Overview of Ziram
Risk Assessment

February 21, 2002

Introduction

This document summarizes EPA's human health and ecological risk findings and conclusions for the fungicide ziram, as presented fully in the documents, "Ziram: Human Health Risk Assessment" dated January 29, 2002, "Environmental Fate and Effects Division Preliminary Risk Assessment for the ziram Reregistration Eligibility Decision Document" dated October 23, 2001, and "Revised Tier II Surface Drinking Water Assessment for Human Health Risk for Ziram" dated January 24, 2002. The purpose of this summary is to assist the reader by presenting the key features and findings of these risk assessments, and to enhance understanding of the conclusions reached in the assessments. This overview was developed in response to comments and requests from the public which indicated that risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

The risk assessments noted above as well as the supporting documents, are available on EPA's Internet site (www.epa.gov/pesticides/reregistration/ziram.htm) and in the Pesticide Docket for public viewing. Meetings with stakeholders (i.e., growers, extension personnel, commodity groups, and other government officials) are planned to discuss the identified risks and to solicit input on risk mitigation strategies. This feedback will be used to complete the Reregistration Eligibility Decision (RED) document, which will include the risk management decisions. The Agency plans to conduct a closure conference call with interested stakeholders to discuss the regulatory decisions presented in the RED.

The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Although it is possible that ziram may express toxicity through a common mechanism with other compounds, at this time, the Agency does not have sufficient reliable information to make this determination. Consequently, the risks summarized in this document are only for ziram. If EPA identifies other substances that share a common mechanism of toxicity with ziram, aggregate exposure assessments will be performed on each chemical followed by a cumulative risk assessment.

Use Profile

- **Fungicide and antimicrobial:** Ziram is a dimethyldithiocarbamate fungicide used to control fungal diseases on stone fruits, pome fruits, nut crops, vegetables and ornamentals. It is used to prevent crop damage in the field and is also applied prior to harvesting in order to prevent fruits from deterioration in storage or transport. Additionally ziram is used as a preservative in adhesives, caulks, sealants, wallboard, and interior latex paint (in-can-preservative). It is also registered for residential use as a rabbit repellant on outdoor ornamentals.

- **Formulations**: Ziram formulations include dry flowable, wettable powder and liquid formulations. Common trade names: Ziram®.

- **Methods of Application**: Ziram may be applied by groundboom, aerial, and airblast sprayers along with hand-held equipment for ornamental uses. For the rabbit repellent, applications may be made using hand-held equipment.

- **Use Rates**: Application rates range from 1.52 lb ai/acre on ornamentals up to 6.08 lb ai/acre for agricultural crops (dormant peach rate of 7.6 lb ai/acre). Antimicorbial use rates are from 0.185 to 0.5 percent in adhesives and wallboard, and up to 3 percent in paints.

- **Annual Poundage:** About 20-26 million pounds of ziram per year are used on approximately 500,000 acres of cropland. Approximately 26% is used on pears, 20% on almonds, 19 % on apricots and 13% on nectarines. About 22 % is used on the remainder of categories.

- **Classification:** General use pesticide

- **Technical Registrants**: CerexAgri, RT Vanderbildt Company, UCB Chemicals

Hazard

Ziram is moderately toxic via oral and inhalation routes and has low toxicity via the dermal route. It is not irritating to the skin but is a severe eye irritant. It is a moderate dermal sensitizer.

The mechanism of ziram-induced toxicity has not been fully investigated. The primary target organs of ziram appear to be the nervous system, liver, and thyroid. A single oral dose causes neurological impairments (ataxia and impaired gait) while repeated short term exposure results in inhibition of brain cholinesterase and brain neurotoxic esterase in rats. Liver effects, sometimes including increases in hepatic serum enzyme levels, were seen at various doses in several studies. When administered orally, ziram is rapidly absorbed, distributed, and excreted within 72 hours with a negligible amount being distributed throughout the body. The tissue

distribution and excretion data suggests minimal dermal absorption, and a 1% dermal absorption factor was applied to the residential and occupational dermal exposure estimates.

While there was no evidence of increased susceptibility in standard developmental and reproductive toxicity studies, there was quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats. Ziram is classified as "likely to be carcinogenic in humans" under the 1999 Draft Agency Cancer Guidelines. It is mutagenic in the Ames test but non-mutagenic in unscheduled DNA synthesis and in vivo mutagenicity assays.

Human Health Risk Assessment

Risks from dietary exposure (food and drinking water), residential exposure, aggregate exposures, and occupational exposures have been evaluated for ziram. The following table summarizes the toxicological endpoints and doses that were used to complete the human health risk assessments for ziram.

