.0	1.63
	Dried fine from peel	1.50, <1.67	1.50
	Molasses	<1.25, <1.67	<1.25
Apples	Washed apples	0.73	0.73
	Peeled apples	< 0.050	< 0.050
	Peel	3.30	3.30
	Wet pomace	< 0.50, 1.20, 1.50 (2), 2.00 (4), 2.11, 2.40, 3.00, 3.44, 5.50, 5.69, 5.79, 6.00	2.06
	Dried pomace	3.50, 5.50, 5.79, 6.00, 8.00, 8.60, 11.6, 15.1	7.00
	Juice	0.016, 0.11, 0.20, < 0.5 (3)	0.11
	Fresh cider	< 0.008	0.008
	Sauce	0.008, < 0.049(3), 0.075	0.042
Grapes	Raisins	0.22, 0.28, 0.64, < 0.67, 1.09, 1.12, 1.70, 2.33, 2.92	1.11
	Juice	nd(2)	0
	Wet pomace	1.88, 1.89	1.89

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors [a]	Median or best estimate
	Dry pomace	1.22, 1.48	1.35
	White wine making	< 0.042, < 0.50 (2)	< 0.042
Strawberries	Canned strawberries	0.16, 0.31	0.24

[a] - 'Less-than' (<) values are derived from cases where residues were not detected in the processed commodity. The 'less-than' processing factor is then calculated from the LOQ of the analyte in the processed commodity and the residue in the raw agricultural commodity.

1.3.2.6 Residue Data for Crops used as Livestock Feed

Wet pomace is a feed item resulting from the processing of apples. An MRL of 0.5 ppm is currently established on apples, and apple processing studies (see Section 1.3.2.5) indicate a processing factor of 5.79 for wet pomace. The USEPA has established a tolerance of 3.0 ppm for wet pomace.

1.3.2.7 Livestock, Poultry, Egg and Milk Residue Data

A cattle feeding study has been previously reviewed by the PMRA and deemed adequate to support currently established MRLs for residues of clofentezine and the 4-OH clofentezine metabolite in livestock and dairy commodities. It should be noted that none of the Canadian registered crop uses can serve as a poultry feedstuff; therefore, information pertaining to the magnitude of the residue in poultry and eggs is not relevant to this re-evaluation.

Appendix VII Supplemental Maximum Residue Limit Information – International Situation and Trade Implications

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Canadian MRLs have been established as clofentezine *per se* at 0.5 ppm on almonds, apples, and pears; 1.0 ppm on nectarines and peaches; and as combined residues of clofentezine and metabolite 4-hydroxy clofentezine at 0.01 ppm on milk and 0.05 ppm on all other livestock products (except liver) and published in Health Canada's List of MRLs Regulated under the *Pest Control Products Act* on the Maximum Residue Limits for Pesticides webpage. Residues in/on raspberries and strawberries are regulated under B.15.002(1) of the *Food and Drugs Regulations* not to exceed 0.1 ppm. The MRLs on almonds, apples, nectarines, peaches and pears were primarily established to cover residues on imported crops, based on American field trial residue data.

Clofentezine is registered for use in at least 25 countries, including Australia, New Zealand, France, Germany, Israel, Spain, Switzerland, United Kingdom, Canada and the United States. Codex MRLs have been established for the residues of clofentezine *per se* on crops such as citrus fruits, cucumbers, currants, grapes, melons, pome fruits, stone fruits, strawberries, tomatoes and tree nuts, as well as on livestock commodities. In the United States, tolerances are currently established under 40 CFR §180.446 for the residues of clofentezine *per se* in/on almond hulls, almonds, apple pomace, apple, apricot, cherry, grape, nectarine, peach, pear, persimmon and walnut. American tolerances are also established for the combined residues of clofentezine and the 3-(2-chloro-4-hydroxyphenyl)-6-(2-chlorophenyl)-1,2,4,5-tetrazine metabolite in/on fat, meat, meat byproducts and dairy products.

Table 1 Canadian MRLs and International Tolerances/MRLs

Commodity	CAN MRL[a] (ppm)	US Tolerance[b] (ppm)	Codex MRL[c] (ppm)
Almond	0.5	0.5	0.5 (all tree nuts)
Almond, hulls	--	5.0	5.0
Apple	0.5	0.5	0.5 (all pome fruits)
Apple, dry pomace	--	3.0	--
Apple, wet pomace	--	3.0	--
Apricot	--	1.0	0.5 (all stone fruits)
Cherry	--	1.0	0.5 (all stone fruits)
Citrus fruits	--	--	0.5
Cucumber	--	--	0.5
Currants, Black, Red, White	--	--	0.2
Dried grapes (= currants, raisins and sultanas)	--	--	2.0
Grape	--	1.0	2.0
Nectarine	1.0	1.0	0.5 (all stone fruits)
Peach	1.0	1.0	0.5 (all stone fruits)
Pear	0.5	0.5	0.5 (all pome fruits)
Persimmon	--	0.05	--

Commodity	CAN MRL[a] (ppm)	US Tolerance[b] (ppm)	Codex MRL[c] (ppm)
Raspberry	*	--	--
Strawberry	*	--	2.0
Tomato	--	--	0.5
Walnut	--	0.02	0.5 (all tree nuts)
Cattle, fat	--	0.05	0.05**
Cattle, liver	--	0.4	0.05**
Cattle, meat	0.05	0.05	0.05**
Cattle, meat byproducts, except liver	0.05	0.05	0.05**
Goat, fat	--	0.05	0.05**
Goat, liver	--	0.4	0.05**
Goat, meat	0.05	0.05	0.05**
Goat, meat byproducts, except liver	0.05	0.05	0.05**
Hog, fat	--	0.05	0.05**
Hog, liver	--	0.4	0.05**
Hog, meat	0.05	0.05	0.05**
Hog, meat byproducts, except liver	0.05	0.05	0.05**
Horse, fat	--	0.05	0.05**
Horse, liver	--	0.4	0.05**
Horse, meat	0.05	0.05	0.05**
Horse, meat byproducts, except liver	0.05	0.05	0.05**
Melons, except water melon	--	--	0.1
Milk	0.01	0.01	0.05**
Sheep, fat	--	0.05	0.05**
Sheep, liver	--	0.4	0.05**
Sheep, meat	0.05	0.05	0.05**
Sheep, meat byproducts, except liver	0.05	0.05	0.05**

*Regulated under B.15.002(1) of the Food and Drugs Regulations not to exceed 0.1 ppm.
**At or below the limit of determination
[a]Maximum Residue Limits for Pesticides webpage
[b]http://ecfr.gpoaccess.gov (40 CFR §180.446)
[c]http://www.codexalimentarius.net/mrls/pestdes/jsp/pest_q-e.jsp

Appendix VIII Monitoring Data Used in Dietary Risk Assessments

The chronic and cancer assessments were refined, using USDA PDP monitoring residue data for apple (translated to crabapple, loquat and quince), apple juice, apple sauce, cherry, grape juice, raisin, peach (translated to apricot, nectarine, and plum/prune), pear, and strawberry; United States anticipated residues for almond, meat, meat byproducts and dairy products; and STMRs from JMPR for all other tree nuts (except walnut) and citrus fruits. MRL/tolerance-level residues were used only for dried currant, persimmon, raspberry, and walnut. In addition, domestic production and import supply weighted average %CT information was used. Experimental processing factors were used for orange juice and wine. Default processing factors were used for all dried fruits and meat, as well as for cherry, grapefruit and tangerine juices [Table 1].

Table 1 Residue Data Summary

Commodity	Proc. Factor Used	Source of Data	Year Span	Number of Samples	Range of Detected Residues (ppm)	Chronic Weighted Average %CT	Chronic Average Residue (ppm)[1]
Almond	1	EPA AR[2]: 0.09 ppm	--	--	--	3	0.0027
Almond oil	1	See almond	--	--	--	3	0.0027
Apple	1	PDP	2002-2008	563	ND[3]-0.19 (N[4]=1)	12	0.000672
Apple, dried	8 (default)	See apple	--	--	--	100	0.0448
Apple, juice	1	PDP	2002-2008	214	ND	37	0.001295
Apple, sauce	1	PDP	2002-2008	730	ND	37	0.003293
Apricot	1	Transl. from peach	--	--	--	14	0.000672
Apricot, dried	6 (default)	See apricot	--	--	--	100	0.0288
Apricot, juice	1	See apricot	--	--	--	14	0.000672
Beef, meat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Beef, meat, dried	1.92 (default)	See beef, meat	--	--	--	--	0.0000768
Beef, meat byproducts	1	See beef, meat	--	--	--	--	0.00004
Beef, fat	1	See beef, meat	--	--	--	--	0.00004
Beef, kidney	1	EPA AR: 0.001 ppm	--	--	--	--	0.001
Beef, liver	1	EPA AR: 0.006 ppm	--	--	--	--	0.006
Brazil nut	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Butternut	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Cashew	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Cherry	1	PDP	2002-2008	122	ND	7	0.000245
Cherry, juice	1.5	See cherry	--	--	--	7	0.000368

Commodity	Proc. Factor Used	Source of Data	Year Span	Number of Samples	Range of Detected Residues (ppm)	Chronic Weighted Average %CT	Chronic Average Residue (ppm)[1]
	(default)						
Chestnut	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Citrus citron	1	JMPR STMR: 0.02 ppm	--	--	--	33	0.0066
Citrus hybrids	1	See citrus citron	--	--	--	33	0.0066
Citrus, oil	1	See citrus citron	--	--	--	33	0.0066
Crabapple	1	Transl. from apple	--	--	--	8	0.000448
Cucumber	1	JMPR STMR: 0.125 ppm	--	--	--	13	0.01625
Currant	1	JMPR STMR: 0.04 ppm	--	--	--	79	0.0316
Currant, dried	1	Codex MRL: 2.0 ppm	--	--	--	79	1.58
Filbert	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Filbert, oil	1	See filbert	--	--	--	35	0.0175
Goat, meat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Goat, meat byproducts	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Goat, fat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Goat, kidney	1	EPA AR: 0.001 ppm	--	--	--	--	0.001
Goat, liver	1	EPA AR: 0.006 ppm	--	--	--	--	0.006
Grape	1	See grape, raisin	--	--	--	73	0.002555
Grape, juice	1	PDP	2002-2008	214	ND	97	0.003395
Grape, raisin	1	PDP	2002-2008	216	ND	100	0.0035
Grape, wine and sherry	0.042 (JMPR)	See grape, raisin	--	--	--	75	0.000110
Grapefruit	1	JMPR STMR: 0.02 ppm	--	--	--	18	0.0036
Grapefruit, juice	2.1	See grapefruit	--	--	--	18	0.00756
Hickory nut	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Horse, meat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Kumquat	1	JMPR STMR: 0.02 ppm	--	--	--	42	0.0084
Lemon	1	JMPR STMR: 0.02 ppm	--	--	--	42	0.0084
Lemon, juice	2	See lemon	--	--	--	33	0.0066

