Proposed Re-evaluation Decision PRVD2016-06

Ziram

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Overview

What is the Proposed Re-evaluation Decision?

After a re-evaluation of the fungicide ziram, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing the cancellation of all ziram uses in Canada.

An evaluation of available scientific information found that, under the current conditions of use, ziram products pose potential risks of concern to human health and the environment. Based on the health and environmental assessments, risks of concern were identified for both workers and the general public in addition to birds, mammals and aquatic organisms.

This proposal affects all end-use products containing ziram registered in Canada. This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for ziram and presents the reasons for the proposed re-evaluation decision.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides additional technical information on the assessment of ziram.

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 indicated on the cover page of this document).

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

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. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program,* presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants published scientific reports, information from other regulatory agencies and any other relevant information.

What is Ziram?

Ziram is a contact protectant fungicide registered for both food and nonfood uses. It is registered for control of diseases on apple, peach, apricot, tomato, and cucurbit vegetables as a foliar application; and as a material preservative to prevent bacterial degradation of dry starch and synthetic latex adhesive formulations. The agricultural uses are applied using ground application equipment by growers, farm workers and professional applicators.

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

Health Considerations

Can Approved Uses of Ziram Affect Human Health?

Based on the human health risk assessment, all uses of ziram are proposed for cancellation.

Exposure to ziram may occur when handling and applying the product in agricultural and industrial settings, entering treated areas, coming in contact with treated materials/products, and through diet. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. For ziram, toxicology endpoints from a developmental neurotoxicity study in rats were used for human health risk assessment. Based on the weight of evidence from the available studies, a cancer unit risk value was also established for ziram.

The risk assessment compares the estimated level of human exposure to the no-effect doses identified in the animal tests. The reference values used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). The estimated dietary exposure to ziram from domestically produced and imported food commodities exceeded the acute and cancer reference values established from the toxicology. Potential risks of concern were identified for workers handling ziram products during mixing/loading and application as well as from re-entering treated agricultural sites following a single application of ziram. Potential risks of concern were also identified following application of ziram to fruit trees in residential settings and from use of adhesives containing ziram as a preservative.

The ziram health risk assessment has considered the currently registered use pattern and label directions as well as additional mitigation measures such as additional personal protective equipment, engineering controls to reduce exposure, and modifications to the use pattern (for example, reduced application rates and cancellation of certain uses).

Environmental Considerations

What Happens When Ziram is Introduced into the Environment?

The use of ziram poses risks to birds, mammals and aquatic organisms that cannot be fully mitigated.

Ziram can enter nontarget terrestrial and aquatic habitats through spray drift and can enter aquatic habitats through run-off. Ziram transforms quickly to thiram, which is also a registered pesticide. Ziram and thiram are soluble in water and do not vaporize when sprayed on crops. They are nonpersistent in soil and water, and are not expected to move through the soil profile or bioaccumulate.

When exposed to high enough concentrations, ziram is toxic to birds and mammals, which may be at risk if they consume food sources that have been sprayed with this pesticide. Aquatic organisms are also potentially at risk due to exposure to ziram and thiram. The environmental risk assessment considered the currently registered use pattern as well as mitigation in the form of spray buffer zones and label statements highlighting the risk of runoff, however, risks to birds and aquatic organisms cannot be fully mitigated.

Value Considerations

What is the Value of Ziram?

Ziram is registered for control of several economically important diseases on apples, peaches, apricots, cucumbers (field), tomatoes (field), melons, pumpkins and squash. Ziram has a multi-site mode of action. It is used in rotation with other single-site fungicides for resistance management, thus prolongs the effective life of these fungicides which are highly prone to the development of resistance.

Proposed Measures to Minimize Risk

Based on the available data and current risk assessments, Health Canada is proposing cancellation of all uses of ziram. Consequently, all maximum residue limits (MRLs) are proposed for revocation.

Next Steps

The PMRA is inviting stakeholders to submit comments on this document, as well as detailed proposals to further refine the risk assessment and mitigate risks. The PMRA will accept comments and proposals for a period of 60 days from the date of publication of this document. Please forward all comments to Publications.

Before making a final decision on ziram, the PMRA will consider all comments or proposals received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on ziram. The PMRA will then publish a re-evaluation decision document, which will include the decision and the reasons for it, a summary of the comments and proposals received on the proposed decision and the PMRA's response to these comments and/or proposals.

If no proposals to refine the risk assessment are received, or if those received are inadequate, then the PMRA will proceed to finalize the re-evaluation decision to cancel all ziram uses in Canada.

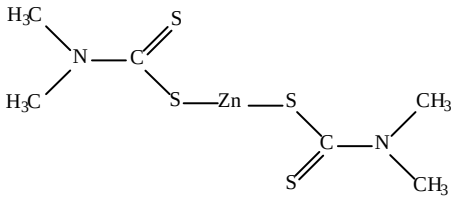
Science evaluation

1.0 Introduction

Ziram is a contact, protectant fungicide with multi-site mode of action and belongs to Mode of Action (MoA) group M3. It is registered for use on apples, peaches, apricots, cucumbers (field), tomatoes (field), melons, pumpkins and squash. Currently, one technical and three end-use products are registered in Canada. The end-use products are formulated as wettable powder (WP), wettable granules (WG) and dust.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient

Common name		Ziram
Function		Fungicide
Chemical Family		Dithiocarbamate
Chemical name		
	1 International Union of Pure and Applied Chemistry (IUPAC)	Zinc bis(dimethyldithiocarbamate)
	2 Chemical Abstracts Service (CAS)	(T-4)-bis(dimethyldithiocarbamato-S,S')zinc
CAS Registry Number		137-30-4
Molecular Formula		$C_6H_{12}N_2S_4Zn$
Structural Formula		
Molecular Weight		305.8

Registration Number	Purity of the Technical Grade Active Ingredient
24713	96% minimum
28426	98.4% nominal (95.45-100%)

2.2 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.

2.3 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	< 1 × 10-3 mPa (extrapolated)
Ultraviolet (UV)/visible spectrum	Does not absorb at λ >350 nm
Solubility in water at 20°C	1.58 – 18.3 mg/L
n-Octanol/water partition coefficient at 20°C	Log K_{ow} = 1.23
Dissociation constant	N/A

2.4 Description of Registered Ziram Uses

Ziram is registered for agricultural use on apple, peach, apricot, tomato, and cucurbit vegetables as foliar application. It is also registered for use as a material preservative in dry starch and synthetic latex adhesive formulations. Agricultural use of ziram belongs to the following use-site categories: terrestrial feed crops and terrestrial food crops.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The ziram database consists of the full array of toxicity studies currently required for hazard assessment purposes. Most of the studies in the database were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data was high and the database was considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product. Overall, study results were consistent and indicated that the liver, thyroid, blood and the nervous system were the targets in the various animal species used in testing.