Table 1. Summary of Doses and Toxicological Endpoints for Ziram

Exposure Scenario	Dose (mg/kg/day)	Endpoint	Study
Acute Dietary (Gen. Population)[1,2]	NOAEL = 15 UF = 300 FQPA SF = 3	Ataxia and slight impairment of gait	Acute Oral Neurotoxicity/Rat
		Acute RfD (Gen. Population)= 0.005 mg/kg Acute Population Adjusted Dose (aPAD) = 0.017 mg/kg/day	
Chronic Dietary	NOAEL = 1.6 UF = 300 FQPA SF = 3	Decreased body weight gain at a LOAEL of 6.6 mg/kg/day	52-Week Oral Toxicity/ Dog
		Chronic RfD = 0.016 mg/kg/day Chronic Population Adjusted Dose (cPAD) = 0.005 mg/kg/day	
Cancer	$Q_1^* = 6.11 \times 10^{-2}$ (mg/kg/day)$^{-1}$	Increase in the incidence of male rat thyroid c-cell adenomas and/or carcinoma	2-year oral rat study
Dermal, Short- and Intermediate-Term [3,4]	NOAEL= 7.5 MOE = 100 (Occupational) and 300 (Residential)	Increased incidence of resorptions and post implantation loss	Prenatal Oral Developmental/ Rabbit
Dermal, Long-Term	NOAEL = 1.6 MOE = 100 (Occupational) and 300 (Residential)	Decreased body weight gain at a LOAEL of 6.6 mg/kg/day	52-Week Oral Toxicity/ Dog
Inhalation, Short-and Intermediate-Term	NOAEL= 7.5 MOE = 100 (Occupational)[5] and 300 (Residential)	Increased incidence of resorptions and post implantation loss	Prenatal Developmental/ Rabbit
Inhalation, Long-Term	NOAEL = 1.6 MOE = 100 (Occupational) and 300 (Residential)	Decreased body weight gain at a LOAEL of 6.6 mg/kg/day	52-Week Oral Toxicity/ Dog

1. The dose and endpoint for the population subgroup Females (13-50) is not selected for risk assessment because the aPAD for Acute Dietary exposure (0.017 mg/kg) for general population is protective of developmental effects which are selected as an endpoint for Females (13-50) (aPAD =0.025 mg/kg).
2. FQPA SF of 3x for all dietary and residential exposure/risk assessments was applied.
3. The appropriate dermal (1%) or inhalation absorption factor (100%) was used since the NOAEL is from an oral study.
4. Residential MOE (Margin of Exposure) - 100 x SF 3x=300; occupational MOE for all durations = 100
5. The dermal and inhalation MOEs for the occupational exposure of short-term duration as well as for intermediate-term duration are combined because the toxicological effects are the same (increased incidence of resorptions and post implantation loss).

The Uncertainty Factor (UF) used in the risk assessments is 100 to account for both interspecies extrapolation (10X) and intraspecies variability (10X). An FQPA safety factor is required for all population subgroups when assessing dietary and residential exposures of all durations since there is quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats. The FQPA Safety Factor was reduced to 3x because: there is no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure to rats and rabbits and/or following pre-/postnatal exposure to rats in the standard developmental and reproduction studies with ziram; and the dietary (food and drinking water) and residential exposure assessments will not underestimate the potential exposure for infants, children, and/or women of childbearing age.

Dietary (Food) Risk Assessments for Ziram

There are currently 51 food commodity tolerances for residues of ziram in/on plant commodities [40 CFR §180.116], expressed in terms of ethylenebisdithiocarbamate.

The acute dietary probabilistic assessments conducted using the Dietary Exposure Evaluation Model (DEEM™) reflect the use of anticipated residues based on field trial data and percent crop treated information, the hazard endpoint and dose derived from an Acute Oral Neurotoxicity Study in Rats, and the FQPA factor. No field trial data were available for strawberries and blackberries, therefore, tolerances were used in the dietary exposure analyses for these commodities. Ziram residues are found on the surface of the fruit and are not systemic in plants. Therefore, use of a reduction factor due to washing is a viable way to refine the risk estimates. In calculating dietary risk, a reduction factor of 0.15x from the peach washing study was applied. It could be refined upon submission of additional washing and processing studies. FDA monitoring data, which was available for some fruits and berries, could not be used since, of these commodities, only tomatoes had enough samples.

For the chronic dietary (food) risk assessments, anticipated residues were primarily calculated using field trial data from fruit, nut and vegetable crops and the dose and endpoints were selected from a chronic oral toxicity study in dogs. Field trial data, percent crop treated data, and the FQPA factor were incorporated into the the Dietary Exposure Evaluation Model (DEEM™). This model also incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic exposure assessments.