Commodity	Proc. Factor Used	Source of Data	Year Span	Number of Samples	Range of Detected Residues (ppm)	Chronic Weighted Average %CT	Chronic Average Residue (ppm)[1]
Lime	1	JMPR STMR: 0.02 ppm	--	--	--	42	0.0084
Lime, juice	2	See lime	--	--	--	33	0.0066
Loquat	1	Transl. from apple	--	--	--	38	0.002128
Macadamia nut	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Meat, game	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Milk	1	EPA AR: 0.0003 ppm	--	--	--	--	0.0003
Nectarine	1	Transl. from peach	--	--	--	19	0.000912
Orange	1	JMPR STMR: 0.02 ppm	--	--	--	26	0.0052
Orange, juice	0.14 (JMPR)	See orange	--	--	--	33	0.000924
Peach	1	PDP	2002-2008	350	0.012-0.100(N=16)	11	0.000528
Peach, dried	7	See peach	--	--	--	53	0.017808
Peach, juice	1	See peach	--	--	--	11	0.000528
Pear	1	PDP	2002-2008	430	0.011-0.012(N=3)	41	0.001435
Pear, dried	6.25 (default)	See pear	--	--	--	100	0.021875
Pear, juice	1	See pear	--	--	--	41	0.001435
Pecan	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Persimmon	1	US tolerance: 0.05 ppm	--	--	--	100	0.05
Pistachio	1	JMPR STMR: 0.05 ppm	--	--	--	35	0.0175
Plum	1	Transl. from peach	--	--	--	24	0.001152
Plum, dried	5	See plum	--	--	--	89	0.02136
Plum, juice	1	See plum	--	--	--	24	0.001152
Pork, meat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Pork, skin	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Pork, meat byproducts	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Pork, fat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Pork, kidney	1	EPA AR: 0.001 ppm	--	--	--	--	0.001
Pork, liver	1	EPA AR: 0.006 ppm	--	--	--	--	0.006
Pummelo	1	JMPR STMR: 0.02 ppm	--	--	--	42	0.0084

Commodity	Proc. Factor Used	Source of Data	Year Span	Number of Samples	Range of Detected Residues (ppm)	Chronic Weighted Average %CT	Chronic Average Residue (ppm)[1]
Quince	1	Transl. from apple	--	--	--	45	0.00252
Rabbit, meat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Raspberry	1	GMRL: 0.1 ppm	--	--	--	25	0.025
Raspberry, juice	1	See raspberry	--	--	--	25	0.025
Sheep, meat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Sheep, meat byproducts	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Sheep, fat	1	EPA AR: 0.00004 ppm	--	--	--	--	0.00004
Sheep, kidney	1	EPA AR: 0.001 ppm	--	--	--	--	0.001
Sheep, liver	1	EPA AR: 0.006 ppm	--	--	--	--	0.006
Strawberry	1	PDP	2002-2008	215	ND	5	0.00026
Strawberry, juice	1	See strawberry	--	--	--	5	0.00026
Tangerine	1	JMPR STMR: 0.02 ppm	--	--	--	89	0.0178
Tangerine, juice	2.3 (default)	See tangerine	--	--	--	33	0.016698
Tomato	1	JMPR STMR: 0.05 ppm	--	--	--	6	0.003
Tomato, paste	5.4	See tomato	--	--	--	0	0
Tomato, puree	3.3	See tomato	--	--	--	0	0
Tomato, dried	14.3	See tomato	--	--	--	0	0
Tomato, juice	1.5	See tomato	--	--	--	0	0
Walnut	1	US tolerance: 0.02 ppm	--	--	--	38	0.0076

[1]The chronic average residue is calculated as the product of the default residue (Monitoring, AR, STMR, MRL/Tolerance), the processing factor used and the average %CT.
[2]AR = anticipated residue; [3]ND = non-detect; [4]N = number of samples with positive (detected) residue.

Appendix IX Environmental Fate, Toxicity and Risk Assessment of Clofentezine

Table 1 Fate and Behaviour of Clofentezine in the Terrestrial Environment

Property	Test substance[1]	Material	DT_{50} (days)	DT_{90} (days)	Rep t1/2 (days)	Kinetic models	Major Transformation Product	Comments [1, 2, 3, 4, 5, 6]	PMRA #
Phototransformation in soil	CFZ	Sandy loam	184.0	613.0	184.0	SFO	None	Not a major route of transformation in the environment	1205373
Aerobic soil biotransformation (non-sterile soils)	CFZ	Speyer 2.2 S. loam Speyer 2.3 S. loam Sandy loam Cottenham L. sand Cottenham L. sand Bottisham C. loam Bottisham C. loam Shelford clay Shelford clay	52.5 15.3 34.0 113.0 104.0 142.0 70.8 32.4 68.4	737.0 71.2 927.0 680.0 346.0 1287.0 235.0 748.0 227.0	311.0 21.4 279.0 205.0 104.0 520.0 70.8 225.0 68.4	DFOP IORE IORE IORE SFO DFOP SFO IORE SFO	Hydrazide-hydrazone, max 13% AR (30 d), 0.7% AR at end. Oxadiazole, max 10.8% AR (21 d), 3.2% AR at end	Slightly persistent to moderately persistent. Not a major route of transformation in the environment	1199872, 1199871, 1142387, 1199870,
	Hydrazide-hydrazone	Cottenham L. sand	43	NR	NR	SFO	NR	Slightly persistent	2147646
Anaerobic soil biotransformation	CFZ	Sandy loam Shelford clay Cottenham L.sand Bottisham C. loam	NR	NR	NR	NR	No transformation products reported CFZ was 47.2% AR (90 d) CFZ was at 48.4% AR (90 d) CFZ was at 33% AR (90 d) CFZ was at 23.4% AR (90 d)	Low rate of transformation Not a route of transformation in the environment	1199872, 1199871
Adsorption/ desorption	CFZ	N/A	K_{oc} = 1064 mL/g		N/A	N/A	N/A	Low mobility	2077910, 2096107, 1740419, 1740421, 1740422, 2147646
		S. loam (0.8% O.M.)[8] S. loam (5.9% O.M.) Silt loam (3.8% O.M.) Clay soil (4.5% O.M.)	K_d = 1.4 mL/g K_d = 10.3 mL/g K_d = 6.6 mL/g K_d = 7.9 mL/g		N/A	N/A	N/A	Low mobility	
	Hydrazide-hydrazone	Loam (pH 6.5, 2.9% OC) S. loam (pH 4.9, 2.0% O.C.) S. loam (pH7.3, 2.1% O.C.)	K_{oc} = 865 mL/g K_{oc} = 1149 mL/g K_{oc} = 701 mL/g		N/A	N/A	N/A	Low mobility	1740420, 1694213

Property	Test substance[1]	Material	DT_{50} (days)	DT_{90} (days)	Rep t1/2 (days)	Kinetic models	Major Transformation Product	Comments [1, 2, 3, 4, 5, 6]	PMRA #
		Loam (pH 6.5, 2.9% OC) S. loam (pH 4.9, 2.0% O.C.) S. loam (pH7.3, 2.1% O.C.)	K_d = 25.1 mL/g K_d= 23 mL/g K_d = 14.7 mL/g		N/A	N/A	N/A		
Soil column leaching	CFZ	Cottenham loamy sand 2.1 Loamy sand 2.2 sandy loam 2.3 sandy loam Cottenham sandy loam soil Redlodge sandy soil Willingham silty loam soil Shelford clay soil Speyer 2.1 sand Speyer 2.2 loamy sand Speyer 2.3 sandy loam	N/A	N/A	N/A	N/A	N/A	Immobile Immobile Immobile Immobile Immobile Immobile Immobile Immobile Immobile Immobile Immobile	1199868, 1205376, 1740425, 2069246, 1205377,
Soil TLC (Helling mobility index)	CFZ		**Index value**		N/A	N/A	N/A		1199866, 1740423, 1740424, 1199866
		Sandy soil Sandy loam Silt loam Clay soil	1 1 1 1					Immobile Immobile Immobile Immobile	
Leaching potential (Leaching criteria of Cohen *et al.* 1984)	CFZ	**Criteria** Solubility > 30 mg/L K_d < 5 and usually < 1 or 2 K_{oc} < 300 HLC[9] < 10^{-2} atm m^3/mol pKa = Negatively charged Hydrolysis $t_{1/2}$ > 140 d Soil photo. $t_{1/2}$ > 7 d Soil biotr. $t_{1/2}$ > 14 to 21 d	**Value** 2.52 µg/L 1.4-10.3 mL/g 1064 mL/g 1.66 × 10^{-6} atm m^3/mole Not measurable $t_{1/2} \leq$ 10.4 days at all pHs DT_{50} = 184 days DT_{50} = 15.3 - 142 days				**Criteria met** No No, except sandy soil No Yes N/A No Yes Yes	Low potential for leaching	-

Property	Test substance[1]	Material	DT_{50} (days)	DT_{90} (days)	Rep t1/2 (days)	Kinetic models	Major Transformation Product	Comments [1, 2, 3, 4, 5, 6]	PMRA #
GUS Score	CFZ	0.31-2.38	N/A		N/A	N/A	N/A	Borderline to non-leacher	-
Volatility	CFZ	**Based on:** -Low vapour pressure (6.0 × 10-7 Pa at 20ºC) -Short atmospheric dissipation rate (DT50 = 5.1 d) -Not volatile in soil lab experiments -Rapidly hydrolyzed, phototransformed and biotransformed (soil and water) -Highly sorbs to soils					N/A	Expected to be relatively non-volatile under field conditions	2147646
Canadian field studies	CFZ	Trenton site 1 Trenton site 2 Osoyoos site 1 Osoyoos site 2	18.6 6.3 15.9 10.7	61.8 45.1 52.7 35.4	18.6 13.6 15.9 10.7	SFO IORE SFO SFO	NR	Non-persistent to slightly persistent. Immobile in soil	1215740, 2147645, 1213005, 1222382
US field studies	CFZ	Apple orchard soil litter Apple orchard soil	< 0.01 mg/kg in 0-7.5 cm horizon after 90 days 0.05 mg/kg in 0-7.5 cm horizon after 156 days					Immobile in soil Immobile in soil	1142474, 2147645, 1205731

[1] = Persistence classification of pesticides in soil according to Goring et al. (1975),
[2] = Persistence classification of pesticides in water according to McEwen and Stephensen, (1979),
[2] = Adsorption/desorption mobility class according to McCall et al. (1981);
[3] = TLC mobility class according to Helling and Turner (1968);
[4] = Leaching potential based on the criteria of Cohen et al. (1984)
[5] = Ground Ubiquity Score (GUS), N/A = Not available; N/D = Not detected; NR = Not reported
[6] = clofentezine = CFZ
[7] (O.M.) = Organic matter
[8] HLC = Henry's Law Constant