After oral administration to rats, a single dose of ziram was rapidly absorbed and excreted. The highest residue levels were found in the blood, liver, kidney, heart, lungs, spleen, and thyroid gland, while the tissues and carcass retained minimal amounts of the administered dose. There was a significant decrease in ziram levels in the blood and liver after 16 hours, with a concomitant increase in the intestine and kidneys, reaching the highest concentration level after one day. Ziram started to appear in the spleen and adrenals after 24 hours and was no longer

detected in the adrenals after three days or in the spleen after six days. The primary routes of excretion were expired air (37-50%, nearly complete <24 hours), urine (17-35%, nearly complete at 72 hours), and feces (9-18%, nearly complete at 72 hours). Following dermal exposure, absorbed ziram was rapidly excreted within 24 hours.

Following acute exposure, ziram was highly toxic by the oral route in the rat, moderately toxic via the inhalation route in the rat, of low dermal toxicity in the rabbit, extremely irritating to the rabbit eye, and a skin sensitizer in guinea pigs, although it was not irritating to skin in the rabbit. Clinical signs of acute oral toxicity included piloerection, diarrhea, lethargy, ptosis, decreased respiratory rate, ataxia and abnormal gait and body carriage.

Twenty-one days of repeated dermal exposure to ziram in rabbits resulted in decreased body weight and food consumption, and hepatotoxicity in females at the limit dose. Similar effects were noted in rodents following short-term repeated oral exposure. In addition, decreased spleen weight with concomitant extra medullary hematopoiesis, as well as hyperkeratosis and hyperplasia of the epithelium in the stomach were noted in mice exposed for 90 days. Degenerative changes in the liver and kidneys, as well as localized areas of epithelial hyperplasia in the stomach were noted in short-term rat studies.

In a 90-day dietary study, dogs exhibited decreased body-weight gains and absolute ovarian weights and liver effects, in addition to increased cholesterol levels in females and thromboplastin time in males. Convulsions, trembling and increased liver damage (focal necrosis with changed enzyme levels) were also observed at higher doses. Effects in one-year dietary study in dogs were more severe. These effects included significant decreases in body-weight gains and treatment-related convulsions (one female sacrificed *in extremis*), a greater degree of hepatotoxicity, hematological changes and some degenerative changes in the testes/epididymides.

A repeat dose inhalation study was not available.

The genotoxic potential of ziram was assessed using a variety of bacterial and mammalian in vitro and in vivo studies. The overall weight-of-evidence suggests that ziram is mutagenic, showing predominantly positive results in several bacterial mutation assays and positive results in recessive lethal and wing mosaic assays in Drosophila. Evidence for clastogenicity was equivocal with increased chromosomal aberrations in CHO cells and human lymphocytes and leukocytes in vitro, and negative results in NMRI cells and mouse micronuclei in vivo.

Effects from chronic oral exposure to ziram in mice and rats indicated that ziram caused tumours and preneoplastic lesions in rats. Studies reviewed included two acceptable chronic studies in F344 rats with ziram preparations of varying purity, one chronic study in SD rats, and two chronic mice studies.

In one of the long term studies, treating F344 rats with ziram (89% purity, with 6.5% thiram) resulted in an increased incidence of thyroid C-cell carcinomas and adenomas with a concomitant increase in thyroid hyperplasia. In a more recent two-year F344 rat study (97.5% purity), an increase in the incidence of thyroid C-cell hyperplasia was not observed, however the

study showed a dose-dependent increase in thyroid enlargement and follicular hypertrophy. Results from a third two-year study in SD rats (98.7% purity) showed prominent ultimobranchial cysts in the thyroid, and hyperplasia of the thyroid C-cell and the parathyroids in mid- and high dose animals, and decreased T4 activity measured at four weeks of dosing. Even though there was no significant increase in the thyroid C-cell adenoma and carcinoma incidence with dosing, the thyroid lesions noted were considered possible preneoplastic lesions.

It is noteworthy that thiram, a major ziram metabolite in mammals and a structural analog, is mutagenic and also showed evidence of oncogenicity with thyroid C-cell adenomas and hepatocellular adenomas noted in rats following long-term exposure.

There was no treatment-related evidence of carcinogenicity in mice.

In summary, one chronic rat study showed increased incidences of thyroid C-cell adenoma and carcinomas with ziram treatment (89% purity , 6.5 % thiram), and the other two studies in rats showed thyroid effects (hypertrophy, hyperplasia and cysts). Studies have also indicated that ziram is likely mutagenic. Overall, it was concluded that the evidence for carcinogenicity of ziram could not be dismissed and a cancer unit risk (q_1*) was therefore calculated. The USEPA has classified ziram as “suggestive of carcinogenicity” (USEPA Reregistration Eligibility Decision, 2003).

Decreased body weight, body-weight gain, food consumption, and food efficiency, as well as hematologic and clinical chemistry effects were generally seen in long term oral studies in rodents. Slight anemia, increased haematopoiesis, and elevated liver enzymes activity were typically observed in rats. Chronic effects also included decreased mobility, calf muscle atrophy and axonal degeneration, narrowing of nerve fibers, hyperkeratosis and degenerative changes in the stomach, hemosiderosis in the spleen and liver, decreased testes weight and retarded closure of the epiphyseal plate in the rats.

Neurotoxic effects were observed in the acute, short-term and developmental neurotoxicity (DNT) studies in rats. In the acute oral neurotoxicity study, rats showed effects in all six functional domains of the functional observation battery (FOB), as well as ataxia, impaired gait, abnormal respiration, and large decreases in the total motor and ambulatory activity counts. A NOAEL was not set as ataxia and impaired gait were observed in all treated males. The altered gait and ataxia observed with ziram treatment has also been noted in organophosphate induced delayed polyneuropathy (OPIDN) in connection with inhibition of the brain neurotoxic esterase (NTE). Inhibition of brain NTE and brain cholinesterase were noted in the 90-day neurotoxicity study. Following ziram exposure there was a decrease in brain NTE (24-38%) in all dose groups. However, the inhibition of NTE activity was not considered of concern, because the dose response was poor, and decreases in NTE were below the levels that result in clinical effects in published literature (hyperactivity effects in mice are noted with 40% inhibition of NTE activity in NTE heterozygote mice, and OPIDN is associated with >70% decrease). No neurotoxic events were identified through functional operational battery testing in this study.

