Re-evaluation Decision RVD2018-39

Ziram and Its Associated End-use Products for Agricultural Uses

Final Decision

(publié aussi en français)

14 Decembre 2018

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: canada.ca/pesticides
hc.pmra.publications-arla.sc@canada.ca
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
hc.pmra.info-arla.sc@canada.ca

Canada

ISSN: 1925-1017 (print)
1925-1025 (online)

Catalogue number: H113-28/2018-39E (print version)
H113-28/2018-39E-PDF (PDF version)

Table of Contents

Re-evaluation Decision

Under the authority of the *Pest Control Products Act,* all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. Health Canada applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Ziram is a protectant fungicide registered for control of various fungal diseases on apples, peaches and apricots regionally in British Columbia; and nationally on cucumbers, tomatoes, melons, pumpkins and squash. Currently registered products containing ziram for agricultural uses are listed in Appendix I.

Ziram is also used as a material preservative. However, Health Canada plans to publish a separate document in the future examining the material preservative use of ziram. Further details may be found in the published document: Re-evaluation Note REV2018-02, *Approach for the Re-evaluation of Pesticides Used as Preservatives in Paints, Coatings and Related Uses*. As such, this document applies to agricultural uses of ziram only.

The regulatory approach for the re-evaluation of ziram was first presented in the Proposed Re-evaluation Decision PRVD2016-06, *Ziram.*[1] PRVD2016-06 proposed the cancellation of all registered uses and the revocation of all maximum residue limits (MRLs) as health and environmental risks were not found to be acceptable. Health Canada received comments relating to the health and value assessments. These comments are summarized in Appendix II along with the responses by Health Canada. These comments and new data/information resulted in revisions to the risk assessments (see Science Evaluation Update section), but did not result in changes to the proposed re-evaluation decision as described in PRVD2016-06. A reference list of data used as the basis for the proposed re-evaluation decision is included in PRVD2016-06, and further data used in the re-evaluation decision is listed in this document.

This document presents the final re-evaluation decision[2] for ziram agricultural uses, which is cancelling all agricultural products containing ziram to protect human health. All agricultural products containing ziram that are registered in Canada are subject to this re-evaluation decision.

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

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

Outcome of Science Evaluation

Health risks from the use of ziram and its associated end-use products have not been shown to be acceptable for any agricultural use, when used according to current label directions, or when additional mitigation measures are considered. The environmental risks associated with the use of ziram and its associated end-use products are acceptable when used according to revised label directions. Health Canada recognises the value of ziram to fruit crops, including the need for control and resistance management of pin-point scab on apples, and coryneum blight (shot hole disease) on peaches and apricots in British Columbia.

Regulatory Decision for Ziram

Health Canada has completed the re-evaluation of ziram for agricultural uses. Under the authority of the *Pest Control Products Act*, Health Canada is cancelling the registration of all currently registered agricultural uses of ziram in Canada. An evaluation of the available scientific information found that all agricultural uses of ziram have not been shown to have acceptable health risks when used according to the current label directions, or when additional mitigation measures are considered. No additional data are required.

All ziram MRLs will be revoked as all currently registered food uses are cancelled. Consultation on the revocation of all ziram MRLs will be conducted via a Proposed Maximum Residue Limit (PMRL) document.

Next Steps

To comply with this decision, products for agricultural uses are to be phased out following the implementation timeline outlined below. Appendix I lists the agricultural products containing ziram that are registered under the authority of the *Pest Control Products Act*.

- One (1) year of sale by registrant from the publication date of this decision document, followed by;
- One (1) year of sale by retailer from the last date of sale by registrant, followed by;
- One (1) year of permitted use from the last date of sale by retailer.

Other Information

Any person may file a notice of objection[3] regarding this decision on ziram within 60 days from the date of publication of this Re-evaluation Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides section of Canada.ca or contact the PMRA's Pest Management Information Service.

[3] As per subsection 35(1) of the *Pest Control Products Act*

Science Evaluation Update

1.0 Impact on Human and Animal Health

1.1 Toxicology Assessment for Ziram

Comments and data were received with respect to PRVD2016-06, *Ziram* regarding a range of issues including a request to exclude the consideration of studies that used a lower purity of ziram, and reconsideration of the genotoxicity conclusion, cancer risk assessment, the use of the developmental neurotoxicity (DNT) study for endpoint selection, and the application of uncertainty factors. A new non-guideline DNT study and two additional genotoxicity studies, of which one was found unacceptable, were submitted by the registrant.

Based on this information, all toxicology reference values outlined in PRVD2016-06 were revised:

- The revised ARfD is based on previous and new DNT studies.
- The revised ADI is based on a 2-year (diet) rat study supported by two co-critical chronic studies (mouse and rat), and a 1-year dog study, using an endpoint that is protective of effects noted in the DNT studies.
- Revised short- and intermediate-term occupational and residential endpoints and aggregate assessment are based on the DNT studies. The revised long term dermal and inhalation occupational endpoints are based on chronic/carcinogenicity study in rat (diet)
- With exclusion of the low purity National Toxicology Program (NTP) cancer study considered in PRVD2016-06, the cancer risk assessment was updated based on a revised q_1* value of 1.82×10^{-2} $(mg/kg\ bw/day)^{-1}$ for combined mesenteric lymph node and spleen hemangiomas in a rat chronic/carcinogenicity study conducted with higher purity ziram.

Detailed responses to the comments received, including details for the basis of the reference value revisions, are provided in Appendix II. Revised reference values are provided in Appendix III, Table 1.

1.2 Dietary Exposure and Risk Assessment

In PRVD2016-06, Health Canada had proposed the cancellation of all food uses and the revocation of all Canadian maximum residue limits (MRLs) as dietary risks were not found to be acceptable. The technical registrant did not submit specific comments for ziram, but cited comments on the PRVD2016-07, *Thiram*. Thus, Health Canada's responses to the submitted comments for thiram also apply to ziram. No new studies were received during the public consultation period.