Table 2 Fate and Behaviour of Clofentezine in the Aquatic Environment

Property	Test substance	Conditions	DT50 (days)	DT90 (days)	Rep t1/2 (days)	Kinetic models	Major Transformation Product	Comments [1,]	PMRA #
Abiotic transformation									
Hydrolysis	CFZ[2]	22ºC, pH 4.95 pH 6.98 pH 9.18	10.4 1.4 0.2	NR	NR	SFO	Hydrazide-hydrazone 38% AR at pH 7	A major route of transformation in the environment	1205370 1205371
	CFZ	25ºC, pH 7	1.0	NR	NR	SFO	Hydrazide-hydrazone 42.2% AR (1 d), 2.5% at end 2-Cl-benzonitrile 95.8% AR at end		1740416
Phototranformation in water	CFZ	6.8-28.4ºC, pH 5.05	5.7	NR	NR	SFO	2-Cl-benzonitrile 74.6% AR at 31 d		1205372
Biotransformation									
Aerobic aquatic biotransformation (whole system)	CFZ	Taunton Weweantic Lode Sadlers	16.5 41.1 13.1 7.1	76.5 95.9 NR NR	23.0 28.9 NR NR	IORE IORE SFO SFO	2-Cl-benzoic acid, 26.7% AR (58 d), 0.6% AR (100 d) 2-Cl-benzoic acid, 17.8% AR (30 d), ND (100 d) NR in whole system NR in whole system	Non-persistent to slightly persistent. An important route of transformation in the environment	209610, 2060524 2077908 1740418 1142450 1205379 2069245 2147646
	Hydrazide-hydrazone	Clay loam whole system	12.6-21.0	NR	NR	SFO	NR	Non-persistent to slightly persistent	1205379 2147646
Anaerobic aquatic biotransformation (whole system)	CFZ	Taunton	44.9	149.0	44.9	SFO	Hydrazide-hydrazone 21.3% AR (2 d), 17.1% AR (180 d) Cl-benzoic acid 15.6% AR (56 d), 12.5% AR (180 d)	Slightly persistent	2060525 2096106 2077909
		Weweantic	33.2	110.0	33.2	SFO	Hydrazide-hydrazone 14.5% AR (2 d), 10.1% AR (180 d) Cl-benzoic acid 37.2% AR (56 d), 18.4% AR (180 d)		
Bioconcentration									
14-day BCF on bluegill sunfish	CFZ	BCF = 230-430, 93% depuration after 3 days			N/A	N/A	Hydrazide-hydrazone	Rapid depuration of residues	1205380 1169462 2147645 DD89-03

[1] = Persistence classification of pesticides in water according to McEwen and Stephensen, (1979)
[2] = CFZ = Clofentezine, NR = Not reported, N/A = Not applicable

Table 3 Toxicity of Clofentezine to Non-Target Terrestrial Organisms

Organism	Species	Compound	Study	Endpoint	Value	Comment[1,2]	PMRA#
Earthworm	*Eisenia foetida*	Apollo 50 SC	Lab acute	LC_{50}	215 mg a.i./kg	-	PPDB 2012 2147646
		Apollo 50 SC	Lab chronic	NOEC	2.6 mg a.i./kg soil	-	PPDB 2012 2147646
		Apollo 50 SC	Field	NOEC	372 g a.i/ha	-	1205581, 2069248,
Honey bee	*Apis mellifera*	TGAI	Acute oral	LD_{50}	>20 µg a.i./bee		2069249
		Apollo 50 SC	Acute oral	LD_{50}	>252.6 µg a.i./bee	-	2147646
		Apollo 50 SC	Acute contact	LC_{50}	>84.5 µg a.i./bee	-	214764, 2147646
Soil beneficials (Collembola)	*Folsomia candida*	Apollo 50 SC	Lab Chronic	NOEC	160 mg a.i./kg soil	-	2147646
Predators and parasitic arthropods	(*Typhlodromus pyri*)	Clofentezine 50 WP	Field acute	LR_{50}	>300 g a.i./ha	-	1205577, 2147646
Parasitoid	*Aphidius rhopalosiphi*	Apollo 50 SC	Lab acute	LR_{50}	36.2 g a.i./ha	-	2147646
Parasitoid	*Trichogramma cacoeciae*	Apollo 50 SC	Lab acute	LD_{50}	>200 g a.i./ha >300 g a.i./ha	No significant effect 18.9% decrease in fecondity	2147646
Predatory mite	*Phytoselius persimilis*	Apollo 50 SC	Lab acute	LD_{50}	>200 g a.i./ha	No significant effect	2147646
Parasitoid	*Aphidius rhopalosiphi*	Apollo 50 SC	Lab acute	LD_{50}	>300 g a.i./ha	37% decrease in reproduction	2147646
Predator	*Chysoperla carnae*‡	Apollo 50 SC	Lab acute	LD_{50}	>300 g a.i./ha	No significant effect	2147646
Predator	*Poecilus cupreus*‡	Apollo 50 SC	Lab acute	LD_{50}	>300 g a.i./ha	No significant effect	2147646
Predator	*Coccinella septempuntata*	Apollo 50 SC	Field acute	LC_{50} NOAEC	>200 g a.i./ha 200 g a.i./ha	No significant effect	169435
Predatory mite	(*Typhlodromus pyri*)	NC 21314 50 WP	Field acute	LC_{50}	>60 g/100L (*ca* . 150 g a.i./ha)	No significant effect	1205570
Predatory mite	*Typhlodromus occidentalis*	SN 84866 80WP	Field acute	LC_{50}	>540 g a.i./ha	No significant effect	1205572
Predatory mite	*Typhlodromus occidentalis*	SN 84866 80WP	Field acute	LC_{50}	>540 g a.i./ha	No significant effect	1205573, 1205574
Predatory mite	*Typhlodromus occidentalis*	NC 21314 80 WP	Field acute	LC_{50}	>1875 g a.i./ha	No significant effect	1205575
Predatory mite	(*Typhlodromus pyri*)	NC 21314 50 WP	Field acute	LC_{50}	>3000 g a.i./ha or >4.8 g a.i./tree	No significant effect	1205576

Organism	Species	Compound	Study	Endpoint	Value	Comment[1,2]	PMRA#
Birds	Bobwhite quail *(Colinus virginianus)*	TGAI NC 21314	Acute oral	14-day LD_{50}	> 7500 mg a.i./kg bw	Practically non-toxic	2069270, 2069271 2147646, 2147645
			5-day dietary	5-day LD_{50}	> 4000 mg a.i./kg bw/day	Practically non-toxic	2069272, 2069275, 2147646, 2147645
			Chronic repro.	22-week NOEL	2.68 mg a.i./kg bw/day	-	1694507, 1694510, 2147646, 2147645
				22-week LOEL	7.82 mg a.i./kg bw/day	-	
	Mallard duck (*Anas platyrhynchos*)	TGAI NC 21314	Acute oral	14-day LD_{50}	> 3000 mg a.i./kg bw	Practically non-toxic	2069268, 2069269 2147646, 2147645
			5-day dietary	5-day LD_{50}	> 4577.8 mg a.i./kg bw/day	Practically non-toxic	2069273, 2069276, 2147645
			Chronic repro.	22-week NOEL	39.2 mg a.i./kg bw/day	-	1694496, 1694627, 2147645)
Mammals	Mice	TGAI NC 21314	Acute oral	LD50	> 3200 mg a.i./kg bw	Practically non-toxic	2147646 1822375
	Rats	TGAI NC 21314	2 gener. Repro. dietary	NOEL	3.9 mg a.i./kg bw/day	Offspring: based on decreased F2a pup body weight at LD 21 (male): F2a altered sex ratios	2147646, 1823375
				LOEL	36.1 mg a.i./kg bw/d		
Terrestrial plants	All species	Apollo 50 SC	Seedling emergence	ER_{50}	> 300 g a.i./ha	Plant dry weight	2147646
	All species		Vegetative vigour	ER_{50}	> 300 g a.i./ha	Shoot fresh weight	
	Dicotyledon Pea (*Pisum sativum*)			ER_{25}	> 296.7 g a.i./ha	Plant dry weight	1740441 1694629 2147646
				NOER	296.7 g a.i./ha		
	Monocotyledon Oats (*Avena sativa*)			ER_{25}	> 291.96 g a.i./ha	Shoot fresh weight	
				NOER	291.96 g a.i./ha		

[1] According to USEPA (1985b) classification scheme.
[2] According to USEPA (1985a) classification scheme.

Table 4 Toxicity Effects of Clofentezine and Transformation Products to Aquatic Organisms

Organism (Species)	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
Freshwater species					
Invertebrate: *Daphnia magna*	Acute	Apollo 50 SC	48-hour EC_{50} > 51.3 mg a.i./L	Slightly toxic	1142413 2069254
		TGAI	48-hour EC_{50} > 0.00 115 mg a.i./L	-	1740427 1694247
		TGAI	48-hour EC_{50} > 0.08 mg a.i./L NOEC = 0.08 mg a.i./L	-	2069255
		Apollo 50 SC	48-hour EC_{50} > 100 mg a.i./L*	Practically non-toxic	1205386
	Chronic	Apollo 50 SC (43.5% CFZ)	21-day NOEC < 0.114 mg a.i./L	-	1740428 1694263 2147646
		Apollo 50 SC (41.4% CFZ)	NOEC < 0.04 mg a.i./L	-	1694297 2147646
		TGAI	21-day NOEC = 0.025-0.026 mg a.i.//L	-	1694253 2147646
Chironomus riparius	Chronic	Apollo 50 SC	28-day NOEC = 0.5 mg a.i./L	-	2147646
Cold fish: Rainbow trout *Onchorynchus mykiss*	Acute	TGAI continuous flow	96-hour LC_{50} > 0.0146 mg a.i./L	-	1740434 1169462
		Apollo 50 SC continuous flow	96-hour LC_{50} > 10 mg a.i./L	-	1205565 2147646
		Semis static flow CFZ	96-hour LC_{50} > 0.005-0.039 mg a.i./L	-	2147645
Warm fish:, Bluegill sunfish, *Lepomis macrochirus*	Acute	Flow through CFZ	96-hour LC_{50} > 0.25 mg a.i./L	-	2147645 2147646
		Apollo 50 SC	96-hour LC_{50}> 12 mg a.i./L	Practically non-toxic	1740437 1694486
Cold fish: Rainbow trout *Onchorynchus mykiss*	ELS	Technical (flow through)	97-Day NOEC = 0.006 mg a.i./L		1740435 1694490
Fathead minnow *Pimephales promelas*	ELS	Apollo 50 SC (flow through)	NOEC = 0.979 mg a.i./L		1740436 1694494
Algae: Green algae, *Scenedescus pannonicus*	Acute	NC 21314	EC_{50} > 0.006 mg a.i./L		1205385 2069279
Algae: green algae *Selenastrum capricornutum*	Acute	Apollo 50 SC	96-hour EC_{50} > 40 mg a.i./L NOEC = 40 mg a.i./L		1740441 2069278
Pseudokirchneriella subcapitata	Acute	Apollo 50 SC	clofentezine - 72-hour EbC_{50} >20 mg a.i./L		2147646

Organism (Species)	Exposure	Test substance	Endpoint value[1]	Degree of toxicity[2]	PMRA#
			clofentezine - 72-hour ErC_{50} >20 mg a.i./L		
			2-chlorobenzonitrile Eb_{50} > 16 mg a.i./L 2-chlorobenzonitrile Er_{50} > 47 mg a.i./L		
Marine species					
Saltwater mysid, *Mysidiopsis bahia*	Chronic	TGAI	28-day NOEC = 0.0033 mg a.i./L	Practically non-toxic	2060527, 2097114

[1]= USEPA classification, where applicable

Screening Level Risk Assessment to Terrestrial Invertebrates

Table 5 Risk Quotients for Earthworms, Soil Benefecials and Bees Exposed to Clofentezine Residues