The DNT study was found acceptable for use in risk assessment but significant limitations were noted, including a lack of brain morphometric evaluations and a full FOB being performed. Increased motor activity was observed in the young animals in the absence of maternal toxicity, indicating developmental sensitivity. Motor activity levels increased in the young animals in all treatment groups, with two to three-fold higher ambulatory and total motor activity levels in the high dose juvenile animals, as compared to the concurrent control (day 17 and 21 post-dosing). There was a decrease in the mean peak startle response noted in juvenile animals treated with the high dose of ziram in the presence of maternal toxicity.

Developmental toxicity studies in rats and rabbits showed similar parental symptoms that included increased water consumption, and salivation, decreased food consumption and decreased body-weight gain, as well as hair loss in rats and death in rabbits. The ziram database also indicated an increased incidence in resorptions and postimplantation loss in rabbits, and a decrease in the number of live fetuses/doe in rabbits and rats, in the presence of maternal toxicity. Developmental toxicity studies conducted in rabbits using ziram showed evidence of malformations, namely the absence of the interparietal bone, at maternally toxic doses (causing decreased body-weight gain and mortality). In a rat developmental toxicity study, a dose-related increase in the incidence of diaphragmatic thinning and protrusion of the liver was observed in fetuses at a dose producing a reduction in maternal body weight, food consumption and excessive postdosing salivation. Increased incidence of unossified sternebrae was also noted at the high dose, in conjunction with more severe maternal toxicity.

In a two-generation reproductive toxicity study in rats, high dose parental animals were observed with decreased food consumption and body-weight gains during premating (F_0 and F_1), as well as decreased body weights (F_1) and body-weight gains (F_1), and decreased food consumption (F_0 and F_1 females) during gestation and lactation. Other parental effects included reddened mesenteric lymph nodes (in F_0 males), and mottled lungs (in F_1 males), and increased relative kidney (F_1 males) and liver (F_0 males) weights. An equivocal decrease in male sex ratio and a significant decrease in live pups per litter (F_1) were noted at high dose treatment. High dose offspring effects included decreased pup body weight during lactation (F_1 and F_2).

Increased relative testes weights were observed in 80 week mouse and two year rat studies, while degeneration of the testes/epididymides and stasis of the sperm cells in the epididymidal tubules were observed in the one year dog study. A supplemental oral (gavage) mouse study showed increased sterility in ziram treated males coupled with untreated female mice.

Exposure to ziram may predispose individuals to Antabuse (disulfiram) reactions if alcohol is ingested after exposure, due to inhibition of the enzyme acetaldehyde dehydrogenase, which is critical to the conversion of acetaldehyde to acetic acid.

Toxicology endpoints for use in the human health risk assessment are summarized in Appendix I.

3.1.1 *Pest Control Products Act* Hazard Characterization

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 threshold effects. This factor should take into account completeness of the data with respect to the exposure and the toxicity to infants and children, as well as 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, studies include a DNT study in rats, two developmental toxicity studies (one in rabbits and one in rats), and a two-generation reproductive toxicity study in rats. Although the DNT study was considered acceptable for regulatory purposes, the lack of brain morphometrics in the study represents a significant limitation in light of the neurotoxicity of ziram (including the degeneration/atrophy of axons). As well, NTE and cholinesterase activities measurements in the acute and the DNT studies would also have served to better characterize ziram toxicity.

Concerns relevant to the assessment of risk to infants and children were identified in the database. The DNT study provided a clear indication of increased susceptibility of rat fetuses to *in utero* and postnatal exposure to ziram (increased motor activity) in the absence of maternal toxicity. The manner in which ziram affects neurobehavioral development is not clearly understood, therefore it is difficult to predict how these effects would manifest in humans.

In a two-generation reproductive toxicity study in rats, a decrease in the number of live pups per litter and decreased body weight (F1 and F2 pups) was noted in the presence of maternal toxicity (decreased body weight and body-weight gain, and select organ weight changes). In rats, developmental effects (diaphragmatic thinning with protrusion of liver and incidence of unossified sternebrae) were observed at a dose level that also resulted in decreased body weight and food consumption, and postdosing salivation in the dams. In the rabbit developmental toxicity assay, an increased incidence of late resorptions, postimplantation loss and absence of the interparietal bone were observed at the high dose, and occurred in the presence of severe maternal toxicity (decreased body-weight gain and mortality). The developmental and reproductive effects noted above occurred at doses greater than those causing neurotoxicity in the DNT study.

In summary, all of the required studies relevant to assessing risk to infants and children were available; however limitations and concerns were identified. In the currently available DNT study, increased motor activity levels were observed at the lowest dose and with the absence of maternal toxicity. With respect to potential pre- and post-natal toxicity, the noted effect increases the concern for the lack of the brain morphometrics, a critical parameter for a chemical demonstrating neurotoxicity. On the basis of the above information, when establishing a reference dose based upon effects noted in this DNT study, the 10-fold factor required under the *Pest Control Products Act* was reduced to three fold.

3.2 Occupational and Non-Occupational Risk Assessment

3.2.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment

Occupational and Bystander (All Durations, Dermal and Inhalation Routes)

For occupational and residential exposures via the dermal and inhalation routes for all durations, the Lowest Observed Adverse Effect Level (LOAEL) of 5 mg/kg bw/day from the ziram DNT study was selected based on the increases in motor activity in juvenile animals in all the treatment groups in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and three fold for the extrapolation from a LOAEL to a NOAEL were applied. The *Pest Control Products Act* factor was retained at three fold for residential scenarios. For occupational scenarios, an additional three fold factor was applied to account for the residual uncertainties and to protect sensitive subpopulations including pregnant workers.

Unit Risk for Cancer Assessment

A linear low dose extrapolation (q_1*) assessment was conducted for thyroid C-cell carcinomas and adenomas in male rats. The calculated q_1* value for tumour incidence was 6.29×10^{-2} $(mg/kg\ bw/day)^{-1}$.

Absorption Factors

For extrapolation of an oral endpoint for dermal risk assessment, a dermal absorption factor of 50% was established based on the physical/chemical properties of the active ingredient (solubility, physical state, molecular size). For inhalation risk assessment, 100% inhalation absorption was assumed.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to ziram while mixing/loading and applying products containing this active ingredient in agricultural or industrial settings, using adhesives containing ziram as a preservative or when entering treated agricultural sites to conduct postapplication activities.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment for Agricultural Uses

The following handler exposure scenarios were considered based on the supported ziram use pattern:

- Mixing/loading of wettable granule (WG) or wettable powder (WP) formulations and applying as liquid spray using groundboom equipment (cucumber, melon, squash, tomato);
- Mixing/loading of WG or WP formulations and applying as liquid spray using airblast equipment (apple, apricot, peach); and
- Mixing/loading of WG or WP formulations and applying as liquid spray using a backpack sprayer (apple, apricot, cucumber, melon, peach, squash, tomato)

For all assessed mixer/loader/applicator (M/L/A) scenarios, occupational exposure was considered to be of short-intermediate-term duration.