When all uses were included in the revised dietary assessment, acute and chronic risks were not shown to be acceptable. Despite the refinements considered, including assessing each use separately, and the high level of mitigation applied in the revised dietary assessment, risks from

drinking water alone were not shown to be acceptable. Details on this revised assessment are provided in Appendix IV.

1.2.1 Maximum Residue Limits for Ziram on Food

Currently, Canadian MRLs for ziram are specified for a number of commodities on the basis of a residue definition expressed as (T-4)-bis(dimethylcarbamodithioato-κS,κS′)zinc (calculated as zineb). All ziram MRLs will be revoked as all currently registered food uses are cancelled. Consultation on the revocation of all ziram MRLs will be conducted via a Proposed Maximum Residue Limit (PMRL) document.

1.3 Occupational and Residential Exposure and Risk Assessment

The occupational and non-occupational assessments for ziram were previously conducted and published in PRVD2016-06. This document addresses comments received for the agricultural uses of ziram only, (unless otherwise specified).

In PRVD2016-06, Health Canada had proposed cancellation of all uses of ziram, including the agricultural uses. Risks of concern were identified for workers handling ziram products during mixing/loading and application as well as from entering treated agricultural sites following a single application of ziram. Risks of concern were also identified following application of ziram to fruit trees in residential settings.

During the PRVD consultation period, additional information and dermal absorption studies were received from the registrant. Health Canada's responses to specific comments are in Appendix II. As discussed in Section 1.2, dietary risks of concern were identified for all food uses of ziram. As these uses are cancelled, the occupational risk assessments from PRVD2016-06 were not revisited. In addition, the occupational assessments for the material preservative uses will be addressed in a separate document in the future.

1.4 Cumulative Risk Assessment

Ziram is a member of the dithiocarbamate class of pesticides along with ferbam and thiram. Ziram and ferbam also degrade to thiram. Since all agricultural uses of ferbam (RVD2018-37) and ziram will be cancelled, there is no requirement for a cumulative assessment of the agricultural uses of ziram, thiram and ferbam. However, ziram also has a material preservative use, which is to be assessed separately as per REV2018-02, Approach for the Re-Evaluation of Pesticides Used as Preservatives in Paints, Coatings and Related Uses. Thus, a cumulative risk assessment for the thiram degradate that results from the material preservative use of ziram, in conjunction with thiram from seed treatment uses, may be required upon completion of the risk assessment for the material preservative use of ziram.

2.0 Revised Environmental Risk Assessment

The environmental risk assessment in PRVD2016-06 considered the registered use pattern at the time as well as mitigation in the form of spray buffer zones and label statements highlighting the risk of runoff. At that time, it was determined that risks to birds and aquatic organisms could not be fully mitigated. However, the risk assessments conducted for the PRVD have since been re-examined by Health Canada. During the public consultation period, no comments were received regarding the environmental assessment conducted for ziram. As ziram degrades rapidly in the environment to thiram, a study received during consultation demonstrating that birds are repelled from thiram treated seed was used as evidence that birds would likely also be repelled from potential food treated with ziram.

2.1 Fate and Behaviour in the Environment

Drinking water estimated environmental concentrations (EECs) were modelled for field tomatoes based on an updated residue definition for ziram which included the transformation products thiram and *N*,*N* dimethyl carbamosulfonic acid (DMCS). These Level 2 scenarios are refined to the extent possible given current information.

2.2 Environmental Risk Characterization

Revisions to the risk quotients were not required and therefore did not change the overall environmental risk profile.

2.2.1 Risks to Terrestrial Organisms

Ziram quickly transforms in the environment to thiram, which is expected to repel birds and mammals. A label statement indicating that ziram is toxic to birds and mammals will remain on the label as this statement is required to indicate inherent toxicity to these organisms.

2.2.2 Risks to Aquatic Organisms

With respect to risk to aquatic organisms, risk assessments conducted for the PRVD were re-examined. The risks associated with spray drift into aquatic habitats at the time of application could be mitigated with spray buffer zones. Risks associated with runoff from agricultural fields were based on conservative modelled EECs (Level 1) and no monitoring information is available for ziram. Although the level of concern was exceeded for amphibians (Risk Quotient = 42.3 for acute and 13.4 for chronic risk for maximum application rates to tomatoes), all other risk quotients were less than 10. Due to the conservative modelling scenarios, risks are not expected to have an impact at the population level for aquatic organisms under conditions of use.

3.0 Incident Reports

Since the publication of PRVD2016-06, no human or domestic animal incidents involving ziram were submitted to Health Canada. Also, since the publication of PRVD2016-06, no additional human or domestic animal incident data were available in the United States Environmental

Protection Agency (USEPA) regulations.gov website and the California Environmental Protection Agency's Pesticide Illness database. No environmental incidents involving ziram were located in the USEPA's Ecological Incident Information System (EIIS) database.

Since the publication of PRVD2016-06, there was one environment incident involving ziram in the Health Canada database. The environment incident was classified as major. In this incident, a large number of fish were exposed to several pesticides including ziram when water used to douse a pesticide warehouse fire overflowed into a creek. The active ziram was not analyzed in the samples collected from the creek and hence, there was insufficient information to conclude if this active played a role in the observed fish mortality. Overall, the incident was determined to be possibly linked to other active ingredients that were analyzed in the water samples collected from the creek.

3.0 Value Assessment

Health Canada recognises the value of ziram to fruit crops, including the needfor control and resistance management of pin-point scab on apples, and coryneum blight (shot hole disease) on peaches and apricots in British Columbia.

4.0 Conclusion of Science Evaluation

Health risks have not been shown to be acceptable for any agricultural use when used according to current label directions, or when additional mitigation measures are considered. The environmental risks associated with the use of ziram and its associated end-use products are acceptable when used according to revised label directions. Use of ziram is important for control of fungal diseases and resistance management on many crops.