Acute Dietary (Food) Risk

The risk assessment incorporates a 0.15x washing factor, based on a peach washing study. Ziram is not absorbed by plants. Based on Agency experience with washing studies, the peach washing study is expected to conservatively estimate other plant commodities. Dietary risks are acceptable for all population subgroups when the reduction factor is applied to all commodities except for nuts and berries (Table 2). The Agency considers this assessment to be conservative especially in light of the lack of actual detections in available FDA monitoring samples. The risks are summarized below in Table 2.

Chronic Dietary (Food) Risk

Chronic dietary risk over a 70-year lifetime is calculated using average residues from field trials in combination with data from nature of residue studies and weighted average percent crop treated data. A risk estimate that is less than 100% of the chronic Population Adjusted Dose (cPAD), the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected, does not exceed the Agency's risk concern. Risk estimates are below EPA's level of concern for all population subgroups assessed (Table 2).

Table 2. Acute and Chronic Dietary Exposure and Risk Summary for Ziram

Population	Acute		Chronic[1]	
	Exposure (mg/kg body wt/day)	%aPAD	Exposure (mg/kg body wt/day)	%cPAD
U.S. Population	0.002457	14	0.000331	7
All Infants	0.004456	26	0.001387	28
Children (1-6 yrs old)	0.009689	57	0.000950	19
Children (7-12 yrs old)	0.003596	21	0.000576	12
Females (13-50 yrs old)	0.001744	10	0.000193	4

1 Chronic risk values do not include a 0.15x reduction factor.

Cancer (Food) Risk

The cancer risk was calculated using a linear low dose extrapolation approach with combined thyroid c-cell adenoma/carcinoma tumor rates, (DEEM™) software, average field trial data and percent crop treated data. Assuming an exposure of 0.00062 mg/kg body wt/day and a 0.15x reduction factor, the estimated cancer dietary risk is 3.8×10^{-6}, which exceeds the Agency's level of concern.

Drinking Water Dietary Risk

Drinking water exposure to pesticides can occur through ground water and surface water contamination. EPA considers both acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution of treated water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food, then determines a "drinking water level of comparison" or DWLOC. The DWLOCs represent the maximum contribution to the human diet (in ：g/L or ppb) that may be attributed to residues of a pesticide in drinking water after dietary exposure is subtracted from the aPAD or cPAD. Risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface water and ground water. The Agency generally has no risk concerns when the EECs are below the DWLOCs.

- **Water Exposure.** Ziram in the environment is expected to be highly mobile and not persistent. In general, ziram degrades quickly in both soil and water and does not bind to

most soils. It is expected to dissipate quickly under a variety of conditions. The main degradates, carbon dioxide and carbon disulfide, are volatile and are not expected to persist either. The application rates (6.1 lbs ai/acre/application and 30 lbs. ai/acre/season) are the most significant contributing factor in the predicted aquatic concentrations. Ziram does not leach beyond 12 inches into the soil.

- **Monitoring data.** No ziram monitoring data are available.

- **Surface Water Modeling.** PRZM 3.12/ EXAMS 2.7.97, a Tier II model, was performed with index reservoir (IR) scenarios and percent cropped area (PCA) adjustment factors. The scenario of 6 lbs ai/acre, applied 5x/season at 3-day intervals, was chosen to represent an upper bound estimate of the concentration that might be found in surface water from the use of ziram on apples and stone fruits.

- **Ground Water Modeling.** The SCI-GROW model, a Tier I model, was used to estimate the concentration of ziram in drinking water from shallow ground water sources. Currently, there is no Tier II assessment tool for groundwater. Since SCI-GROW, unlike the PRZM/EXAMS surface water model, does not require a specific crop scenario, EFED used the highest use rate of 2 applications at 7.6 lbs ai/acre as used for dormant peaches to estimate the concentration of ziram in drinking water from shallow ground water sources.

For surface water, the Expected Environmental Concentrations (EECs) slightly exceeded the Drinking Water Level of Concerns (DWLOCs) only for the group Children 1-6. Acute peak surface water EECs are estimated at 98 ppb, and the chronic (annual average) concentrations are 1.98 ppb. Ground water EECs are below the Agency's level of concern, with an EEC of 0.03 ppb. The EECs for surface water (PRZM/EXAM) and ground water (SCI-GROW) were less than the chronic DWLOCs, indicating that chronic exposure to ziram in food and water is below the Agency's level of concern. The cancer DWLOC was not calculated since the potential cancer risks to U.S. population from food exposure alone is of concern.