Combined (dermal and inhalation) exposure estimates for workers mixing/loading and applying ziram using groundboom, airblast, or backpack equipment were calculated using unit exposure values for mixers/loaders and applicators from the Canadian Pesticide Handlers Exposure Database (PHED) Version 1.1 and the Agriculture Handler Exposure Task Force (AHETF).

Default area treated per day (ATPD) values was assumed for the groundboom, airblast and backpack assessments. Additional assumptions included the maximum application rates and a worker body weight of 80 kg. Lifetime average daily dose values were calculated by amortizing exposure over the lifetime assuming workers would work 30 days per year for 40 years with a life expectancy of 78 years.

Personal protective equipment (PPE) to be used by occupational handlers is not specified on all ziram product labels. For the purpose of the mixer/loader/applicator risk assessment, exposure estimates were determined for workers wearing different levels of PPE (baseline up to full PPE). The use of engineering controls such as closed mixing/loading systems, water soluble packaging and enclosed cab application equipment were also considered in the risk assessment.

The combined (dermal and inhalation) mixer/loader/applicator risks are not of concern for cucumber, melon, squash and tomato uses when applied using groundboom and/or backpack equipment provided additional PPE (chemical resistant coverall over a single layer of clothing and chemical resistant gloves for workers using backpack sprayers) and use of engineering controls (closed mixing/loading systems for ground boom applications) were implemented.

However, the combined (dermal and inhalation) mixer/loader/applicator risks of concern were identified for the remaining ziram uses (apple, apricot, peach) even when the risk assessment assumes maximum PPE and the use of engineering controls. Establishing limits to the amount of ziram handled (for example, reduced application rate or limits to the area treated per day) were not considered adequate to address potential risk concerns.

3.2.2.2 Postapplication Occupational Exposure and Risk Assessment for Agricultural Uses

The postapplication occupational risk assessment considers exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (such as handharvesting, thinning, or scouting).

For workers entering treated fields to conduct agronomic activities, dermal exposure is considered to be the primary route of exposure. Considering low volatility of this active ingredient and assuming at least 12 hours have passed before re-entry, inhalation exposure to ziram is not expected for postapplication workers re-entering treated sites.

Postapplication dermal exposure to ziram residues on fruits and vegetables is expected to be short-intermediate-term based on the application timing and re-entry activities.

Potential exposure of postapplication workers was estimated following a single application at the maximum registered rate using activity-specific transfer coefficients and dislodgeable foliar residue values. The dislodgeable foliar residue refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. In the ziram risk assessment this was assumed to be 25% of the application rate. A transfer coefficient is a measure of the relationship between exposure and the dislodgeable foliar residue for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies (Agricultural Re-entry Task Force, ARTF). The transfer coefficients are specific to a given crop and activity combination and reflect standard agricultural work clothing worn by adult workers.

Exposure estimates for workers re-entering treated areas on the day of application, resulted in potential risks of concern for all assessed crop/activity combination following a single application.

To protect workers involved in postapplication activities, restricted-entry intervals (REIs) were calculated which is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures below the level of concern. Assuming a residue dissipation of 10% per day, REIs of minimum 22 days would be required following the first application. The REIs are not expected to be agronomically feasible for all crops except cucurbits given the need to re-enter fields sooner. For cucurbits, risk is not of concern for up to three applications at intervals of 14 days, with an REI of seven days for scouting and hand weeding activities, and a preharvest interval of 25 days.

3.2.2.3 Exposure and Risk for Material Preservative Uses

Ziram is added during the manufacturing process of dry starch and synthetic latex adhesive as a material preservative. Based on the use pattern, the following exposure scenarios were considered:

- Primary handlers
  - Mixing/loading during manufacturing of dry starch and synthetic latex adhesives

- Secondary handlers (end users)
  - Use of dry adhesives containing ziram in manufacturing facilities (for example, production of paper bags and boxes, carton sealing, case sealing)
  - Point of use applications of dry adhesives containing ziram by trade workers (for example, wallpapering workers)

- Postapplication workers
  - Clean-up/repair/maintenance activities at manufacturing facilities
  - Workers handling finished products made with treated adhesives (for example, paper bags and boxes)

Primary handlers:
During manufacturing of dry starch and synthetic latex adhesives workers are expected to scoop material into a weighing container or directly into a mixing vessel (in other words, open pour). Exposure of primary handlers applying ziram during the adhesive manufacturing process is expected to be of an intermediate to long-term duration. Exposure estimates (dermal and inhalation) for primary chemical handlers wearing gloves were calculated using 90th percentile exposure estimates derived from the Chemical Manufacturers Association Antimicrobial Exposure Study normalized to an 80 kg body. Lifetime average daily doses were calculated based on daily exposure estimates assuming the frequency of exposure of 250 days per year for 40 years. Based on the risk assessment, potential risks of concern were identified for primary handlers of ziram during manufacturing of dry starch and synthetic latex adhesives.

Secondary handlers – manufacturing facilities:
The adhesive product is expected to be supplied as a dry formulation to secondary manufacturing facilities where the adhesive is mixed with water prior to use for the production of a variety of products including paper bags and boxes, laminated paper boards, and carton sealing. Exposure of secondary handlers is expected to be of an intermediate- to long-term duration, and is expected to occur via both dermal and inhalation routes of exposure. It is assumed that the amount of active handled per day in the secondary manufacturing facility would be comparable to exposure (dermal and inhalation) of primary handlers. Given the results of the risk assessment for primary handlers, risks for secondary handlers at manufacturing facilities are also considered to be of concern.

Secondary handlers – point of use:
Point of use workers are expected to mix dry adhesive products with water on site and apply the product (for example, wallpaper paste) using a paintbrush, spatula, or trowel. Exposure of workers (dermal and inhalation) handling/applying ziram-treated adhesives was assessed using surrogate exposure data from the PHED. Additional assumptions included the minimal and maximum application rates and the average worker body weight of 80 kg. Lifetime average daily doses were calculated assuming frequency of exposure of 250 days per year for 40 years. Based on the risk assessment, potential risks of concern were identified for secondary handlers mixing/loading the dry adhesive products and applying the using paintbrush/spatula/trowel.

Postapplication workers:
The potential for postapplication exposure in industrial settings (for example workers handling treated products such as paper bags or/and involved in maintenance activities) is expected to be low based on the low concentration of ziram in dry adhesive product and potential further dilution during the manufacturing process, low volatility of this active, and potential removal of residues with water during the production process. On this basis, the risk to postapplication industrial workers is not expected to be of concern.

3.2.3 Residential Handler Exposure and Risk Assessment

There are no residential uses of ziram registered in Canada.