Organism	Exposure	Endpoint value	EEC	RQ	Off-field RQ
Earthworms	Acute	14 d-LC_{50} ÷ 2 = 215 mg a.i./kg soil ÷ 2 = 107.5 mg a.i./kg soil	0.111 mg a.i./kg soil	0.001	-
	Chronic Lab Reproduction	NOEC = 2.6 mg a.i./kg soil	0.111 mg a.i./kg soil	0.043	-
	Chronic field	NOEC = 372 g a.i./ha	250 g a.i./ha	0.67	-
Soil beneficial *Folsomia candida*	Chronic	NOEC = 160 mg a.i./kg soil	0.111 mg a.i./kg soil	0.0007	
Bees	Acute contact	LD_{50} > 84.5 µg a.i./bee equivalent to > 94 600 g a.i./ha	250 g a.i./ha	0.003	-
	Acute oral	LD_{50} > 20 µg a.i./bee equivalent to > 22 400 g a.i./ha	250 g a.i./ha	0.01	-
	Brood	No data available, but are not required	-	-	-

Table 6 Risk Quotients for Predators and Parasitic Arthropods Exposed To Clofentezine, Based On EFSA (2009)

Organism	Crop	Exposure	Endpoint[1]	EEC	RQ[2]
Aphidius rhopalosiphi (parasitic wasp) foliar dwelling	Strawberry and raspberry	Groundboom in-field	LR_{50} = 36.2 g ai/ha	250	6.9
		Groundboom off-field (6% drift)	LR_{50} = 36.2 g ai/ha	15	0.4
	Apple, pear, peach, nectarine	Early Airblast in-field	LR_{50} = 36.2 g ai/ha	150	4.1
		Early Airblast off-field (74% drift)	LR_{50} = 36.2 g ai/ha	111	3.1
		Late Airblast in-field	LR_{50} = 36.2 g ai/ha	150	4.1
		Late Airblast off-field (59% drift)	LR_{50} = 36.2 g ai/ha	88.5	2.4
Typhlodromus pyri (Predatory phytoseiid mite)	Strawberry and raspberry	Groundboom in-field	Lab LR_{50} > 300 g a.i./ha Field LR_{50} > 3000 g a.i./ha	250	< 0.83 < 0.083
Coccinella semptempunctata	Strawberry and raspberry	Groundboom in-field	Field LR_{50} > 200 g a.i./ha	250	< 1.25
	Apple, pear, peach, nectarine	Early Airblast In-field	LR_{50} > 300 g a.i./ha ER_{50} > 300 g a.i./ha	150	< 0.5
Chrysoperla carnea	Strawberry and raspberry	Groundboom in-field	LR_{50} > 300 g a.i./ha ER_{50} > 300 g a.i./ha	250	< 0.83
	Apple, pear, peach, nectarine	Early Airblast In field	LR_{50} > 300 g a.i./ha ER_{50} > 300 g a.i./ha	150	< 0.5

[1] Arthropod data are based on tier 1 (glass plate) tests.
[2] Risk Quotient (RQ) = EEC / endpoint; shaded cells indicate that the screening level RQ exceeds the LOC of 2.0 for *A. rhopalosiphi* and *T. pyri* and 1.0 for others.

Screening Level and Refined Risk Assessment for Birds and Mammals

Table 7 Toxicity Endpoints Selected for the Avian Risk Assessment

Test	Toxicity endpoints selected for the avian risk assessment	
	Endpoint	Value
Acute oral	LD50 ÷ 10	>3000 mg a.i./kg bw ÷ 10
Dietary	LC50 ÷ 10	Dietary exposure not considered at the screening level
Reproduction	NOEL	2.68 mg a.i./kg body weight/day (PMRA) or 30 ppm (FAO)
	LOEL	7.82 mg a.i./kg body weight/day (PMRA) or 90 ppm (FAO). Decrease in embryo viability

Table 8 Screening Level Risk Assessment for Birds

Endpoint	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE[1] (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)				
Acute	> 300	Insectivore (small insects)	12.60	< 0.04
Reproduction	2.68	Insectivore (small insects)	12.60	4.70
Medium Sized Bird (0.1 kg)				
Acute	> 300	Insectivore (small insects)	9.83	< 0.03
Reproduction	2.68	Insectivore (small insects)	9.83	3.67
Large Sized Bird (1 kg)				
Acute	> 300	Herbivore (short grass)	10.26	< 0.03
Reproduction	2.68	Herbivore (short grass)	10.26	3.83

[1] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = $0.398(\text{BW in g})^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = $0.648(\text{BW in g})^{0.651}$.
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC are used.
Shaded cells indicate that the level of concern is exceeded (LOC = 1)

Table 9 Toxicity Endpoints for Mammalian Risk Assessment

Test	Mammal	Toxicity endpoint for the risk assessment	
		Endpoint	Value
Acute oral	Mice	$LD_{50} \div 10$	> 3200 mg a.i./kg bw ÷ *10*
Reproduction	Rats	NOEL	3.9 mg a.i./kg bw/day
		LOEL	36.1 mg a.i./kg bw/day (loss of body weight in F2 pups)

Table 10 Screening Level Risk Assessment for Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE[1] (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)				
Acute	> 320	Insectivore (small insects)	7.25	< 0.02
Reproduction	3.90	Insectivore (small insects)	7.25	1.86
Medium Sized Mammal (0.035 kg)				
Acute	> 320	Herbivore (short grass)	22.70	< 0.07
Reproduction	3.90	Herbivore (short grass)	22.70	5.82
Large Sized Mammal (1 kg)				
Acute	> 320	Herbivore (short grass)	12.13	< 0.04
Reproduction	3.90	Herbivore (short grass)	12.13	3.11

[1]EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g) $^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC are used.
Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 11 Screening Level Risk Assessment and Risk Quotients for Terrestrial Vascular Plants at the Maximum Rate of Application For Clofentezine (250 g a.i./ha)

Study	Plant type	Parameter	Endpoints(g ai/ha)	EEC	RQ	Off-field RQ
Seedling emergence	All type	Plant dry weight	ER_{50}> 300 g a.i/ha	*250 g a.i./ha*	< 0.83	-
Vegetative vigour	All type	Shoot fresh weight	ER_{50}> 300 g a.i/ha	*250 g a.i./ha*	< 0.83	-
	Dicotyledon (pea)	Plant dry weight	ER_{25}> 296.7 g a.i./ha NOER = 296.7 g a.i./ha	*250 g a.i./ha*	< 0.84	-
	Monocotyledon (Oats)	Shoot fresh weight	ER_{25}> 291.96 g a.i./ha NOER = 291.96 g a.i./ha	*250 g a.i./ha*	< 0.86	

Screening Level Risk Assessment on Non-Target Aquatic Species

Table 12 Toxicity Effects of Clofentezine to Aquatic Organisms Following Ground Boom Application in Strawberry and Rasberry Productions (250 g a.i/ha)

Organism (Species)	Substance	Exposure	Test substance	Most conservative endpoint values (mg a.i./L) ÷ safety factor[1]	EEC (mg a.i/.L)	RQ[2]
Freshwater species						
Invertebrate: *Daphnia magna*	Clofentezine	Acute	Apollo 50 SC	48-hr EC_{50} > 51.3 mg a.i./L ÷ 2 = > 25.65	0.0313	<0.001
		Chronic	Apollo 50 SC	21-day NOEC = 0.05 mg a.i./L = 0.05	0.0313	0.63
	2-chlorobenzonitrile	Acute	NR	48-hr static EC_{50} = 13.00 mg a.i./L ÷ 2 = 6.50	0.0313	0.005
Invertebrate: *Chironomus riparius*	Clofentezine	Chronic	Apollo 50 SC	28-day NOEC = 0.50 mg a.i./L = 0.50	0.0313	0.06
Cold fish: Rainbow trout: *Onchorynchus mykiss*	Clofentezine	Acute	Apollo 50 SC	96-hour LC_{50} > 10.00 mg a.i./L ÷ 10 = > 1.00	0.0313	< 0.03
	2-chlorobenzonitrile	Acute	NR	96-hour LC_{50} = 22.00 mg a.i./L ÷ 10 = > 2.20	0.0313	< 0.01
Warm fish:Bluegill sunfish: *Lepomis macrochirus*	Clofentezine	Acute	Apollo 50 SC	96-hour LC_{50} > 12.00 mg a.i./L ÷ 10 = > 1.20	0.0313	<0.03
Fathead minnow: *Pimephales promelas*	Clofentezine	Early Life Stage	Apollo 50 SC	33-day NOEC = 0.98	0.0313	0.03
Amphibians: 15 cm water depth Surrogate: Rainbow trout: *Onchorynchus mykiss*	Clofentezine	Acute	Apollo 50 SC	96-hour LC_{50} > 10.00 mg a.i./L ÷ 10 = >1.00	0.167	< 0.17
Amphibians: 15 cm water depth Surrogate: Fathead minnow: *Pimephales promelas*	Clofentezine	Early Life Stage	Apollo 50 SC	NOEC = 0.98	0.167	0.17
Green algae: *Pseudokirchneriella subcapitata*	Clofentezine	Acute	Apollo 50 SC	72-hr EbC_{50} = 20.00 mg a.i./L÷ 2 = > 10.00	0.0313	<0.003
	2-chlorobenzonitrile	Acute	NR	72-hr static EbC_{50} = 16.00 mg a.i./L ÷ 2 = 8.00	0.03	0.004
Green algae: *Selenastrum capricornutum*	Clofentezine	Acute	Apollo 50 SC	96-hour EC_{50} >40.00 mg a.i./L÷ 2 = >20.00	0.03	<0.002
Marine species						
Saltwater mysid *Mysidiopsis bahia*	Clofentezine	Chronic	TGAI	28-Day NOEC = 0.0033 mg a.i./L = 0.0033	0.03	9.1

[1]Risk quotients shown in bold exceed the level of concern (RQ > 1).

Refined Risk Assessment on Non-Target Species

Table 13 First Risk Assessment Refinement (Using Foliar Deposition Factor) and Corresponding Risk Quotients for Predators And Parasitic Arthropods Exposed To Clofentezine, Based On EFSA (2009)

Organism	Crop	Exposure	Endpoint[1]	EEC	RQ[2]
Aphidius rhopalosiphi (parasitic wasp) foliar dwelling	Strawberry and raspberry	Groundboom in-field	LR_{50} = 36.2 g ai/ha	250	6.9
		Groundboom in-field foliar dep. factor	LR_{50} = 36.2 g ai/ha	200	5.5
		Groundboom off-field (6% drift)	LR_{50} = 36.2 g ai/ha	15	0.4
	Apple, pear, peach, nectarine	Early Airblast in-field	LR_{50} = 36.2 g ai/ha	150	4.1
		Early Airblast in-field foliar dep factor	LR_{50} = 36.2 g ai/ha	120	3.3
		Early Airblast off-field (74% drift)	LR_{50} = 36.2 g ai/ha	111	3.1
		Early Airblast off-field (74% drift × 0.1)	LR_{50} = 36.2 g ai/ha	11.1	0.3
		Late Airblast in-field	LR_{50} = 36.2 g ai/ha	150	4.1
		Late Airblast in-field foliar dep factor	LR_{50} = 36.2 g ai/ha	120	3.3
		Late Airblast off-field (59% drift)	LR_{50} = 36.2 g ai/ha	88.5	2.4
		Late Airblast off-field (59% drift × 0.1)	LR_{50} = 36.2 g ai/ha	8.85	0.2
Typhlodromus pyri (Predatory phytoseiid mite)	Strawberry and raspberry	Groundboom in-field	Lab LR_{50} > 300 g a.i./ha Field LR_{50} > 3000 g a.i./ha	250	< 0.83 < 0.083
Coccinella semptempunctata	Strawberry and raspberry	Groundboom in-field	Field LR_{50} > 200 g a.i./ha	250	< 1.25
	Strawberry and raspberry	Groundboom in-field foliar dep. factor	Field LR_{50} > 200 g a.i./ha	200	< 1.00
	Apple, pear, peach, nectarine	Early Airblast In-field	LR_{50} > 300 g a.i./ha ER_{50} > 300 g a.i./ha	150	< 0.5
Chrysoperla carnea	Strawberry and raspberry	Groundboom in-field	LR_{50} > 300 g a.i./ha ER_{50} > 300 g a.i./ha	250	< 0.83
	Apple, pear, peach, nectarine	Early Airblast In field	LR_{50} > 300 g a.i./ha ER_{50} > 300 g a.i./ha	150	< 0.5

[1] Arthropod data are based on tier 1 (glass plate) tests.