List of Abbreviations

ADI	Acceptable daily intake
ARfD	Acute reference dose
bw/bwg	Body weight/bodyweight gain
CAF	Composite assessment factor
CARC	Cancer Assessment Review Committee
DACO	Data code
DEEM	Dietary Exposure Evaluation Model
DMCS	N, N dimethyl carbamosulfonic acid
DNT	Developmental neurotoxicity
EBDC	Ethylene bis(dithiocarbamate) pesticides (mancozeb, metiram)
EEC	Estimated environmental concentration
EFSA	European Food Safety Authority
fc	Food consumption
FCID	Food Commodity Intake Database
FOB	Functional Observational Battery
GD	Gestational day
GLP	Good Laboratory Practice
HDT	Highest dose tested
kg	Kilogram
LD	Lactational day
LOAEL	Lowest observed adverse effect level
MDT	Mid-dose tested
mg	Milligram
MOA	Mode of action
MOE	Margin of exposure
MRID	Master Record Identification
MRL	Maximum residue limit
NHANES	National Health and Nutrition Examination Survey
NOAEL	No observed adverse effect level
nss	Not statistically significant
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
PCPA	*Pest Control Product Act*
PMRL	Proposed maximum residue limit
PRVD	Proposed re-evaluation decision
PND	Post-natal day
ppm	Parts per million
RVD	Re-evaluation decision
ss	Statistically significant
TGAI	Technical grade active ingredient
USEPA	United States Environmental Protection Agency
WOE	Weight of evidence
WWEIA	What We Eat in America

Appendix I Registered Agricultural Ziram Products in Canada[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
28426	Technical	Taminco US LLC.	Ziram Technical (98.4%)	Dust	98.4%
29140	Commercial	Loveland Products Canada Inc.	Ziram 85W Fungicide	Wettable powder	85%
29685	Commercial	Taminco US LLC.	Ziram Granuflo	Wettable granules	76%

[1] as of 17 May 2018, excluding discontinued products and products with a submission for discontinuation.

Appendix II Comments and Responses

Following publication of the Proposed Re-evaluation Decision PRVD2016-06, *Ziram*, Health Canada received written comments from the registrants, the public and other stakeholders such as Canadian Horticultural Council. The comments and Health Canada's responses were summarized or grouped together based on common scientific themes and presented below.

1.0 Comments Relating to the Health Risk Assessments

1.1 Comments and Responses Related to Toxicology

Comments related to the toxicology assessment were received from the registrant.

1.1.1 Comment Relating to Endpoint Selection

The registrant requested that the point of departure chosen for the acute reference dose (ARfD) and the chronic dietary reference dose be revised.

The registrant requested that Health Canada reconsider the use of the developmental neurotoxicity (DNT) study NOAEL for all exposure assessment endpoints, in order to be in agreement with the USEPA. The registrant did not support the use of the DNT study to set an ARfD for the general population specifically. Furthermore, the registrant questioned the appropriateness of the duration of exposure in the DNT study and the choice of the DNT study NOAEL as a point of departure for the chronic dietary reference dose.

Response

New information was submitted in response to PRVD2016-06 which impacts the point(s) of departure selection for the ARfD and the chronic dietary reference dose. This information consisted of a new non-guideline DNT study, which supplements the original DNT study, as well as information concerning the lower purity ziram used in some toxicology studies.

As discussed further in the Response to Comment 1.1.4 relating to cancer risk assessment, studies conducted using low purity ziram were excluded from consideration in the hazard characterization of ziram. This affected some studies considered previously in PRVD2016-06 as a basis for the chronic dietary reference dose. The reconsideration of the points of departure for the acute dietary reference dose and the chronic dietary reference dose are discussed further below.

The Health Canada evaluation of the original DNT study identified a maternal NOAEL of 13 mg/kg bw/day, and an offspring LOAEL of 5 mg/kg bw/day at the lowest dose tested. Sensitivity of the young was identified based on the observation of offspring toxicity in the absence of maternal toxicity. This study and offspring LOAEL were utilized for all toxicology reference values identified in PRVD2016-06.

A composite assessment factor/margin of exposure (CAF/MOE) of 1000 was established based on the application of the standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability, as well as a 3-fold uncertainty factor for the lack of NOAEL

and a 3-fold *Pest Control Products Act* factor. Deficiencies were also noted in the conduct of this study.

A new, non-guideline DNT study (PMRA#2647409) was submitted by the registrant, which was an acceptable study but limited, as this new study was designed to address the deficiencies previously noted in the original DNT study (USEPA review: PMRA# 252231).

In the new study, the total motor activity and ambulatory activity were affected more consistently than in the original study, with statistical significance achieved in the mid- and high-dose groups starting on postnatal day (PND) 17. Young males were more sensitive to these effects than females. Habituation was achieved; however the baseline occurred at a higher activity level for mid- and high-dose animals, especially males, than the concurrent control. Brain morphometry data showed clear effects in the mid- and high-dose groups, with males being affected at a lower dose than females.

At the same dose level and above, maternal effects included decreased body weight, body weight gain, and food consumption. A NOAEL of 5 mg/kg bw/day was identified for maternal animals and a conservative LOAEL was identified at the same dose for the offspring based on a slight, non-statistically significant, decrease in body weight in males on PND 21. However, given the marginal response and nature of the effect, the level of concern for sensitivity of the young, relative to parental animals in this new DNT study, was low. Although the original DNT study identified an offspring LOAEL of 5 mg/kg bw/day based on increased motor activity in all treatment levels, motor activity was not affected at this dose in the new DNT study which had more robust and clear motor activity data.

Thus, taking into consideration the strength of results in both of the DNT studies, an overall NOAEL of 5 mg/kg bw/day for maternal and offspring was determined, with no indication of overt sensitivity of the young. The brain morphometry effects in the new DNT study were considered serious effects observed in the presence of maternal toxicity. The *Pest Control Products Act* factor was retained at threefold for seriousness of effect in the presence of maternal toxicity when the combined DNT studies were used for end-point selection. The *Pest Control Products Act* Hazard Characterization is discussed in more detail in the Response to Comment 1.1.2 relating to the uncertainty factors and *Pest Control Products Act* hazard characterization.