3.2.4 Residential Postapplication Exposure and Risk Assessment for Agricultural Uses

Residential postapplication exposure may occur following application of commercial class ziram products to fruit trees in residential areas (for example, residential orchards and gardens). In contrast to professional workers who generally perform one task on one crop throughout the day (for example, harvesting of apples), individuals in residential settings are likely to conduct various activities related to tree maintenance on the same day. Further, the dermal contact is expected to occur as early as on the day of pesticide application and individuals are expected to wear shorts and short-sleeved shirts.

Dermal exposure is considered to be the primary route of postapplication exposure in the residential setting. Considering low volatility of this active ingredient, inhalation exposure to ziram is not expected for the general public re-entering treated sites.

Dermal exposure estimates for individuals in residential settings conducting postapplication activities related to tree maintenance were calculated using default peak dislodgeable foliar residue values (25% of application rate) and activity specific transfer coefficients (USEPA, 2012). Lifetime average daily dose values were calculated assuming exposure duration of one day per year and a 78-year lifespan.

Potential risks of concern were identified from residential postapplication exposure following a single application of commercial class ziram products to fruit trees in residential areas for all population groups (including children, youths and adults).

3.2.5 Residential Postapplication Exposure and Risk Assessment for Material Preservative Use

Homeowners are expected to mix dry adhesive products containing ziram with water and apply the product (for example, wallpaper paste) using a paintbrush, spatula, or trowel. Exposure of homeowners (dermal and inhalation) handling/applying ziram-treated adhesives was assessed using surrogate exposure data from the PHED. Additional assumptions included the minimal and maximum application rates and the average body weight of 80 kg. Lifetime average daily doses were calculated assuming frequency of exposure of 4 days per year for 63 years.

Based on the risk assessment, risks of concern were identified for a homeowner using ziram-treated adhesives for home improvement projects.

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 ziram from potentially treated imports 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. Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticides in Food – A User's Guide*, presents detailed acute, chronic and cancer dietary risk assessments procedures used by the PMRA.

The ziram dietary risk assessment considered exposure from all food sources that could potentially contain ziram. Residue estimates for ziram were based on field trial data where available. When field trial data were not available, the Canadian Maximum Residue Limit (MRL) was used to estimate residues in crops. Surveillance data suitable for the purpose of dietary risk evaluation from the Canadian Food Inspection Agency National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program were not available for ziram. Processing factors, percent of crop treated and food supply information were also used to refine the assessment.

Acute, chronic and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (Version 2.16) which uses food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994-1996 and 1998.

3.3.1 Toxicology Endpoint Selection for Acute Dietary Risk Assessment

Acute Reference Dose (ARfD)

For characterization of acute dietary risk, the LOAEL of 5 mg/kg bw/day from the developmental neurotoxicity study was selected based on the increases in motor activity in juvenile animals in all the treatment groups in the absence of maternal toxicity. A composite assessment factor (CAF) of 1000-fold is warranted, including standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability, as well as a threefold uncertainty factor for the lack of NOAEL and a threefold *Pest Control Products Act* factor. The ARfD is considered to be protective of all sub-populations including infants and children.

$$\textbf{ARfD} = \frac{\textbf{5 mg/kg bw}}{\textbf{1000}} = \textbf{0.005 mg/kg bw}$$

3.3.2 Acute Dietary Exposure and Risk

Acute dietary risk is calculated considering the highest ingestion of ziram that would be likely on any one day, and using food consumption and food residue values. A statistical analysis compiles all possible combinations of consumption and residue levels to estimate a distribution of the amount that might be consumed in a day. A value representing the high end (99.9th percentile) of this distribution is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects.

The probabilistic assessment results show that based on the current use pattern, the acute dietary (food only) exposure to ziram (at the 99.9th percentile) results in potential risks of concern for all populations. Several mitigation approaches were explored to decrease the acute dietary exposure (for example, cancelling high-residue or high-consumption commodities).Despite the approach taken to limit the dietary exposure, dietary risks of concern remain. Therefore, all registered uses of ziram are proposed for cancellation and all established MRLs are proposed for revocation.

3.3.3 Toxicology Endpoint Selection for Chronic/Cancer Dietary Risk Assessment

Acceptable Daily Intake (ADI)

To estimate dietary risk from repeated exposure, the LOAEL of 5 mg/kg bw/day from the developmental neurotoxicity study was selected based on the increases in motor activity in juvenile animals in all the treatment groups in the absence of maternal toxicity. A CAF of 1000-fold is warranted, including standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability, as well as a threefold uncertainty factor for the lack of NOAEL and a threefold *Pest Control Products Act* factor.

$$\textbf{ADI} = \frac{\textbf{5 mg/kg bw/day}}{\textbf{1000}} = \textbf{0.005 mg/kg bw/day}$$

Unit Risk for Cancer Assessment

A linear low dose extrapolation (q_1*) assessment was conducted for thyroid C-cell carcinomas and adenomas in male rats. The calculated q_1* value for tumour incidence was 6.29×10^{-2} $(\text{mg/kg bw/day})^{-1}$.

3.3.4 Chronic/Cancer Dietary Exposure and Risk

The chronic dietary exposure was calculated by using the average consumption of different foods and the residue values on those foods. This expected intake of residues was then compared to the ADI for determining chronic risk; or multiplied by the q_1* to determine the cancer risk.

The chronic assessment results show that based on the current use pattern the chronic dietary (food only) risk is not of concern for all populations. However, cancer dietary (food only) risk is of concern for the general population. As with the acute assessment, several mitigation approaches were explored to decrease the chronic/cancer dietary exposure. Despite this, dietary risks are of concern. Therefore, all registered uses of ziram are proposed for cancellation and all established MRLs are proposed for revocation.

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Concentrations of ziram in Canadian drinking water sources were modelled using Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) for surface water and Leaching Estimation and Chemistry Model (LEACHM) for groundwater. The modelling results indicate that ziram has the potential to leach into groundwater and run off to surface water.

It is expected that exposure to ziram via drinking water would contribute to the overall dietary exposure. However, given the acute/cancer risks of concern for ziram from food sources alone, a refined ziram drinking water exposure and risk assessment has not been conducted at this time.

3.5 Aggregate Risk Assessment

An aggregate exposure and risk assessment for the general public combining the different routes of exposure to ziram has not been conducted at this time since individual exposure components (residential and dietary exposures) result in potential risks of concern individually.