[2] Risk Quotient (RQ) = EEC / endpoint; shaded cells indicate that the screening level RQ exceeds the LOC of 2.0 for *A. rhopalosiphi and T. pyri* and 1.0 for others.

Table 14 Second Risk Assessment Refinement And Corresponding Risk Quotients For The Parasitic Wasp *Aphidius Rhopalosiphi*

Organism	Crop	Exposure	Endpoint[1]	EEC	RQ[2]
Aphidius rhopalosiphi (parasitic wasp) foliar dwelling	Strawberry and raspberry	Groundboom in-field	LR_{50} >300 g ai/ha ER_{50} >300 g ai/ha	250	0.83 0.83
	Apple, pear, peach, nectarine	Early Airblast in-field	LR_{50} >300 g ai/ha ER_{50} >300 g ai/ha	150	0.5 0.5

[1] Arthropod data are based on tier 1 (glass plate) tests.
[2] Risk Quotient (RQ) = EEC / endpoint

Table 15 Further Characterization of the Avian Reproductive Risk (NOEL = 2.68 mg a.i./kg bw/day) Following Exposure to Clofentezine in Strawberry and Raspberry Productions (Application with Ground Boom at 250 g a.i./ha)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Reproduction	2.68	Insectivore (small insects)	12.60	4.70	0.76	0.28	7.03	2.62	0.42	0.16
	2.68	Granivore (grain and seeds)	3.15	1.18	0.19	0.07	1.50	0.56	0.09	0.03
	2.68	Frugivore (fruit)	6.30	2.35	0.38	0.14	3.00	1.12	0.18	0.07
Medium Sized Bird (0.1 kg)										
Reproduction	2.68	Insectivore (small insects)	9.83	3.67	0.59	0.22	5.48	2.05	0.33	0.12
	2.68	Insectivore (large insects)	2.46	0.92	0.15	0.06	1.17	0.44	0.07	0.03
	2.68	Granivore (grain and seeds)	2.46	0.92	0.15	0.06	1.17	0.44	0.07	0.03
	2.68	Frugivore (fruit)	4.92	1.83	0.29	0.11	2.34	0.87	0.14	0.05
Large Sized Bird (1 kg)										
Reproduction	2.68	Insectivore (small insects)	2.87	1.07	0.17	0.06	1.60	0.60	0.10	0.04
	2.68	Insectivore (large insects)	0.72	0.27	0.04	0.02	0.34	0.13	0.02	0.01
	2.68	Granivore (grain and seeds)	0.72	0.27	0.04	0.02	0.34	0.13	0.02	0.01
	2.68	Frugivore (fruit)	1.44	0.54	0.09	0.03	0.68	0.26	0.04	0.02
	2.68	Herbivore (short grass)	10.26	3.83	0.62	0.23	3.64	1.36	0.22	0.08
	2.68	Herbivore (long grass)	6.26	2.34	0.38	0.14	2.05	0.76	0.12	0.05
	2.68	Herbivore (forage crops)	9.49	3.54	0.57	0.21	3.14	1.17	0.19	0.07

Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 16 Further Characterization of the Avian Reproductive Risk (LOEL = 7.82 mg a.i./kg bw/day) Following Exposure to Clofentezine in Strawberry and Raspberry Productions (Application with Ground Boom at 250 g a.i./ha)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Reproduction	7.82	Insectivore (small insects)	12.60	1.61	0.76	0.10	7.03	0.90	0.42	0.05
	7.82	Granivore (grain and seeds)	3.15	0.40	0.19	0.02	1.50	0.19	0.09	0.01
	7.82	Frugivore (fruit)	6.30	0.81	0.38	0.05	3.00	0.38	0.18	0.02
Medium Sized Bird (0.1 kg)										
Reproduction	7.82	Insectivore (small insects)	9.83	1.26	0.59	0.08	5.48	0.70	0.33	0.04
	7.82	Insectivore (large insects)	2.46	0.31	0.15	0.02	1.17	0.15	0.07	0.01
	7.82	Granivore (grain and seeds)	2.46	0.31	0.15	0.02	1.17	0.15	0.07	0.01
	7.82	Frugivore (fruit)	4.92	0.63	0.29	0.04	2.34	0.30	0.14	0.02
Large Sized Bird (1 kg)										
Reproduction	7.82	Insectivore (small insects)	2.87	0.37	0.17	0.02	1.60	0.20	0.10	0.01
	7.82	Insectivore (large insects)	0.72	0.09	0.04	0.01	0.34	0.04	0.02	0.00
	7.82	Granivore (grain and seeds)	0.72	0.09	0.04	0.01	0.34	0.04	0.02	0.00
	7.82	Frugivore (fruit)	1.44	0.18	0.09	0.01	0.68	0.09	0.04	0.01
	7.82	Herbivore (short grass)	10.26	1.31	0.62	0.08	3.64	0.47	0.22	0.03
	7.82	Herbivore (long grass)	6.26	0.80	0.38	0.05	2.05	0.26	0.12	0.02
	7.82	Herbivore (forage crops)	9.49	1.21	0.57	0.07	3.14	0.40	0.19	0.02

Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 17 Further Characterization of the Avian Reproductive Risk (NOEL = 2.68 mg a.i./kg bw/day) Following Exposure to Clofentezine in in Apple, Pear, Peach and Nectarine Productions (Airblast Application at 150 g a.i./ha)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Reproduction	2.68	Insectivore (small insects)	7.56	2.82	5.59	2.09	4.22	1.57	3.12	1.16
	2.68	Granivore (grain and seeds)	1.89	0.71	1.40	0.52	0.90	0.34	0.67	0.25
	2.68	Frugivore (fruit)	3.78	1.41	2.80	1.04	1.80	0.67	1.33	0.50
Medium Sized Bird (0.1 kg)										
Reproduction	2.68	Insectivore (small insects)	5.90	2.20	4.36	1.63	3.29	1.23	2.43	0.91
	2.68	Insectivore (large insects)	1.47	0.55	1.09	0.41	0.70	0.26	0.52	0.19
	2.68	Granivore (grain and seeds)	1.47	0.55	1.09	0.41	0.70	0.26	0.52	0.19
	2.68	Frugivore (fruit)	2.95	1.10	2.18	0.81	1.41	0.52	1.04	0.39
Large Sized Bird (1 kg)										
Reproduction	2.68	Insectivore (small insects)	1.72	0.64	1.27	0.48	0.96	0.36	0.71	0.27
	2.68	Insectivore (large insects)	0.43	0.16	0.32	0.12	0.21	0.08	0.15	0.06
	2.68	Granivore (grain and seeds)	0.43	0.16	0.32	0.12	0.21	0.08	0.15	0.06
	2.68	Frugivore (fruit)	0.86	0.32	0.64	0.24	0.41	0.15	0.30	0.11
	2.68	Herbivore (short grass)	6.15	2.30	4.55	1.70	2.19	0.82	1.62	0.60
	2.68	Herbivore (long grass)	3.76	1.40	2.78	1.04	1.23	0.46	0.91	0.34
	2.68	Herbivore (forage crops)	5.69	2.12	4.21	1.57	1.88	0.70	1.39	0.52

Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 18 Further Characterization of the Avian Reproductive Risk (LOEL = 7.82 mg a.i./kg bw/day) Following Exposure to Clofentezine in Apple, Pear, Peach and Nectarine Productions (Airblast Application at 150 g a.i./ha)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)										
Reproduction	7.82	Insectivore (small insects)	7.56	0.97	5.59	0.72	4.22	0.54	3.12	0.40
	7.82	Granivore (grain and seeds)	1.89	0.24	1.40	0.18	0.90	0.12	0.67	0.09
	7.82	Frugivore (fruit)	3.78	0.48	2.80	0.36	1.80	0.23	1.33	0.17
Medium Sized Bird (0.1 kg)										
Reproduction	7.82	Insectivore (small insects)	5.90	0.75	4.36	0.56	3.29	0.42	2.43	0.31
	7.82	Insectivore (large insects)	1.47	0.19	1.09	0.14	0.70	0.09	0.52	0.07
	7.82	Granivore (grain and seeds)	1.47	0.19	1.09	0.14	0.70	0.09	0.52	0.07
	7.82	Frugivore (fruit)	2.95	0.38	2.18	0.28	1.41	0.18	1.04	0.13
Large Sized Bird (1 kg)										
Reproduction	7.82	Insectivore (small insects)	1.72	0.22	1.27	0.16	0.96	0.12	0.71	0.09
	7.82	Insectivore (large insects)	0.43	0.06	0.32	0.04	0.21	0.03	0.15	0.02
	7.82	Granivore (grain and seeds)	0.43	0.06	0.32	0.04	0.21	0.03	0.15	0.02
	7.82	Frugivore (fruit)	0.86	0.11	0.64	0.08	0.41	0.05	0.30	0.04
	7.82	Herbivore (short grass)	6.15	0.79	4.55	0.58	2.19	0.28	1.62	0.21
	7.82	Herbivore (long grass)	3.76	0.48	2.78	0.36	1.23	0.16	0.91	0.12
	7.82	Herbivore (forage crops)	5.69	0.73	4.21	0.54	1.88	0.24	1.39	0.18

Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 19 Further Characterization of the Mammalian Reproductive Risk (NOEL = 3.9 mg a.i./kg bw/day) Following Exposure to Clofentezine in Strawberry and Raspberry Productions (Application with Ground Boom at 250 g a.i./ha)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./ kg bw)	RQ	EDE (mg a.i./ kg bw)	RQ	EDE (mg a.i./ kg bw)	RQ
Small Mammal (0.015 kg)										
Reproduction	3.90	Insectivore (small insects)	7.25	1.8578	0.43	0.1115	4.04	1.0361	0.24	0.0622
	3.90	Granivore (grain and seeds)	1.81	0.4644	0.11	0.0279	0.86	0.2215	0.05	0.0133
	3.90	Frugivore (fruit)	3.62	0.9289	0.22	0.0557	1.73	0.4430	0.10	0.0266
Medium Sized Mammal (0.035 kg)										
Reproduction	3.90	Insectivore (small insects)	6.35	1.6286	0.38	0.0977	3.54	0.9082	0.21	0.0545
	3.90	Insectivore (large insects)	1.59	0.4071	0.10	0.0244	0.76	0.1942	0.05	0.0117
	3.90	Granivore (grain and seeds)	1.59	0.4071	0.10	0.0244	0.76	0.1942	0.05	0.0117
	3.90	Frugivore (fruit)	3.18	0.8143	0.19	0.0489	1.51	0.3884	0.09	0.0233
	3.90	Herbivore (short grass)	22.70	5.8205	1.36	0.3492	8.06	2.0671	0.48	0.1240
	3.90	Herbivore (long grass)	13.86	3.5538	0.83	0.2132	4.53	1.1604	0.27	0.0696
	3.90	Herbivore (forage crops)	21.00	5.3852	1.26	0.3231	6.94	1.7802	0.42	0.1068
Large Sized Mammal (1 kg)										
Reproduction	3.90	Insectivore (small insects)	3.39	0.8702	0.20	0.0522	1.89	0.4853	0.11	0.0291
	3.90	Insectivore (large insects)	0.85	0.2176	0.05	0.0131	0.40	0.1038	0.02	0.0062
	3.90	Granivore (grain and seeds)	0.85	0.2176	0.05	0.0131	0.40	0.1038	0.02	0.0062
	3.90	Frugivore (fruit)	1.70	0.4351	0.10	0.0261	0.81	0.2075	0.05	0.0125
	3.90	Herbivore (short grass)	12.13	3.1101	0.73	0.1866	4.31	1.1045	0.26	0.0663
	3.90	Herbivore (long grass)	7.41	1.8989	0.44	0.1139	2.42	0.6201	0.15	0.0372
	3.90	Herbivore (forage crops)	11.22	2.8775	0.67	0.1726	3.71	0.9512	0.22	0.0571

Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 20 Further Characterization of the Mammalian Reproductive Risk (LOEL = 36.1 mg a.i./kg bw/day) Following Exposure to Clofentezine in Strawberry and Raspberry Productions (Application with Ground Boom at 250 g a.i./ha)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)										
Reproduction	36.10	Insectivore (small insects)	7.25	0.20	0.43	0.01	4.04	0.11	0.24	0.01
	36.10	Granivore (grain and seeds)	1.81	0.05	0.11	0.00	0.86	0.02	0.05	0.00
	36.10	Frugivore (fruit)	3.62	0.10	0.22	0.01	1.73	0.05	0.10	0.00
Medium Sized Mammal (0.035 kg)										
Reproduction	36.10	Insectivore (small insects)	6.35	0.18	0.38	0.01	3.54	0.10	0.21	0.01
	36.10	Insectivore (large insects)	1.59	0.04	0.10	0.00	0.76	0.02	0.05	0.00
	36.10	Granivore (grain and seeds)	1.59	0.04	0.10	0.00	0.76	0.02	0.05	0.00
	36.10	Frugivore (fruit)	3.18	0.09	0.19	0.01	1.51	0.04	0.09	0.00
	36.10	Herbivore (short grass)	22.70	0.63	1.36	0.04	8.06	0.22	0.48	0.01
	36.10	Herbivore (long grass)	13.86	0.38	0.83	0.02	4.53	0.13	0.27	0.01
	36.10	Herbivore (forage crops)	21.00	0.58	1.26	0.03	6.94	0.19	0.42	0.01
Large Sized Mammal (1 kg)										
Reproduction	36.10	Insectivore (small insects)	3.39	0.09	0.20	0.01	1.89	0.05	0.11	0.00
	36.10	Insectivore (large insects)	0.85	0.02	0.05	0.00	0.40	0.01	0.02	0.00
	36.10	Granivore (grain and seeds)	0.85	0.02	0.05	0.00	0.40	0.01	0.02	0.00
	36.10	Frugivore (fruit)	1.70	0.05	0.10	0.00	0.81	0.02	0.05	0.00
	36.10	Herbivore (short grass)	12.13	0.34	0.73	0.02	4.31	0.12	0.26	0.01
	36.10	Herbivore (long grass)	7.41	0.21	0.44	0.01	2.42	0.07	0.15	0.00
	36.10	Herbivore (forage crops)	11.22	0.31	0.67	0.02	3.71	0.10	0.22	0.01

Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 21 Further Characterization of the Mammalian Reproductive Risk (NOEL = 3.9 mg a.i./kg bw/day) Following Exposure to Clofentezine in Apple, Pear, Peach and Nectarine Orchards (Airblast Application at 150 g a.i./ha)

			Maximum nomogram residues				Mean nomogram residues			
			On-field		Off Field		On-field		Off Field	
	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Mammal (0.015 kg)										
Reproduction	3.90	Insectivore (small insects)	4.35	1.1147	3.22	0.8249	2.42	0.6216	1.79	0.4600
	3.90	Granivore (grain and seeds)	1.09	0.2787	0.80	0.2062	0.52	0.1329	0.38	0.0983
	3.90	Frugivore (fruit)	2.17	0.5573	1.61	0.4124	1.04	0.2658	0.77	0.1967
Medium Sized Mammal (0.035 kg)										
Reproduction	3.90	Insectivore (small insects)	3.81	0.9771	2.82	0.7231	2.13	0.5449	1.57	0.4033
	3.90	Insectivore (large insects)	0.95	0.2443	0.71	0.1808	0.45	0.1165	0.34	0.0862
	3.90	Granivore (grain and seeds)	0.95	0.2443	0.71	0.1808	0.45	0.1165	0.34	0.0862
	3.90	Frugivore (fruit)	1.91	0.4886	1.41	0.3615	0.91	0.2330	0.67	0.1724
	3.90	Herbivore (short grass)	13.62	3.4923	10.08	2.5843	4.84	1.2402	3.58	0.9178
	3.90	Herbivore (long grass)	8.32	2.1323	6.15	1.5779	2.72	0.6963	2.01	0.5152
	3.90	Herbivore (forage crops)	12.60	3.2311	9.32	2.3910	4.17	1.0681	3.08	0.7904
Large Sized Mammal (1 kg)										
Reproduction	3.90	Insectivore (small insects)	2.04	0.5221	1.51	0.3864	1.14	0.2912	0.84	0.2155
	3.90	Insectivore (large insects)	0.51	0.1305	0.38	0.0966	0.24	0.0623	0.18	0.0461
	3.90	Granivore (grain and seeds)	0.51	0.1305	0.38	0.0966	0.24	0.0623	0.18	0.0461
	3.90	Frugivore (fruit)	1.02	0.2611	0.75	0.1932	0.49	0.1245	0.36	0.0921
	3.90	Herbivore (short grass)	7.28	1.8660	5.39	1.3809	2.58	0.6627	1.91	0.4904
	3.90	Herbivore (long grass)	4.44	1.1394	3.29	0.8431	1.45	0.3720	1.07	0.2753
	3.90	Herbivore (forage crops)	6.73	1.7265	4.98	1.2776	2.23	0.5707	1.65	0.4223

Shaded cells indicate that the level of concern is exceeded (RQ > 1)

Table 22 Refined risk assessment and risk quotients for the Saltwater Mysid Obtained From Spray Drift of Clofentezine from Groundboom and Airblast Scenario

Parameters	Groundboom Strawberry (250 g a.i./ha)
Saltwater mysid NOEC (mg a.i./L)	0.0033
EEC in 80 cm deep water body (0.03 mg ai/L × 0.06)	0.0018
RQ	0.545
Parameters	**Airblast Apple (150 g a.i./ha)**
Saltwater mysid NOEC (mg a.i./L)	0.0033
EEC in 80 cm deep water body (0.0188 mg ai/L × 0.74)	0.014
RQ	4.2

Table 23 Risk Quotient for the Saltwater Mysid Determined for Clofentezine in Run-off

Province	Application Rate (g a.i./ha)	Target crop	NOEC (mg ai/L)	EEC: 90th percentile of 21 day average (mg/L)	RQ (EEC/NOEC)
Atlantic	150	Apple	0.0033	0.00018	0.05

Table 24 Toxic Substances Management Policy Considerations – Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Clofentezine Endpoints	Hydrazide-hydrazone Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	15.3 - 142 days (aerobic soils) (no data for anaerobic soils)	43 days (aerobic soils) (no data for anaerobic soils)
	Water	Half-life ≥ 182 days	1-5.4 days (water phase in aerobic system)	6.3 days (water phase in aerobic system)
	Sediment	Half-life ≥ 365 days	26-58.1 days (sediment phase in aerobic system)	10.3-14.1 days (sediment phase in aerobic system)
	Air	Half-life ≥ 2 days or evidence of long range transport	Clofentezine has a low vapour pressure of 6.0×10^{-7} Pa at 20ºC (4.5×10^{-9} mm Hg) and according to the classification of Kennedy and Talbert (1977) is expected to be relatively non-volatile under field conditions. However, the Henry's law constant of 0.168 Pa m^3/mole (equivalent to 1.66×10^{-6} atm m^3/mole and a calculated 1/H = 3.38×10^4) indicates that clofentezine is slightly volatile from water surface or moist soil. The EFSA (2009) reported that clofentezine volatilization from water, soil, plant surfaces is expected to be low.	
Bioaccumulation[4]	Log $K_{OW} \geq 5$		Log K_{ow} = 4.1	Log K_{ow}[5] = 3.34
	BCF ≥ 5000		BCF = 248-430	BCF[5] = 73.8
	BAF ≥ 5000		NA	No data
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (i.e., all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meets one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).
Log k_{ow} and BCF estimated using USEPA's EPISuite™

Appendix X Modelling Results

Aquatic Ecoscenario Assessment: Level 1 Modelling

For Level 1 aquatic ecoscenario assessment, estimated environmental concentrations (EECs) of clofentezine from runoff into a receiving water body were simulated using the PRZM/EXAMS models. The PRZM/EXAMS models simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. For the Level 1 assessment, the water body consists of a 1 ha wetland with an average depth of 0.8 m and a drainage area of 10 ha. A seasonal water body was also used to assess the risk to amphibians, as a risk was identified at the screening level. This water body is essentially a scaled down version of the permanent water body noted above, but having a water depth of 0.15 m.

Six standard regional scenarios were modelled to represent different regions of Canada. Several initial application dates between May and June were modelled. The EECs are for the portion of the pesticide that enters the water body via runoff only; deposition from spray drift is not included. The models were run for 50 years for all scenarios.

The EECs are calculated from the model output from each run as follows. For each year of the simulation, PRZM/EXAMS calculates peak (or daily maximum) and time-averaged concentrations. The time-averaged concentrations are calculated by averaging the daily concentrations over five time periods (96-hour, 21-day, 60-day, 90-day, and 1 year). The 90th percentiles over each averaging period are reported as the EECs for that period.

The largest EECs of all selected runs of a given use pattern/regional scenario are reported in Table 1 below. Note that the solubility was increased by 10 to 40 times for different runs in order to bypass the EXAMS model's restriction that concentrations not exceed the half of the solubility. In some cases, this resulted in predicted EECs greater than the chemical's solubility of 2 µg /L. In these instances, the limit of solubility is reported and should be considered for water exposure assessment. EECs are reported in the following Tables 1 and 2.