Table 3. Drinking Water Levels of Comparison for Acute Dietary Exposure using 0.15x reduction factor in DEEM.

Population Subgroup	Acute PAD (mg/kg/day)	Food Exposure (mg/kg/day) at the 99.9th percentile	Max. Water Exposure (mg/kg/day)	$DWLOC_{acute}$ (ppb)	Surface Water (ppb) max.	Ground Water (ppb)
US Population	0.017	0.002457	0.014543	509	98	0.03
All Infants	0.017	0.004456	0.012544	125	98	0.03
Children 1-6	0.017	0.009689	0.007311	**73**	98	0.03
Children 7-12	0.017	0.003596	0.013404	134	98	0.03
Females 13-50	0.017	0.001744	0.015256	457	98	0.03

Table 4. Drinking Water Levels of Comparison for Chronic Dietary Exposure.

Population Subgroup	Chronic PAD (mg/kg/day)	Food Exposure (mg/kg/day)	Max. Water Exposure (mg/kg/day)	$DWLOC_{chronic}$ (ppb)	Surface Water (ppb) max.	Ground Water (ppb)
US Population	0.005	0.000331	0.004669	163	4.2	0.03
All Infants	0.005	0.001387	0.003613	36	4.2	0.03
Children 1-6	0.005	0.00095	0.00405	40.5	4.2	0.03
Children 7-12	0.005	0.00576	0.004424	44.2	4.2	0.03
Females 13-50	0.005	0.000193	0.004807	144	4.2	0.03

Non-dietary (Residential/Public) Risks

Ziram residential use by homeowners is limited to outdoor applications as a granular rabbit repellant. Indirect residential exposures are also possible during the application of paint that contains ziram as an in-can preservative. The Agency has estimated residential handler exposure and risks using data from the Pesticide Handler's Exposure Database (PHED, version 1.1), a surrogate carbaryl duster study, as well as the toxicological endpoints (increased incidence of resorptions and postimplantation loss in rabbit developmental study). An FQPA 3x safety factor was applied to short-term residential risks assessments. Residential postapplication exposures to the rabbit repellant are expected to be minimal because the product is only applied to outdoor-grown ornamentals. Unlike lawns, the ornamentals are expected to have a low potential for dermal contact from adults and children. Only short-term residential exposures are expected.

General assumptions and calculations used in the residential handler risk assessment from the use as a rabbit repellent as well as application of ziram-treated paint are as follows:

- Dermal unit exposures were calculated assessing short pants and short sleeved shirts.
- Application rates are based on the ziram label (RABBIT SCAT EPA Reg. No. 3772-24).
- Amount treated is based on the entire 10 ounce contents for dust application and a 2.5 gallon sprayer for the ornamental foliar dilute spray once per year for 30 years.
- Total daily absorbed dose (mg/kg/day) = [((dermal unit exposure (mg/lb ai) * 1 percent dermal absorption) + (inhalation unit exposure (mg/lb ai) * 100 % inhalation absorption)) * Appl. rate (lb ai handled or lb ai/gallon) * Acres or gallons] / Body weight (70 kg).
- LADD (Lifetime average daily dose) mg/kg/day = Total daily absorbed dose (mg/kg/day) * (1 day/ year/365 days/ year)*(50 yrs worked/75 yr lifetime).
- Risk = LADD (mg/kg/day) * Q_1^* (6.11×10^{-2} (mg/kg/day)).

Table 5. Short-Term Ornamental Use of Ziram

Exposure Scenario	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (µg/lb ai)	Appl. Rate	Amount Treated	Absorbed Dermal Dose (mg/kg/day)	Dermal MOE	Inhalation Dose (mg/kg/day)	Inhalation MOE	Total MOE
Loading/Applying as a Dust	140	1200	0.14 lb ai	1 container	0.0028	2700	0.0024	3100	1400
Low Pressure Handwand application	100	30	0.0345 lb ai per gallon	2.5 Gallons	0.0012	6300	0.000037	200,000	6100

The calculated combined MOEs for short term dermal and inhalation exposure/risk for homeowners (combined mixer/loader/applicator) using rabbit repellant are greater than or equal to 1400 (Table 5). The MOEs are greater than the target MOE of 300 for both scenarios and are below the level of concern. The estimated cancer risks are in the range of 10^{-7} and are not of concern.