3.6 Human Health Conclusion

The current assessment has considered the currently registered use pattern and label directions as well as additional mitigation measures such as PPE, engineering controls, reduced application rates and removal of certain uses. Potential risks of concern have been identified for most of the assessed human health scenarios (including occupational, residential and dietary scenarios) despite consideration of additional measures to reduce exposure:

- Occupational mixer/loader/applicator risks were identified for apple, apricot and peach uses. Cucurbit and tomato uses would be acceptable provided additional mitigation measures were implemented.
- Occupational postapplication risks were identified on the day of application for all uses. Required REIs are not agronomically feasible for all uses except cucurbits.
- Occupational worker and postapplication risks were identified for material preservative uses.
- Residential postapplication risks were identified for material preservative uses.
- Residential postapplication risks were identified for agricultural uses.
- Acute and cancer dietary exposure (food only) results in potential risks of concern based on the current use pattern.

In most cases, the risks were identified in both the noncancer and cancer risk assessments.

No further refinements to the risk assessment were considered at this time. Given the toxicological properties of ziram, it is not expected that further refinements to the exposure assessments would change the overall risk conclusions.

4.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report pesticide incidents to the PMRA that are related to their products. In addition, the general public, medical community, government and nongovernmental organizations are able to report pesticide incidents directly to the PMRA. Incidents were searched and reviewed for the active ingredient ziram. As of 10 June 2015, there have been no health-related incident reports for ziram submitted to the PMRA.

5.0 Value

Ziram is registered for use as a foliar spray for the control of a number of economically important diseases on apples, peaches, apricots, cucumbers (field), tomatoes (field), muskmelon, watermelon, pumpkin and summer squash. It is particularly important for the management of coryneum blight (shot hole) on peaches and apricots. Ziram is also registered for the prevention of bacterial degradation of dry starch and synthetic latex adhesive formulations during adhesive manufacturing.

Ziram is important for the management of fungal diseases due to its multi-site mode of action, low risk for the development of resistance and relatively low cost. Consequently, ziram is used in rotation with other active ingredients in an integrated pest management (IPM) program for disease and resistance management and thus prolongs the life of single-site fungicides that are at high risk for the development of resistance.

6.0 Environment

6.1 Fate and Behaviour in the Environment

Ziram is soluble in water. It has a low potential to volatilize from dry or moist surfaces. Hydrolysis is rapid under acidic conditions and is an important route of transformation for ziram (half-life 0.17 hours at pH 5 to 18 days at pH 8). Phototransformation is also an important route of transformation for ziram in soil and aquatic systems with half-lives of approximately 8 to 9 hours. Ziram is nonpersistent to slightly persistent in soil with DT_{50}'s of 1.75 and 14.1 days in aerobic and anaerobic biotransformation studies, respectively, making biotransformation an important route degradation for ziram in soil. Ziram is classified as nonpersistent in aerobic water/sediment systems (DT_{50} 5–7 hours). No information was available to evaluate the aquatic biotransformation of ziram under anaerobic conditions. The log K_{ow} (1.086-1.23) indicates that ziram is not likely to bioaccumulate.

Ziram is classified as immobile to moderately mobile in soils (K_{oc} = 314-12,010), adsorbing more strongly to clay soils as compared to sand, silt loam, loamy sand, or sandy loam soils. Soil column leaching studies indicate a low potential for ziram to leach below the top 2.5 cm soil layer. Field information from studies conducted in the United States indicate that ziram dissipates in soils with a DT_{50} of 5.2-6.7 days; however, dissipation was bi-phasic, becoming slower after the first two weeks. Given its' short duration in the terrestrial environment ziram is unlikely to volatilize to the atmosphere. It has a potential to leach into groundwater in soils in which it is not tightly bound.

The major transformation product of ziram in water is thiram, which itself is a registered fungicide. It is formed during aquatic biotransformation and reaches a maximum of 31.9 % of applied ziram. The maximum DT_{50} of thiram in aerobic aquatic biotransformation studies is 2.2 days. Thiram is also a major transformation product in aerobic soil biotransformation studies, and reaches a maximum of 49.8% of applied ziram in the first 6 hours. The maximum DT_{50} of thiram in soil was 3.1 days.

6.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on nontarget 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. 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 (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to nontarget 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). 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 nontarget 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.

6.2.1 Risks to Terrestrial Organisms

The assessment of the risk posed by ziram to terrestrial organisms was based on an evaluation of toxicity data of ziram to bees, beneficial arthropods, two species of birds and one species of mammal. No data on toxicity to earthworms or to plants were available for review. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with ziram.

Ziram does not pose a risk to bees or beneficial arthropods. It does present a potential risk to some birds and mammals, in particular herbivores and small insectivores.

For birds, since foliar dissipation DT_{50} data were not available, a refined risk assessment was carried out using a default half-life for ziram on vegetation of 10 days, as well as the mean nomogram residues to calculate the estimated daily exposure. There were some exceedances of the LOC; however the risk quotients were not large. The largest risk quotient was 19.7 for small insectivore, acute toxicity, peaches and apples. For birds consuming food in treated areas, the risk from acute, dietary and reproductive toxicity exceeded the LOC for small and medium sized birds (mainly acute oral and dietary risk) of all feeding guilds as well as large sized herbivorous birds. Exceedances of the LOC for birds consuming food off-site from spray drift exposure was limited to applications on apples, peaches and apricots. When risk quotients exceeded the LOC, the percentage of the diet required to reach the LOC values ranged from as low as 5.1% (the largest risk quotient, small insectivores, peaches and apricots) to 99.6% of the diet (large herbivores, forage crops). This risk is elevated for small and medium frugivores, small insectivores and herbivores. 5.1% of the diet contaminated with ziram is equivalent to 73.5 minutes of feeding on contaminated food to reach the LOC. This information indicates that the use of ziram presents potential risks to some birds.

For mammals, since foliar dissipation DT_{50} data were not available, a refined risk assessment was conducted using a default half-life for ziram on vegetation of 10 days, as well as the mean nomogram residues to calculate the estimated daily exposure. For the acute oral and reproductive risk assessments, there were some risk quotients in the treated area (in-field) that exceeded the LOC, but the risk quotients were not large. The largest risk quotient was 14.8 (medium herbivores, short grass). For exposures off-site resulting from spray drift there were a few exceedances of the LOC at the higher application rates on apples, peaches and apricots. For the risk quotients which exceeded the LOC, the percentage of the diet required to reach the LOC for acute oral and reproductive refined risk quotients ranged from 6.7% of the diet (reproduction, medium herbivores, short grass) to 100% (acute, medium frugivores). 0.1% of the diet contaminated with ziram is equivalent to 96.5 minutes of feeding on contaminated food to reach the LOC.

6.2.2 Risks to Aquatic Organisms

Assessment of acute and chronic risk to aquatic organisms was based on an evaluation of toxicity data for ziram with17 freshwater species (five invertebrates, eight fish, three algae and one amphibian) and three estuarine/marine species (two invertebrates and one fish). Chronic toxicity data was not available for estuarine/marine invertebrates or fish.