Table 1 Level 1 Aquatic Ecoscenario Modelling Eecs (µg a.i./L) For Clofentezine In A Water Body 0.8 m Deep, Excluding Spray Drift

Region	EEC (µga.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apple use, 1 × 0.3 kg a.i./ha						
British Columbia	0.46	0.17	0.036	0.013	0.009	0.002
Ontario	1.7	0.60	0.13	0.075	0.053	0.017
Quebec	1.4	0.51	0.13	0.056	0.044	0.014
Atlantic	2[1]	0.78	0.18	0.094	0.070	0.021
Raspberry and strawberry use, 1 × 0.25 kg a.i./ha						
British Columbia	0.38	0.14	0.045	0.019	0.014	0.005
Quebec	1.6	0.63	0.17	0.080	0.065	0.029

[1] predicted EEC exceeded the limit of solubility of 2.52 µg/L

Table 2 Level 1 Aquatic Ecoscenario Modelling Eecs (µg a.i./L) For Clofentezine In A Water Body 0.15 m Deep, Excluding Spray Drift

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apple use, 1 × 0.3 kg a.i./ha						
British Columbia	2[1]	0.57	0.13	0.053	0.036	0.009
Ontario	2[1]	2[1]	0.49	0.28	0.21	0.071
Quebec	2[1]	1.8	0.48	0.22	0.18	0.057
Atlantic	2[1]	2[1]	0.67	0.37	0.27	0.088
Raspberry and strawberry use, 1 × 0.25 kg a.i./ha						
British Columbia	2.0	0.50	0.16	0.075	0.056	0.019
Quebec	2[1]	2[1]	0.61	0.31	0.26	0.12

[1] predicted EEC exceeded the limit of solubility of 2.52 µg/L

Appendix XI Monitoring Data

Table 1 Level 1 estimated environmental concentrations of clofentezine in potential drinking water sources

Compound	Groundwater EEC (µg a.i./L)		Surface Water EEC (µg a.i./L)			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
Clofentezine	0	0	2[5]	0.095	2[5]	0.066

Notes:
1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peak concentrations
4 90th percentile of yearly average concentrations
5 predicted EEC exceeded the limit of solubility of 2.52 µg/L

Water Monitoring Data

In addition to water modelling, a search for clofentezine water monitoring data in Canada was undertaken. Results of the search revealed that routine analysis for this chemical is not conducted in Canada. No monitoring data were available for this compound.

The United States' databases were also searched for data on clofentezine in water. Data on residues present in water samples taken in the United States are important to consider in the Canadian water assessment given the extensive monitoring programs that exist in the United States. Runoff events, local use patterns, site specific hydrogeology as well as testing and reporting methods are probably more important influences on residue data rather than Northern versus Southern climate. As for the climate, if temperatures are cooler, residues may break down more slowly, on the other hand if temperatures are warmer, growing seasons may be longer and applications may be more numerous and frequent.

Clofentezine was not part of the analyte list of the United States Geological Survey National Water Quality Assessment program (NAWQA), the United States Environmental Protection Agency's STORET data warehouse, or the United States Department of Agriculture Pesticide Data Program for either surface water or groundwater.

Discussions and Conclusions

The paucity of monitoring data available to the PMRA did not allow for an estimation of the residues of clofentezine in both surface and drinking water using monitoring data. The concentrations of clofentezine in surface and drinking water that should be considered in the risk assessment are the EECs determined by water modelling.

Given the rapid dissipation of clofentezine via hydrolysis, aqueous phototransformation as well as biotransformation in water-sediment systems, it would not be expected to persist in water. It is unlikely that humans or aquatic organisms would be chronically exposed to clofentezine residues in surface water or groundwater. This is supported by the low EECs predicted by the water models for longer time periods.

Appendix XII Label Amendments for Products Containing Clofentezine

The following label amendments are required for technical and end-use products as applicable.

A) Label Changes Relating to Human Health

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements below.

The labels of end-use products in Canada must be amended to include the following statements to further protect workers.

PRECAUTION STATEMENTS:

The following label statements are proposed to be added to all labels:

> *Apply only when the potential for drift to areas of human habitation or areas of human activity (e.g,. houses, cottages, schools and recreational areas) is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.*
>
> *Not for use in greenhouses.*

RESTRICTED-ENTRY INTERVAL:

The restricted-entry intervals (REI) listed in Table 1 below must be added to the appropriate labels. Where deemed necessary, REIs are sub-divided according to re-entry activities.

Table 1 Required Restricted Entry Intervals

Crop	Activity	REI
Apples, Pears, Peaches, Nectarines	Hand Thinning	2 days
	All Other Activities	12 hrs
Raspberries	Hand Pruning, Training, Tying	10 days
	All Other Activities	12 hrs
Strawberries	All Activities	12 hrs
Outdoor Deciduous Nursery Stock	All Activities	12 hrs

Add to DIRECTIONS FOR USE:

To support the current MRL of 0.5 ppm in/on apples, the following statement must be added to the label directions for use on apples:

> *Do not harvest within 21 days after application.*

To ensure no clofentezine residue uptake by secondary (rotational) crops for which clofentezine

is not registered, the following statement must be added to the label directions for use on strawberries:

> *A minimum rotational crop plant back interval of 12 months must be observed for all crops other than those registered for use with clofentezine.*

B) Label Changes Relating to Environment

LABEL AMENDMENTS FOR CLOFENTEZINE TECHNICAL INSECTICIDE

Add the following statements before the section entitled **STORAGE:**

> ***ENVIRONMENTAL HAZARDS:***
>
> ***TOXIC** to birds*
> ***TOXIC** to small mammals*
> ***TOXIC** to aquatic organisms*

Remove the following statement under the "**DISPOSAL AND DECONTAMINATION**" section:

> *Canadian formulators of this technical should dispose of unwanted active and containers in accordance with municipal or provincial regulations. For information on disposal of unused, unwanted product, contact the manufacturer or the provincial regulatory agency. Contact the manufacturer and the provincial regulatory agency in the case of a spill, and for clean-up of spills.*

And **Replace** with the following statement:

> *Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean up of spills, contact the manufacturer or the provincial regulatory agency.*

LABEL AMENDMENTS FOR COMMERCIAL CLASS PRODUCTS CONTAINING CLOFENTEZINE

Add to ENVIRONMENTAL HAZARDS:

> ***TOXIC** to birds*
> ***TOXIC** to small mammals*
> ***TOXIC** to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE.*
>
> *To reduce runoff from treated areas into aquatic habitats, do not apply to areas with a moderate to steep slope, compacted soil or clay.*
>
> *Do not apply when heavy rain is forecast.*

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

Add to GENERAL DIRECTIONS FOR USE:

The following statements are required for all agricultural and commercial pesticide products:

***DO NOT** use to control aquatic pests.*

***DO NOT** contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.*

***DO NOT** apply by air.*

For **field applications using conventional boom sprayers** (agricultural or commercial products), the following statements are required:

*Field sprayer application: **DO NOT** apply during periods of dead calm. **DO NOT** apply this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.*

For **airblast applications** (agricultural or commercial products), the following statements are required:

*Airblast application: **DO NOT** apply during periods of dead calm. **DO NOT** apply this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.*

The following buffer zone statements and Table 1 are required to be added:

Buffer Zones:
*Use of the following spray methods or equipment **DOES NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.*

The buffer zones specified in Table 1 below are required between the point of direct application and the closest downwind edge of sensitive estuarine/marine habitats.

Table 1 Buffer Zones for the Protection of Aquatic Life from Spray Drift of Clofentezine

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:	
			Estuarine/Marine Habitats of Depths:	
			Less than 1 m	Greater than 1 m
Field sprayer	Strawberry, raspberry		1	1
Airblast	Apple, pear, peach, nectarine	Early growth stage	5	2
		Late growth stage	3	1

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

C) Label Changes Relating to Value

LABEL AMENDMENTS FOR COMMERCIAL CLASS PRODUCTS CONTAINING CLOFENTEZINE

Under **DIRECTIONS FOR USE, Use on Apples and Pears**, the following statements below must be removed**:**

Target Species:
European red mite (*Panonychus ulmi*), Two-spotted spider mite (*Tetranychus urticae)*, McDaniel spider mite (*Tetranychus mcdanieli*).

Apply with ground equipment using either dilute or concentrate sprays. Apply 300–600 mL APOLLO® SC OVICIDAL MITICIDE per hectare. When high dilution rate is used (3800 litres or more of water) use no less than 75 mL of APOLLO® SC OVICIDAL MITICIDE per 950 litres of spray. Use sufficient volume of water to obtain complete coverage but not less than 475 litres per hectare. Do not use less than 300 mL of APOLLO® SC OVICIDAL MITICIDE per hectare in concentrate sprays. APOLLO® SC OVICIDAL MITICIDE works best applied to eggs or young motile stages. It is not effective against adults.

Apples
APOLLO® SC OVICIDAL MITICIDE may be applied any time from delayed dormant through first cover. Best results in early season will be obtained if treatments are made at petal fall before mites hatch. Do not apply after first cover (provided first cover is not more than 14 days after petal fall).

Pears
APOLLO® SC OVICIDAL MITICIDE may be applied early season (after delayed dormant) through to summer. Apply at first sign of mite activity when mite populations are predominantly in the egg stage, with few early motiles (less than 3 per leaf). Do not apply within 21 days of harvest.

NOTE:
Factors which may warrant consideration of rates higher than 300 mL APOLLO® SC OVICIDAL MITICIDE per hectare include:
1. Earliest seasonal timings for blocks with high overwintering European red mite egg populations.
2. When mite predator populations are low.
3. To ensure adequate coverage of full size standard trees and/or trees with heavy leaf densities.

and replaced with the following statements:

Target Species:
European red mite (*Panonychus ulmi*), Two-spotted spider mite (*Tetranychus urticae*), McDaniel spider mite (*Tetranychus mcdanieli*).

Apply with ground equipment using air assist sprayer. Apply 300 mL APOLLO® SC OVICIDAL MITICIDE per hectare. Use sufficient volume of water to obtain complete coverage but not less than 475 litres per hectare. APOLLO® SC OVICIDAL MITICIDE works best when applied to eggs or young motile stages. It is not effective against adults.

Apples
APOLLO® SC OVICIDAL MITICIDE may be applied any time from delayed dormant through first cover. Best results in early season will be obtained if treatments are made at petal fall before mites hatch. Do not apply after first cover (provided first cover is not more than 14 days after petal fall). Do not apply within 21 days of harvest.

Pears
APOLLO® SC OVICIDAL MITICIDE may be applied early season (after delayed dormancy) through to summer. Apply at first sign of mite activity when mite populations are predominantly in the egg stage, with few early motiles (less than 3 per leaf). Do not apply within 21 days of harvest.