With respect to the reconsideration of the point of departure chosen for the ARfD, endpoints considered to have resulted from an acute exposure were identified in the acute neurotoxicity study (ataxia and impaired gait in males, minimal FOB effects at LOAEL = 15 mg/kg bw/day), and in the offspring of the combined DNT studies (brain morphometry changes in males, increased motor activity, with NOAEL = 5 mg/kg bw/day).

Results from the two DNT studies pertain to findings in the most sensitive life-stages and can apply to acute and longer durations of exposure for various populations, since even a single exposure during a critical point of gestational or post-natal development could lead to a permanent treatment-related effect in the fetus or the young. OECD Guidance Document 124 states that evidence of neurotoxicity should be considered relevant to setting an ARfD for all/various populations, unless it can be demonstrated that the effects occur after repeated dosing only. In the ziram toxicity database, there was insufficient information to determine whether the findings observed in the DNT study resulted from a single or repeated dose. Thus, these effects

were considered relevant for setting an ARfD for all populations since the DNT study spans various lifestages. The effects noted on motor and ambulatory activity, habituation and brain morphometry are considered relevant to the general population, including the young.

The revised ARfD was derived from both developmental neurotoxicity studies for which an overall developmental NOAEL of 5 mg/kg bw/day was established. A composite assessment factor (CAF) of 300-fold was applied, including standard uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability, as well as a 3-fold *Pest Control Products Act* factor (as discussed in Response to Comment 1.1.2). This endpoint selection is supported by the acute neurotoxicity rat study with LOAEL = 15 mg/kg bw/day based on ataxia, impaired gait (males), and minimal FOB effects.

The revised ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5 \text{ mg/kg bw}}{300} = 0.017 \text{ mg/kg bw of ziram}$$

This ARfD is considered protective of all sub-populations, including infants and children.

For the chronic assessment, as mentioned in PRVD2016-06, 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 dietary studies in rodents. Slight anemia, increased haematopoiesis, and elevated liver enzyme activity were typically observed in rats. Chronic effects of note 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 delayed closure of the epiphyseal plate in the rats.

With respect to the reassessment of the point of departure chosen for the chronic dietary reference value (ADI), endpoints considered to have resulted from chronic exposure were identified in: a chronic rat study (Maita, NOAEL of 0.7 mg/kg bw/day), a 2 year dietary rat study (Powell, LOAEL of 2.5 mg/kg bw/day), an 80-week dietary mouse oncogenicity study (LOAEL of 3 mg/kg bw/day) and a 1-year oral dog study (NOAEL of 1.6 mg/kg bw/day). The combined DNT studies were also considered since, as mentioned previously, treatment-related findings pertain to the most sensitive life-stages and can apply to acute and longer durations of exposure.

The revised chronic dietary reference value was based on the chronic dietary rat study (Maita) with a NOAEL of 0.7 mg/kg bw/day, the lowest NOAEL in the database, and a CAF of 100. (This study was also the basis of the long-term duration occupational endpoint with a target MOE of 100).

The revised ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.7 \text{ mg/kg bw/day}}{100} = 0.007 \text{ mg/kg bw/day of ziram}$$

This ADI provides a margin of 714 to the NOAEL of 5 mg/kg bw for altered brain morphometric parameters and increased motor activity noted in the DNT study.

Based on the consideration of the new information and comments submitted in response to PRVD2016-06, and as discussed above, the Toxicology Reference Values were revised and are presented in Appendix III, Table 1.

1.1.2 Comment Relating to the Uncertainty Factors and *Pest Control Products Act* Hazard Characterization

The registrant suggested that the magnitude of the Pest Control Products Act uncertainty factor (threefold) applied in PRVD2016-06 should be reduced to onefold. This comment was based on the registrant's characterization of the completeness of the database and the lack of identified sensitivity of the young or residual uncertainty as a result of the submission of the second DNT study.

Response

Health Canada has revisited the *Pest Control Products Act* hazard characterization presented in PRVD2016-06 in light of the new data and comments submitted to Health Canada.

In PRVD2016-06, a threefold *Pest Control Products Act* factor was retained based on motor activity changes and the lack of morphometric data in the original DNT study. The newly submitted DNT study has addressed the data deficiencies noted in the original DNT study. The brain morphometry effects observed in the new DNT study are considered serious effects; however, the level of concern for these findings is tempered by the presence of maternal toxicity at the same dose level. Taking into consideration the strength of results in both of the DNT studies, an overall NOAEL of 5 mg/kg bw/day for dams and offspring was determined, with no indication of sensitivity of the young. The original DNT study identified a developmental LOAEL of 5 mg/kg bw/day based on increased motor activity; however, this effect was not confirmed in the new DNT study at the same dose level. The new DNT study showed a slight reduction in male body weights on PND 21 which reached statistical significance, only at a higher dose.

Based on the above noted considerations, and those previously outlined in the *Pest Control Products Act* Hazard Characterization section of PRVD2016-06, when establishing a reference dose based upon effects noted in the combined DNT studies, a threefold *Pest Control Products Act* factor was retained. The retention of the threefold *Pest Control Products Act* factor for seriousness of effect (brain morphometry changes), in the presence of maternal toxicity, is consistent with Health Canada's routine application of SPN2008-01: The Application of Uncertainty Factors and the *Pest Control Products Act* Factor in the Human Health Risk Assessment of Pesticides.

1.1.3 Comment Relating to Evaluation of Mutagenicity

The registrant commented that a weight of evidence approach (WOE) for attributing genotoxic potential to a compound, as "discussed recently for genetic toxicology testing" (USFDA, 2006; Dearfield et al, 2011), indicates that ziram is not mutagenic.

The registrant noted that the only evidence of a mutagenic effect was in a single bacterial strain, while the results of in vitro mammalian cell studies and an in vivo study in mice were negative. The registrant suggested, in agreement with the USEPA (2003), that when NTP studies were excluded as "unacceptable in vitro" studies, there was no mutagenic concern for ziram. Two new genotoxicity studies were submitted by the registrant in response to PRVD2016-06: The registrant suggested a selection of six studies be used in a revised WOE consideration of genotoxicity potential.