The risk from acute and chronic exposure of ziram and of the major transformation product thiram exceeded the LOC for freshwater aquatic invertebrates at the screening level (direct overspray). For spray drift, the acute risk quotients exceeded the LOC at the highest application rates (apples and peaches/apricots) for freshwater invertebrates, and at all application rates for estuarine/marine species. The chronic risk quotients for spray drift exceeded the LOC at all application rates. A refined acute and chronic risk assessment for freshwater and estuarine/marine invertebrates was conducted to determine the risk from runoff using EEC's from the PRZM/EXAMS model for a tomato scenario in Manitoba (six applications at 1170 g a.i./ha) and a peach/apricot scenario in BC (single application at 6800 g a.i./ha). Both the acute and chronic risk quotients exceeded the LOC for the tomato scenario but were less than the LOC for the peach/apricot scenario.

Both the acute and chronic screening level risk assessment for freshwater fish and estuarine/marine fish showed that the risk quotients exceeded the LOC for direct overspray, as well as for spray drift. In many instances these exceedances were very large, particularly chronic risks with risk quotients ranging from 11.7 to 1567.2. A refined risk assessment was conducted to determine the risk from runoff using the EEC's generated with the PRZM/EXAMS model for a Manitoba tomato scenario (six applications at 1170 g a.i./ha) and a BC peach scenario (single application at 6800 g a.i./ha). Using these scenarios, both the acute risk quotient for freshwater and estuarine/marine fish and the chronic risk quotients for freshwater fish exceeded the LOC for the tomato scenario. The LOC was not exceeded for the peach/apricot scenario.

Risk quotients exceeded the LOC for direct overspray for algae. For risk from spray drift, the risk quotients exceeded the LOC for applications to apples and peaches at 4250 and 6800 g a.i./ha, respectively. A refined risk assessment was conducted using EEC's generated by a runoff model for the Manitoba tomato scenario and the BC peach/apricot scenario. Neither scenario produced runoff results that exceeded the LOC for algae.

6.3 Environmental Conclusion

Ziram presents significant risks to certain terrestrial organisms (mammals and birds) from consuming food sources contaminated by direct application as well as sites contaminated by spray drift. Risks posed to birds and mammals cannot be fully mitigated. Ziram also presents risks to some aquatic organisms from runoff and spray drift.

7.0 Pest Control Product Policy Considerations

7.1 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: in other words, 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, ziram and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[2] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Ziram does not meet Track 1 criteria, and is not considered a Track 1 substance. See Table 1 in Appendix I for comparison with Track 1 criteria.
- Thiram, the major transformation product of ziram, does not meet Track 1 criteria.
- Ziram does not form any transformation products that meet all Track 1 criteria.

7.2 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[3] and is based on existing policies and regulations including DIR99-03 and DIR2006-02[4], 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 Ziram (pest control product number 28426) does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*.

[2] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

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

[4] DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

- The use of formulants in registered pest control products identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[5] is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.[6]

8.0 Proposed Regulatory Decision

After a re-evaluation of ziram, Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing cancellation of all ziram uses in Canada. Furthermore, all established MRLs for ziram are proposed for revocation.

5 *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern*.

6 DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

List of Abbreviations

ADI	Acceptable Daily Intake
AHETF	Agricultural Handlers Exposure Task Force
ARTF	Agricultural Re-entry Task Force
ARfD	Acute reference dose
ATPD	Area treated per day
CAF	Composite Assessment Factor
DNT	Developmental Neurotoxicity
DT_{50}	dissipation time to 50%
EP	End Use Product
EXAMS	Exposure Analysis Modeling System
LEACHM	Leaching Estimation and Chemistry Model
LOAEL	Lowest Observed Adverse Effect Level
MoA	Mode of Action
MOE	Margin of exposure
MRL	Maximum Residue Limit
NMRI	Mouse strain identification
NOAEL	No Observed Adverse Effect Level
NTE	neurotoxic esterase
PRZM	Pesticide Root Zone Model
PHED	Pesticide Handlers Exposure Database
PPE	Personal protective equipment
USEPA	United States Environmental Protection Agency
WG	Wettable granule
WP	Wettable powder

Appendix I Toxicology Endpoints for Health Risk Assessment for Ziram

	RfD (mg/kg bw/day)	**Study NOAEL (or LOAEL)**	**CAF or Target MOE and Rationale**[1]
ARfD (all populations)	0.005	LOAEL = 5 mg/kg bw/day Rat developmental neurotoxicity study (Increased motor activity)	CAF = 1000 (PCPA = 3-fold)
ADI (all populations)	0.005		CAF = 1000 (PCPA = 3-fold)
Residential (all durations and all routes)			MOE = 1000 (PCPA = 3-fold)
Occupational (all durations and all routes)			MOE = 1000
Cancer Assessment	$q_1^* = 6.29\times10^{-2}$ $(mg/kg\ bw/day)^{-1}$	Based on incidences of liver tumours in a chronic/carcinogenicity study in rats	

[1]CAF (Composite assessment factor) refers to the total of uncertainty and *Pest Control Products Act* (PCPA) factors for dietary and residential risk assessments; MOE refers to target margin of exposure for dermal and inhalation assessments

Appendix II Toxicity to Non-Target Species

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
Terrestrial Species							
Invertebrate	Acute contact	Honey bee (*Apis mellifera*)	Ziram	48 h LD_{50}	>100 µg a.i. /bee	Mortality	PMRA 1310576; 1310708; 1129667
				48 h LD_{50}	**46.7µg a.i. /bee**	Mortality	PMRA 1129667
	Acute contact	Predator green lacewing (*Chrysoperla carnea Steph.*)	Ziram	NOEC	**10.5 kg a.i./ha**	Mortality and reproduction	PMRA 924934
	Acute contact	Earthworm (*Eisenia foetida*)	Ziram		No data		
Birds	Acute oral	Mallard (*Anas platyrhynchos*)	Ziram	LD_{50}	196 mg a.i./kg bw	Mortality	PMRA 1310576; 1310708
		Bobwhite Quail (*Coturnix virginianus*).		LD_{50}	**97 mg a.i./kg bw**	Mortality	PMRA 1310576; 1310708
	Dietary	Bobwhite Quail (*Coturnix virginianus*).	Ziram	LC_{50}	>5200 mg a.i./kg diet	Mortality	PMRA 1310576; 1310708; 1129667
		Mallard (*Anas platyrhynchos*)		LC_{50}	**5156 mg a.i./kg diet**	Mortality	PMRA 1310576; 1310708;1129667
	Reproduction	Bobwhite Quail (*Coturnix virginianus*).	Ziram	NOEC	**500 mg a.i./kg diet**	Mortality, body wt, food consumption, egg production, embryonic development	PMRA 1129667
Mammals	Acute oral	Rat	Ziram	LD_{50}	320 mg a.i./kg bw	Mortality	
				LD_{50}	**267 mg a.i./kg bw**	Mortality	
	Reproduction	Rat	Ziram	NOEL	**14.8 mg a.i./kg bw /day**	Reproduction	
				NOEC	207 mg a.i./kg diet	Loss of body weight, decreased food consumption	