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1227685 Residues of … in Plums Treated with 50SC and 50W Formulation in Yugoslavia, 1983 (Resid/83/109), DACO: 7.4.2
1227687 Residues of … in Aubergines, Cucumbers and Peppers Following Treatment with the 50W Formulation in Cyprus, 1983 (Resid/84/5), DACO: 7.4.2
1227688 Residues of Clofentezine in Apples Treated with Apollo 50WP in Switzerland, 1983, DACO: 7.4.2
1227689 Decline of Clofentezine Residues in Apples and Pears Treated with the 50SC Formulation in South Africa (Resid/84/99), DACO: 7.4.2
1227690 Residues of Clofentezine in Mature Apples from Trials with 50SC Formulation in the U.K., 1983 (Resid/84/58), DACO: 7.4.2
1227692 Residues of Clofentezine in Oranges Following Treatment with the 50W Formulation in Spain, 1983/84 (Resid/84/51), DACO: 7.4.2
1227694 Residues of Clofentezine in Apples Treated with the 50W and 50SC Formulations in Belgium, 1983 (Resid/84/59), DACO: 7.4.2
1227695 Residues of Clofentezine in Peaches Following Treatment with the 50W and 50SC Formulations in Chile, 1983/84 (Resid/84/65), DACO: 7.4.2
1227696 Residues of Clofentezine in Blackcurrants Treated with the 50SC Formulation in the U.K., 1984 (Resid/85/1), DACO: 7.4.2
1227697 Decline of Clofentezine Residues in Apples Following Treatment with the 50SC Formulation in West Germany, 1984 (Resid/85/9), DACO: 7.4.2
1227698 Residues of Clofentezine in Cherries Treated with the 50SC Formulation in Holland, 1984 (Resid/85/11), DACO: 7.4.2
1227699 Residues of Clofentezine in Apples Treated with the 50SC Formulation in France, 1984 (Resid/85/12), DACO: 7.4.2
1227700 Residues of Clofentezine in Apples From Trials with a 50SC Formulation in Italy, 1983 (Resid/85/18), DACO: 7.4.2
1227703 Decline of … Residues in Grapes Following Treatment with the 50W Formulation in West Germany, 1982 (Resid/83/80), DACO: 7.4.2
1227705 Residues of Clofentezine in Grapes Treated with the 50SC Formulation (Resid/85/45), DACO: 7.4.2
1227706 Residues of Clofentezine in Small-Berry Fruits Treated with the 50SC Formulation in France, 1985 (Resid/86/42), DACO: 7.4.2
1227707 Residues of Clofentezine in Small-Berry Fruits Treated with the 50SC Formulation in the Netherlands, 1985 (Resid/86/43) (COON'T ON 776), DACO: 7.4.2
1227774 Residue Decline Study on Apples Following One and Two Applications of NC 21314 (50W) in the UK, 1980 (Resid/81/32), DACO: 7.4.2
1227775 Residues in Apples Following the Application of NC 21314 (50W) in the U.S.A (Resid/81/37), DACO: 7.4.2
1227776 Residues in Apples Following the Application of NC 21314 (50) in Europe, 1980 (Resid/81/42), DACO: 7.4.2
1227777 Residues Found at Harvest in Apples Treated with NC 21314 (50W) in the U.K., 1979 (Resid/81/56), DACO: 7.4.2
1227778 Decline of Residues in Apples Following a Late Application of NC 21314 in Australia, 1981 (Resid/81/73), DACO: 7.4.2
1227780 Residues in Apples Following a Application of NC 21314 (50W) in South Africa, 1980/81 (Resid/81/77), DACO: 7.4.2
1227781 Residues in Mature Apples Following the Application of NC 21314 (50W, CR 15456) in Holland, 1981 (Resid/82/5), DACO: 7.4.2

1227782 Decline of NC 21314 Residues in Apples after Early, Mid-Season and Late Season Applications (80W) in Virginia, U.S.A, 1981 (Resid/82/21), DACO 7.4.2

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1227786 Residues of … in Mature Apples from Regional Trials with 80W Formulation in the U.S.A., 1981 (Resid/82/24), DACO: 7.4.2

1227787 Residues of … in Apples Treated with 50W Formulation in France, 1981 (Resid/82/69), DACO: 7.4.2

1227788 Decline of … Residues in Apples after One and Two Applications of the 50W Formulation in the UK, 1981 (Resid/82/75), DACO: 7.4.2

1227792 Residues in Mature Apples Following Treatment with … (50W) in South Africa, 1981/82 (Resid/83/43), DACO: 7.4.2

1227793 Residues of … in Mature Apples and Pears Following Mid- and Late-Season Applications of the 80W Formulation in Australia, 1981/82 (Resid/82/105), DACO: 7.4.2

1227794 Decline of Residues Following Early and Mid-Season Applications of … (80W) in Australia, 1981/82 (Resid/82/106), DACO: 7.4.2

1227795 Residues of … in Peaches Treated with the 50W Formulation in France, 1982 (Resid/82/112), DACO: 7.4.2

1227797 Residues of … in Apples Treated with 50W Formulation in Holland, 1982 (Resid/83/18), DACO: 7.4.2

1227798 Residues of … in Apples Treated in Early Season with the 50W Formulation in West Germany (Resid/83/26), DACO: 7.4.2

1227800 Taint Tests with Apples and Pears Treated with … (Resid/83/35), DACO: 7.4.2

1227801 Residues of … in Plums and Cherries Treated with the 50W Formulation in the U.K., 1982 (Resid/83/46), DACO: 7.4.2

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1228428 Decline of Clofentezine in Peaches Following Both Early and Mid-Season Application in Trials Conducted in the U.S.A. in 1986 (15022), DACO: 7.4.2

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1228465 Residues of Clofentezine in Cottonseed Treated with the 50SC Formulation in Brazil, 1985 (Resid/86/72), DACO: 7.4.2

1228476 Residues of Clofentezine in Peaches and Nectarines Resulting from Late Season Treatment of NC 21314 50SC (15005), DACO: 7.4.2

1228487 Residues of Clofentezine in Almondhulls and Nutmeats Following Application of Apollo 50SC at Early and Mid-Season (15006), DACO: 7.4.2

1228499 Residues Decline Study of Clofentezine on Peaches Following Late Season Application of Apollo 50SC (15007), DACO: 7.4.2

1228510 Residues of Clofentezine in Raspberries Treated with a 50SC Formulation in Tasmania, 1986 (Resid/86/117), DACO: 7.4.2

1227672 Residues of Clofentezine and Metabolites in the Tissues and Milk of Cattle Following a 28-day Feeding Study in the U.K., 1984 (Resid/85/122), DACO: 7.5

1224786 Summary, DACO: 7.1

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Environment Assessment

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1142413	W76-Clofentezine: Determination of the Acute Toxicity of Apollo 50SC To Daphnia Magna (Envir/87/41). DACO: 9.3.2
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1142450	(Clofentezine/Apollo) The Degradation of NC 21314 in Surface Water/Sediment Microcosms (W37; 46j; Metab/83/17). DACO: 8.2.3.5.4
1142474	Decline of Clofentezine Residues in Soil Following Orchard Treatment With 50SC Formulation in Washington, Usa,1985 (NC21314/W63;073/04/009;Resid/85/114). DACO: 8.3.2.3
1199865	The Kinetics of the Hydrolysis of NC 21314 Under Acid, Neutral & Basic Conditions. DACO: 8.2.3.2
1199866	Metabolism-Leaching of NC 21314 in Four Soil Types Using Soil Tlc. DACO: 8.2.4.4
1199868	The Degradation and Leaching of NC 21314 in a Loamy Sand Soil. DACO: 8.2.4.3
1199870	The Degradation of NC 21314 in a Clay Loam and Loamy Sand Soil at 15C. DACO: 8.2.3.4.2, 8.2.4.4
1199871	The Degradation of NC 21314 in Three Soil Types Under aerobic, Sterile and Anaerobic Conditions. DACO: 8.2.3.4.2, 8.2.3.4.4
1199872	The Laboratory Decline of NC 21314 in a Clay Soil Under Aerobic, Sterile & Anaerobic Conditions. DACO: 8.2.3.4.2, 8.2.3.4.4
1199875	Oral Tox. Mallard Duck. DACO: 9.6.2.2
1199876	Oral Tox...Bobwhite Quail. DACO: 9.6.2.1
1199877	SubAcute Dietary Tox-Bobwhite Quail. DACO: 9.6.2.4
1199878	SubAcute Dietary Tox-Mallard Duck. DACO: 9.6.2.5
1199879	Acute Toxicity-Rainbow Trout. DACO: 9.5.2.1
1199881	Acute Toxicity-Rainbow Trout. DACO: 9.5.2.1
1199882	Acute Toxicity-Bluegill Sunfish. DACO: 9.5.2.2
1205368	Apollo Technical- Summary of Environmental Chemistry. DACO: 8.1
1205369	The Vapor Pressure of Technical Clofentezine. DACO: 8.2.1
1205370	The Kinetic of the Hydrolysis of NC 21314 Under Acid, Neutral and Basic Conditions. DACO: 8.2.3.2
1205371	Characterization of Hydrolysis Products of Clofentezine In Aqueous Solution Under Acid, Neutral And Basic Conditions. DACO: 8.2.3.2
1205372	The Photodegradation of (^{14}C)-Clofentezine In Water Under Natural Sunlight Conditions. DACO: 8.2.3.3.2
1205373	The Photodegradation of (^{14}C)-Clofentezine on Soil. DACO: 8.2.3.3.1
1205374	Solubility of Clofentezine aqueous Solution Under acid, Neutral and Basic Conditions. DACO: 8.2.1
1205375	Octanol- Water Partition Coefficient at 20 Degrees Celsius. DACO: 8.2.1
1205376	Laboratory Leaching Study With NC 21314 in Three Standard Soils From West Germany. DACO: 8.2.4.3
1205377	The Immediate Leaching of Apollo 50 SC in Three West German (Speyer) Soils. DACO: 8.2.4.3
1205379	The Degradation of NC 21314 in Surface Water/Sediment Microcosms. DACO: 8.2.3.5.4
1205380	Determination of the Accumulation of NC 21314 in Bluegill Sunfish...Using a Dynamic Test System. DACO: 9.5.6

1205382 Dietary LC_{50} of Technical NC 21314 To Bobwhite Quail-NC 21314 Dietary Concentrations. DACO: 9.6.2.4

1205383 Dietary LC_{50} of Technical NC 21314 To Mallard Duck-NC 21314 Dietary Concentrations. DACO: 9.6.2.5

1205384 Apollo Technical Summary of Fish Toxicity Data. DACO: 9.5.1

1205385 Apollo Technical Summary of Non-Target invertebrate Toxicity. DACO: 9.2.1

1205386 Determination of the Acute Toxicity of Technical NC 21314 To the Water Flea.... DACO: 9.3.2

1205387 The Effect of the Product NC 21314 Technical on the Growth of Green Alga.... DACO: 9.8.2

1205565 Summary of Acute Toxicity To Rainbow Trout. DACO: 9.5.1

1205566 Acute Toxicity of Apollo 50 Sc To Rainbow Trout.... DACO: 9.5.2.1

1205570 Effect of NC 21314 on Typhlodromus Pyri- Results From Dr.J.E. Cranham, East Malling Research Station. DACO: 9.2.5

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1205573 Programmes To Control Two Spotted Mites...in Apple Orchards: Nashdale, New South Wales.... DACO: 9.2.5

1205574 Control Two Spotted Mites...in Apples, and Its Subsiquent Effect on the Predator Mite.... DACO: 9.2.5

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1205577 Effect of NC 21314 on the Predatory Mite...on Apples- Results From East Mailing- 1982.... DACO: 9.2.5

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1205581 The Toxicity of NC 21314 To Earthworms in the Field.... DACO: 9.2.3.1

1205731 Decline of Clofentezine Residues in Soil Following Orchard Treatment With the 50 SC Formulation in New York, USA, 1984. DACO: 8.3.2.2

1213005 Dissipation of Clofentezine in Soil Following Both Early & Mid-Season Application in Trials Conducted in Canada (15023). DACO: 8.3.2.1

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