The registrant also noted limitations in many genotoxicity studies used by Health Canada. These studies were from the published scientific literature and, in some cases, did not include positive controls, or purity of the tested material, the methods and results were poorly reported and/or not confirmed in a second experiment, and were not conducted in accordance with Good Laboratory Practices regulations (GLP).

Response

The genotoxic potential of ziram was assessed in PRVD 2016-06 using a variety of bacterial and mammalian in vitro and in vivo genotoxicity studies with ziram of varying purity (~86% to 98.5% or unreported). After receiving additional information regarding the history and source of the low purity ziram used in some toxicology studies, Health Canada excluded genotoxicity studies conducted with lower purity ziram from the revised WOE genotoxicity assessment. The current international manufacturing standard for ziram is for high purity (~98%) product. The studies that utilized ziram of unknown purity were retained as supplemental information. Health Canada agrees with the registrant's comment that many studies show negative genotoxicity results for ziram. Nevertheless, Health Canada has noted that positive genotoxicity results were found among the studies that used high purity ziram. For example, Mosesso et al. (1994, PMRA#1900467), in a GLP study with a positive control, noted evidence of increased structural chromosome aberrations in CHO and CHEL cells exposed in vitro to ziram (98.5% purity). Ardito et al. (1997, PMRA#1900465) reported that ziram (98% purity) induced a significant increase in micronuclei frequencies in in vitro human lymphocytes. Some supplemental studies also showed positive results. In a recent USEPA scoping document (2015) for ziram, two published genotoxicity studies showed positive genotoxicity results for ziram: a chromatid exchange test in Chinese Hamster Ovary Cells in vitro by Gulati (1989, positive for chromosomal aberrations (±S9), and a mouse lymphoma cell assay by McGregor et al., (1988, positive for gene mutation induction (-S9)). Health Canada examined these during initial evaluation, but very limited data and protocol details were available for these studies.

Two new genotoxicity studies were submitted by the registrant for review: Mammalian cell mutation assay (1999) (PMRA#2647411) and a dietary peripheral blood micronucleus test in the mouse (1992) (PMRA#2647412). The mammalian cell mutation assay (PMRA#2647411) was considered negative for mutagenic response. The in vivo cytogenetics study (PMRA#2647412) was considered unacceptable due to the lack of a positive control, inadequate dose levels, and use of non-standard procedures.

Overall, in studies using high purity ziram, ziram may have some mutagenic and clastogenic activity, although there is uncertainty concerning its potential for other types of genotoxicity due to the mixed results obtained in assays that were considered acceptable and devoid of limitations.

For thiram, a related chemical and metabolite of ziram, Health Canada reached a similar conclusion regarding its genotoxic potential.

1.1.4 Comment Relating to Cancer Risk Assessment

The registrant suggested that the NTP cancer study in rats (2 year rat: PMRA#1122400) should not be included in the carcinogenicity WOE for ziram, as the study was not conducted in compliance with GLP regulations, and only two dose levels with lower purity ziram were used. It was additionally noted that historical control data from two-year carcinogenicity studies conducted in 1994 showed higher spontaneous rates of thyroid c-cell adenomas/carcinomas. The registrant stated that newer cancer studies with higher purity ziram do not show increased incidence of thyroid tumours and mutagenicity studies were negative. The USEPA classified ziram as "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" (CARC, 2003), and recommended against the use of a linear cancer risk assessment approach.

Of note, the USEPA conclusion was not changed in the scoping document (2015) and the USEPA has "determined that quantification of risk using a non-linear approach (RfD, MOE based WOE approach) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to ziram".

Response

Based on the additional information submitted in response to PRVD2016-06 regarding the history and source of low purity ziram, and the current manufacturing standard, Health Canada excluded the NTP cancer studies, which tested low purity ziram, from consideration in a revised carcinogenicity WOE assessment.

Two chronic dietary studies in rats and one in mice (PMRA#1900463; 1900457; 1210409) were retained for carcinogenicity hazard assessment.

In an oncogenicity dietary mouse study, liver histopathology (enlargement, vacuolation), and decreased food consumption (females) were noted at all doses tested, however there was no evidence of oncogenicity in the study.

A chronic dietary toxicity study in SD rats (purity 98.7%, Powell, 1994; PMRA#1210432, USEPA MRID 43404201) showed evidence of oncogenicity with an increased incidence of benign tumors (hemangioma) in the spleen and in the mesenteric lymph nodes of high-dose group males. The incidence of these benign neoplastic changes at the high-dose was statistically significantly increased ($p<0.05$) compared to concurrent and historical controls. This study was included in the previous Health Canada assessment, however the thyroid c-cell tumours noted in the NTP cancer study (now excluded) supported a higher (more conservative) cancer slope factor. Thus the hemangiomas were not used as the basis for the cancer risk assessment described in PRVD2016-06. In a second chronic dietary toxicity study in Fisher rats (purity 97.5%, Maita, 1997; PMRA# 1900457, USEPA MRID # 45770201), male rats had a statistically significant increasing trend for the incidence of preputial gland adenomas; the incidence in the high-dose group exceeded the range of historical controls. Additionally, the incidence of preputial glandular hyperplasia at the high-dose exceeded the historical control.

In absence of a valid mode of action (MOA) addressing the observed hemangiomas and their relevance to humans, and a residual concern for genotoxicity, the oncogenicity potential of ziram could not be dismissed. Therefore, a linear low dose extrapolation (q_1*) assessment based on the combined mesenteric lymph node and spleen hemangiomas in a chronic/carcinogenicity study in male rats was conducted. The calculated q_1* value for this tumour incidence was 1.82×10^{-2} $(mg/kg\ bw/day)^{-1}$.