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
Aquatic Species							
Freshwater Invertebrates	Acute	*Daphnia magna*	Ziram	48-h LC_{50}	**0.048 mg a.i./L**	Immobility	PMRA 1310576; 1310708
		Daphnia magna		48-h LC_{50}	0.14 mg a.i./L	Immobility	PMRA 1310576; 1310708
		Crayfish *(Procamburus clarkii*)		48-h LC_{50}	>40 mg a.i./L	Immobility	PMRA 1129667
		Mosquito (*Culex fatigans*)		24-h LC_{50}	instar I <0.1 mg a.i./L instar II 0.18 mg a.i./L instar III 0.55 mg a.i./L instar IV 1.31 mg a.i./L pupae 8.1 mg a.i./L	Immobility	PMRA 1129667
		Zebra mussel (*Dreissena polymorpha*)		5-d LC_{50}	1.8 mg a.i./L		PMRA 1129667
	Acute	*Daphnia magna*	Thiram	48-h LC_{50}	**0.011 mg a.i./L**	Immobility	PMRA 1752918 & or 1830692
	Acute	*Daphnia magna*	Thiram	48-h EC_{50}	0.21 mg a.i./L	Immobility	PMRA 1752918 & or 1830692
	Chronic	*Daphnia magna*	Ziram	21 day NOEC	**0.001 mg a.i./L**	Mortality	PMRA 924934
	Chronic	*Daphnia magna*		21 day NOEC	<0.0018 mg a.i./L	Caparace length	PMRA 1129667
	Chronic	*Chironomus riparius 1st larval stage*		28 day NOEC	0.242 mg a.i./L	emergence	PMRA 924934
	Chronic	*Daphnia magna*	Thiram	21 d NOEC	**0.001mg a.i. /L**	Growth and reproduction	PMRA 1752918 & or 1830692
Estuarine/ marine Invertebrates	Acute	Eastern oyster (*Crassostrea gigas*)	Ziram	96-h EC_{50}	0.077 mg a.i./L	Mortality	PMRA 1310576; 1310708
		Mysid shrimp (M*ysidopsis bahia*)		96-h LC_{50}	**0.014 mg a.i./L**	Mortality	PMRA 1310576; 1310708
	Acute	Mysid shrimp (M*ysidopsis bahia*)	Thiram	96-h LC_{50}	**0.0036 mg a.i./L**	Mortality	PMRA 1752918 & or 1830692

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
		Eastern oyster (*Crassostrea gigas*)		96-h EC_{50}	0.0047 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
	Chronic		Thiram		No data		
Freshwater Fish	Acute	Carp (*Cyprinus carpio*)	Ziram	96-h LC_{50}	0.27 mg a.i./L	Mortality	PMRA 1310576; 1310708
		Fathead minnow (*Pimephales promelas*)		96-h LC_{50}	0.0008 mg a.i./L	Mortality	PMRA 1310576; 1310708
		Rainbow trout (*Oncorhynchus mykiss*) (*Salmo gairdnerii*)		96-h LC_{50}	1.7 mg a.i./L	Mortality	PMRA 1310576; 1310708
				96-h LC_{50}	0.27 mg a.i./L	Mortality	PMRA 1129667
				96-h LC_{50}	0.3 mg a.i./L	Mortality	PMRA 1310576; 1310708; 1129667
		Bluegill sunfish (*Lepomis macrochirus*)		96-h LC_{50}	**0.0097 mg a.i./L**	Mortality	PMRA 1310576; 1310708
		Carp (*Cyprinus carpio*)		96-h LC_{50}	0.27 mg a.i./L	Mortality	PMRA 1310576; 1310708
				96-h LC_{50}	0.075 mg a.i./L	Mortality	PMRA 1129667
		Rainbow trout (*Oncorhynchus mykiss*)	Thiram	96-h LC_{50}	0.50 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.13 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.28 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
		Bluegill sunfish (L*epomis macrochirus*)		96-h LC_{50}	**0.042 mg a.i./L**	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.28 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.13 mg a.i./L	Mortality	PMRA 1752918 & or 1830692

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
		Fathead minnow (*Pimephales promelas*)		96-h LC_{50}	0.27 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
	Chronic (Early Life Stage)	Bluegill sunfish (*Lepomis macrochirus*)	Ziram	28-d NOEC	0.189 mg a.i./L	Mortality	PMRA 924934
		Rainbow trout (*Oncorhynchus mykiss*)		60-d NOEC	**<0.00032 mg a.i./L**	Mortality, length and teratogenicity	PMRA 1129667
	Chronic (Early Life Stage)	Rainbow trout (*Oncorhynchus mykiss*)	Thiram	60-d NOEC	**0.00032 mg a.i./L**	Mortality	PMRA 1752918 & or 1830692
Estuartine/ marine Fish	Acute	Sheepshead minnows (*Cyprinodon variegatus*)	Ziram	96-h LC_{50}	**0.84 mg a.i./L**	Mortality	PMRA 1310576; 1310708
	Acute	Sheepshead minnows (*Cyprinodon variegatus*)	Thiram	96-h LC_{50}	**0.54 mg a.i./L**	Mortality	PMRA 1310576; 1310708
	Chronic		Ziram/ thiram		No data		
Freshwater Plants & Algae	Acute	Green alga (*Selenastrum capricornutum*)	Ziram	120 h EC_{50}	**0.067 mg a.i./L**	Growth inhibition	PMRA 1310576; 1310708
		Algae *(Chlorella pyrenoido)*		96 h EC_{50}	1.2 mg a.i./L	Growth inhibition	PMRA 1129667
	Acute	Algae *(Chlorella pyrenoido)*	Thiram	96 h EC_{50}	1.0 mg a.i./L	Biomass	PMRA 1752918 & or 1830692
		Green alga (*Selenastrum capricornutum*)		48 h EC_{50}	**0.14 mg a.i./L**	Biomass	PMRA 1752918 & or 1830692
		Duckweed (*Lemna gibba)*		96 h EC_{50}	1.6 mg a.i./L	Biomass	PMRA 1752918 & or 1830692
* Values Used In Risk Assessment Highlighted In Bold Font							

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1210395	1992, Ziram Preliminary Toxicity to Rats by Dietary Administration for 13 Weeks. DACO: 4.3.4
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