1.2 Comments and Responses Related to Dietary Exposure

The registrant did not provide specific comments on the dietary risk assessment for ziram presented in the PRVD2016-06, but cited their comments on the dietary risk assessment for thiram presented in the PRVD2016-07. Thus, the Health Canada responses to the submitted comments for thiram also apply to ziram. However, certain comments need to be addressed separately; responses related to ziram are provided below. Please refer to the thiram RVD for other comments and responses.

1.2.1 Comments Concerning Processing Factors for Tomato Puree and Juice

The registrant commented on the default concentration factors from DEEM used by Health Canada in the absence of processing studies. The registrant indicated that the one apple washing and processing study available shows considerable reduction in residues from washing (0.21×), and making juice (0.12×) and puree (0.18×). The same study showed concentration in dried apples. Although these factors cannot be applied directly to a commodity like tomato, the study does show that thiram is likely to wash off of tomatoes, and to not concentrate in juice or puree. In the dietary assessment conducted by the registrant, the processing factors for both tomato juice and puree were set to 1.0 instead of using the default factors of 1.5 and 3.3, respectively, while the default processing factors for tomato paste and dried tomatoes were applied.

The registrant had previously submitted a processing study conducted with ziram on tomatoes.

Response:

Ziram-specific processing factors obtained from the tomato processing study of ziram, submitted previously by the registrant, were used in the present dietary risk assessment for tomato paste (0.6× and 0.5× for acute and chronic, respectively), and tomato puree (0.34× and 0.3× for acute and chronic, respectively). There are no ziram-specific data for the dried tomato; therefore, the default processing factor was applied in the present dietary risk assessment. For tomato juice, PMRA agrees with the registrant's proposal and applied a processing factor of 1.0.

1.2.2 Comment Concerning the Dietary Exposure and Risk Assessments

a) Acute Dietary Exposure Estimation

The registrant did not propose detailed refinements for the dietary exposure assessment for ziram, but stated that the dietary assessment they had conducted for thiram would be applicable for ziram. It was noted that the registrant's assessment for thiram exceeded the acute reference dose for thiram.

Response:

Health Canada's 2016 assessment used Canadian MRLs of ziram and field trial data of ziram and/or thiram as residue inputs for the exposure estimation. Therefore, further refinements were considered in the revised dietary assessment for food and drinking water. However, despite these refinements, acute and chronic dietary risks were not shown to be acceptable. See Appendix IV for further information on the dietary assessment.

1.3 Comments and Responses Related to Occupational Exposure

1.3.1 Dermal Absorption

The registrant commented that the dermal absorption value of 50% selected by Health Canada is conservative. To refine the dermal absorption value, a human in vitro dermal absorption study was submitted.

Response:

For PRVD2016-06, no dermal absorption studies for ziram were available; therefore, a dermal absorption value of 50% was established based on the physical/chemical properties of the active ingredient (solubility, physical state, molecular size). As all food uses are cancelled due to dietary risks, the occupational risk assessments from PRVD2016-06 were not revisited for these uses.

Although the occupational risk assessments (food use and material preservative uses) were not updated as part of the RVD, the dermal absorption value was updated based on the data submitted in response to PRVD2016-06. These dermal absorption values will be considered in the revised risk assessment for the material preservative uses that will be conducted under REV2018-02, 'Approach for the Re-Evaluation of Pesticides Used as Preservatives in Paints, Coatings and Related Uses'.

To update the dermal absorption value for the material preservative use of ziram, Health Canada considered a wide range of information: the dermal absorption study submitted by the registrant, a rat in vivo dermal absorption study, and rat metabolism data. In addition, a comparison of the dose solution used in the dermal absorption studies with commercial-class ziram product solutions being handled for the material preservative scenarios was also considered.

Based on the high dose group in the rat in vivo study, a dermal absorption value of 2% was selected for workers mixing/loading the commercial-class dust product during the manufacture of impregnated adhesives. For scenarios where the impregnated adhesive products are being handled or for potential post-application scenarios, a dermal absorption value of 30% was selected from the low dose group in the rat in vivo study. These values are supported by the human in vitro data and are considered to be protective, given the conservatisms in the supporting data.

These dermal absorption values will be considered in the revised risk assessment for the material preservative uses that will be conducted under REV2018-02, *Approach for the Re-Evaluation of Pesticides Used as Preservatives in Paints, Coatings and Related Uses*.

1.3.2 Use Pattern Information

During the PRVD2016-06 consultation period, the registrant and the Canadian Horticulture Council provided information on the agricultural use pattern of ziram (such as, application rates, timing of application).

Response:

Use pattern information is important in the refinement of occupational risk assessments. However, as discussed in Section 1.2, dietary risks of concern were identified for all food uses of ziram. Therefore, the occupational and residential risk assessments from PRVD2016-06 were not revisited for these crops.

2.0 Comments Relating to the Value Assessment

In response to the proposed re-evaluation decision consultation for ziram, comments related to value were received from Loveland Products and the Canadian Horticultural Council.

2.1 Comment: Ziram is Important for Sustainable Disease Management

The use of ziram is part of a system approach to disease management in tree fruit and field vegetables and is of critical importance to sustainable disease management. Ziram, along with other multi-site fungicides, are essential as rotational fungicides to manage pathogen resistance in those populations where resistance has been reported. Although ziram is a low-use fungicide in Canada, this active does have an important place in sustainable disease management.

Response

Health Canada acknowledges the importance of ziram in sustainable disease management, including the need for management of pin-point (late season) scab on apples, and coryneum blight (shot hole disease) on apricots and peaches in British Columbia. However, there are a number of fungicides from different mode of action groups, including the multi-site fungicides captan and folpet that are registered to manage late season scab. Health Canada also acknowledges that there are only two alternative active ingredients, copper and trifloxystrobin, available for control of coryneum blight on apricots and peaches in British Columbia.

The use of ziram on field vegetables is minimal. A number of other alternatives including the multi-site fungicides: copper, sulphur, captan, folpet and chlorothalonil, are registered for control of most of the labelled diseases on field vegetables. Growers may use these fungicides for disease control and resistance management.

Appendix III Updates to Toxicology Reference Values for Risk Assessment

Table1 Revised Toxicology Reference Values for Ziram Health Risk Assessment

Exposure Scenario	Point of Departure and Endpoint	Study	CAF or MOE[1]
Acute dietary (All populations)	NOAEL = 5 mg/kg bw/day brain morphometry changes (males), increased motor activity (Supported by acute neurotoxicity rat study with LOAEL = 15 mg/kg bw/day based on ataxia, impaired gait (males), minimal FOB effects)	Developmental neurotoxicity studies in rats	300
	ARfD = 0.017 mg/kg bw		
Chronic dietary (All populations)	NOAEL = 0.7 mg/kg bw/day anemia, increased organ weights (thyroid, liver, spleen), histopathological changes (forestomach, thyroid), degeneration of the sciatic nerve and calf muscle, retarded closure of epiphyseal plate of crus	2-year rat dietary study (Maita) with supporting studies:	100
	LOAEL = 2.5 mg/kg bw/day reduced RBC, splenic hemosiderosis, non-glandular epithelium hyperplasia of stomach, subepithelial edema of stomach, effect on skeletal muscle, hypertrophy with vacuolation of adrenal cortex (males), increased incidence of cysts in the thyroid (females)	2-year rat dietary study (Powell),	
	LOAEL = 3 mg/kg bw/day liver histopathology (enlargement, vacuolation), decreased fc (females)	80-week mouse dietary oncogenicity study,	
	NOAEL = 1.6 mg/kg bw/day decreased body weight gain (females), liver histopathology (males)	and a 1-year dietary dog study	
	ADI = 0.007 mg/kg bw/day		
Occupational short- and intermediate-term dermal and inhalation	NOAEL = 5 mg/kg bw/day brain morphometry changes (males), increased motor activity (Supported by acute neurotoxicity rat study with LOAEL = 15 mg/kg bw/day based on ataxia, impaired gait (males), minimal FOB effects)	Developmental neurotoxicity studies in rats	300
Occupational long term dermal	NOAEL = 0.7 mg/kg bw/day anemia, increased organ weights	2-year rat dietary study (Maita) with Co-critical studies:	100

Exposure Scenario	Point of Departure and Endpoint	Study	CAF or MOE[1]
and inhalation	(thyroid, liver, spleen) , histopathological changes (forestomach, thyroid), degeneration of the sciatic nerve and calf muscle, retarded closure of epiphyseal plate of crus LOAEL = 2.5 mg/kg bw/day reduced RBC, splenic hemosiderosis, non-glandular epithelium hyperplasia of stomach, subepithelial edema of stomach, effect on skeletal muscle, hypertrophy with vacuolation of adrenal cortex (males), increased incidence of cysts in the thyroid (females) LOAEL = 3 mg/kg bw/d liver histopathology (enlargement, vacuolation), decreased fc (females) NOAEL = 1.6 mg/kg bw/d decreased body weight gain (females), liver histopathology (males)	2-year rat dietary study (Powell), 80-week mouse dietary oncogenicity study, and a 1-year dietary dog study	
Residential short-term dermal and inhalation	NOAEL = 5 mg/kg bw/day brain morphometry changes (males), increased motor activity (Supported by acute neurotoxicity rat study with LOAEL = 15 mg/kg bw based on ataxia, impaired gait (males) and minimal FOB effects)	Developmental neurotoxicity studies in rats	300
Short-term dermal and inhalation aggregate	NOAEL = 5 mg/kg bw/day brain morphometry changes (males), increased motor activity (Supported by acute neurotoxicity rat study with LOAEL = 15 mg/kg bw based on ataxia, impaired gait (males), minimal FOB effects)	Developmental neurotoxicity studies in rats	300
Cancer	$q_1^* = 1.82 \times 10^{-2}$ $(mg/kg\ bw/day)^{-1}$ Based on incidences of combined mesenteric lymph node and spleen benign hemangiomas in a chronic/carcinogenicity study in rats		

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

Table 2 Summary of Newly Submitted Toxicity Studies by the Registrant.

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Neurotoxicity Studies	
Developmental Neurotoxicity Oral (diet) Rat (SD) 25/sex/group PMRA# 2647409 MRID 47900401	**Maternal:** NOAEL = 5 mg/kg bw/day No signs of toxicity or neurobehavioral alterations in dams. ≥13 mg/kg bw/day: ↓ bw, bwg GD 0-20 during gestation and lactation 27 mg/kg bw/day: ↓ overall fc **Developmental:** A LOAEL = 5 mg/kg bw/day **Combined DNT studies NOAEL (PMRA# 2647409 and 252231) = 5 mg/kg bw/day** ≥5 mg/kg bw/day: ↓ bw (PND 21 nss) (♂) ≥13 mg/kg bw/day: ↓ bw (PND 21), ↑ motor activity (PND 21 and 61); ↓ abs brain wts (ss PND 21 and 72, PND 72 at HDT), ↓ level 3 radial thickness cortex (PND 21), level 4 length of ventral limb dentate hilus (PND 21 MDT, PND 21 and PND 72 nss HDT) (♂) 27 mg/kg bw/day: ↓ brain wt (ss PND 72), ↓ brain length (PND 21 (♂) PND 72 (♀)); ↑ incidence of runts (11/6 vs 5/2 in control), ↓ brain width (PND 21); equivocal ↑ ectopic basal ganglia (PND 72) (♂);↓ level 1 height of hemisphere (ss PND 72), ↓ level 3 radial thickness cortex (nss PND 72) (♀) **No sensitivity of the young (combined DNT studies)**
Genotoxicity Studies	
In vitro mammalian cell assay (TK +/-) Mouse lymphoma cells PMRA# 2647411	**Negative** Note: Ziram induced mutation frequency of 3.77×10^{-4} (ss) vs 1.79×10^{-4} in solvent control at 2 µg/mL in absence of metabolic activation in the first test, with only 30% of relative survival. This result was however not reproducible at this dose in the second test as relative survival (%) differed.
In vivo cytogenetics Micronucleus assay in mice (CD-1) PMRA# 2647412 (animals from PMRA#1210409)	**Unacceptable study** No positive control, no SD There was not a significant ↑ in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time in this study.

Appendix IV Revised Dietary Exposure and Risk Estimates

The dietary exposure and health risk assessment was revised as follows:

1) Updated toxicological reference values and potency factor for ziram.
2) In addition to an assessment that included all currently registered food uses, each food use was also assessed separately.
3) Field trial data of ziram and monitoring data from the Canadian Food Inspection Agency (CFIA) were used to refine the dietary exposure and risk assessment.
4) For both the acute and chronic assessments, updated percent crop treated estimates and percent domestic/import food supply information were used to adjust the available residue data.
5) Refined drinking water estimated environmental concentrations (EECs) were used in the risk assessment.
6) The acute and chronic dietary assessments for ziram were conducted using the latest version of the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02, 05-10-c) program, which incorporates food consumption data from the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) dietary survey for the years 2005-2010 available through Centers for Disease Control and Prevention's National Center for Health Statistics.

When all uses were included in the dietary assessment, acute, chronic and cancer risks were not shown to be acceptable. Therefore, each use was assessed separately in the dietary assessment.

- For apples, dietary risks were not shown to be acceptable from exposure through food alone, or drinking water alone (i.e., exposure to residues in drinking water that result from applying ziram in apple orchards was not shown to be acceptable).
- For apricots and peaches, dietary risks were not shown to be acceptable from exposure through drinking water alone.
- For tomatoes, dietary risks were not shown to be acceptable from exposure through drinking water alone.
- For cucurbits, dietary risks were not shown to be acceptable from exposure through drinking water alone.

Health risks were not shown to be acceptable, despite the refinements considered and the high level of mitigation applied in the revised dietary assessment. Therefore, cancellation of all registered food uses and revocation of all MRLs for ziram are required.

References

A. Information Considered in the updated Health Assessment

Toxicology

List Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2647411	(1999). Ziram technical: Mammalian cell mutation assay Huntingdon Life Sciences, Ltd. For Ziram Task Force. DACO 4.5.5
2647412	(1992) Ziram (technical): Peripheral blood micronucleus test in mouse after 89 days of dietary exposure. Proudlock and Taylor. Ziram Task Force. DACO 4.5.7
2647409	(2009) A dietary developmental neurotoxicity study of ziram in rats. WIL Research Laboratories, LLC for Ziram Task Force. DACO 4.4.14

Additional Information Considered

Published Information

PMRA Document Number	Reference
2759088	Marquea D. King, Ph.D et al. Ziram Scoping Document. (September 1, 2015) Office of Chemical Safety And Pollution Prevention. EPA. DACO 12.5.4
2860990	2001, USEPA (U.S. Environmental Protection Agency). The determination of whether dithiocarbamate pesticides share a common mechanism of toxicity, DACO 12.5.4
	NAFTA technical working group on pesticides' Developmental Neurotoxicity Study (DNT) guidance document. DACO 12.5.4 { https://www.epa.gov/sites/production/files/2017-02/documents/developmental_neurotoxicity_study_internal_guidance_document_final_0.pdf }
2907220	Gulati, D. K., Witt, K., Anderson, B., Zeiger, E. and Shelby, M. D. (1989) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro III: Results with 27 chemicals. Environ Mol Mutagen 13:133-193.
2907216	McGregor, D. B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C. and Caspary, W. J. (1988). Responses of the L5178Y TK^{+}/TK^{-} mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen 12: 85-154.

Unpublished Information

PMRA Document Number	Reference
2759086	(2003). Jessica Kidwell. Ziram: Second Report of the Cancer Assessment Review Committee.

Dietary
Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1129401	Ziram: Magnitude of Residue on Tomatoes (Summary Information)
1129402	Ziram: Magnitude of Residue on Tomatoes
1129406	Ziram: Magnitude of Residue on Tomatoes (Summary Information)
2646650	Registrant Comments for the Consultation on Thiram, Proposed Re-Evaluation Decision PRVD2016-07.
2647407	Registrant Comments for the Consultation on Ziram, Proposed Re-Evaluation Decision PRVD2016-06.

Additional Information Considered

Published Information

PMRA Document Number	Reference
2906733	Cajka, T., Riddellova, K., Zomer, P., Mol, H. and Hajslova, J. 2011. Direct analysis of dithiocarbamate fungicides in fruit by ambient mass spectrometry, Food Additives & Contaminants: Part A, 28:10, 1372-1382, DOI: 10.1080/19440049.2011.590456.
2906734	CFIA. 2014. National Chemical Residue Monitoring Program 2012-2013 Report.
2907099	EFSA. 2016. Draft Renewal Assessment Report Prepared According to Regulation (EC) NO 1141/2010: Ziram.
2907100	EFSA. 2017. Public consultation on the active substance ziram.
2906740	Schmidta, B., H.B. Christensena, A. Petersena, J.J. Slotha and M.E. Poulsena, 2013. Method Validation and Analysis of Nine Dithiocarbamates in Fruits and Vegetables by LC-MS/MS. Food Additives & Contaminants Part A, 30(7): 1287-1298.
2907101	USEPA. 2014. Ziram (034805) Screening Level Usage Analysis (SLUA) Date: 20 June 2014. EPA-HQ-OPP-2015-0568-0007.
2907102	USEPA. 2015. Ziram Final Work Plan. EPA-HQ-OPP-2015-0568-0015.

Occupational and Residential Assessment
List Studies/Information Submitted by Registrant

PMRA Document Number	Reference
2647410	2006, ZIRAM (76 WG) IN VITRO DERMAL PENETRATION STUDY AT TWO DOSE LEVELS USING HUMAN SKIN, DACO: 5.8
1210449	1991, Dermal Absorption of 14C- Ziram in Male Rats, DACO: 4.3.8