Residential applications of the exterior grade latex paint include painting with an airless sprayer and paint brushes (paint roller exposure data are not available but the magnitude of exposure is believed to be similar to that monitored for use of a paint brush). Although there is potential exposure during the application of the other treated materials (e.g., caulks and sealants), they are not included because no data are available to assess the uses. These exposures, however, are expected to be substantially lower than those associated with paint. The residential short-term dermal and inhalation exposures to individuals exposed while using an airless sprayer is of concern; however, a similar exposure from use of a paint brush is not of concern. The combined dermal and inhalation MOEs are 74 for the airless sprayer and 350 for the paint brush (Table 6). No mitigation measures, such as the use of chemical resistant gloves, are available for these exposures because the individuals that are being exposed to paint containing ziram are exposed to products with no pesticide labels (i.e., in-can preservative use).

Table 6. Residential Short- and Intermediate-term In-Can-Preservative Use of Ziram and MOEs*

Exposure Scenario	Dermal Unit Exposure (mg/lb ai)	Inhalation Exposure (µg/lb ai)	Amount Treated	Absorbed Dermal Dose (mg/kg/day)	Dermal MOE	Inhalation Dose (mg/kg/day)	Inhalation MOE	Total MOE
Secondary Handlers: Short-term Residential Exposure Duration								
Airless Sprayers	79	830	15 gallons	0.049	150	0.052	150	**74**
Paint Brush	230	280	2 gallons	0.019	390	0.0023	3,200	350

* Assuming a maximum application rate of 0.29 lbai/gal and Short pants, short sleeved shirt.

The estimated cancer risks for painters while using an airless sprayer is of concern; however, the paint brush scenario is not of concern. The cancer risks are 1.1×10^{-5} for airless sprayers and 2.3×10^{-6} for paint brush applications.

Postapplication exposures to ziram-containing paint are also expected to be minimal based on the low vapor pressure of ziram and the low potential contact with treated surfaces such as exterior painted surfaces, adhesives, and caulks.

Aggregate Risk

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require that for establishing a pesticide tolerance "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food, and drinking water), residential and other non-

occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Aggregate risk assessments are typically conducted for acute (1 day), short-term (1-30 days), intermediate-term (30 days to several months), chronic (several months to lifetime) exposure, and for cancer risk assessment.

The aggregate risk assessment includes combined exposure from food, drinking water, and non-dietary (residential/public) uses. Residential exposure and risk from the use of ziram was limited to short-term exposure scenarios associated with use of the rabbit repellant and ziram-treated paint (dermal and inhalation) because intermediate-term and chronic residential exposure to ziram is not expected to occur. The aggregate acute exposure to ziram in food and water slightly exceeds the Agency's level of concern only for the group Children 1-6 (Refer to Table 3).

The residential short-term dermal and inhalation exposures to individuals exposed to paint while using an airless sprayer alone is of concern. Therefore, no aggregate assessment for average daily dietary, short-term residential dermal and inhalation exposures was conducted . Also no DWLOCs $_{\text{short-term}}$ were calculated.

Short-Term Aggregate Risk. An aggregate risk assessment for average daily dietary, short-term residential dermal and inhalation exposures of homeowners to rabbit repellant or residential painters to paint from use of paint brush was conducted, and the aggregate risk estimates indicate that risks from use of rabbit repellant or paint (using paint brush) are not of concern (Table 7).

Table 7: Short-Term and Aggregate Risk and DWLOC Calculations*

Population	*Short-Term* Scenario									
	NOAEL mg/kg/ day	Target MOE[1]	Max Exposure[2] mg/kg/day	Average Food Exposure mg/kg/day	Residential Exposure[3] mg/kg/day	Aggregate MOE (food and residential)[4]	Max Water Exposure[5] mg/kg/day	Ground Water EEC[6] (µg/L)	Surface Water EEC[6] (µg/L)	Short-Term DWLOC[7] (µg/L)
Homeowners/ loading/ applying Rabbit Scat as a dust	7.5	300	0.025	0.000331	0.0052	1356	0.0195	0.03	4	680
Residential painters/paint brush	7.5	300	0.025	0.000331	0.0213	350	0.0034	0.03	4	120

* Inhalation/Oral/Dermal Endpoints are the same (see Table 1).

[1] The basis for the target MOE includes the standard inter- and intra- species safety factors totaling 100 as well as an additional 3x safety factor as appropriate.

[2] Maximum Exposure (mg/kg/day) = NOAEL (30 mg/kg/day)/Target MOE of 300.

[3] Residential Exposure = [Dermal exposure + Inhalation Exposure]

[4] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]

[5] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)

[6] The crop product the highest level was used.

[7] DWLOC (ppb) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (70 kg)}}{\text{[water consumption (2L) x } 10^{-3} \text{ mg/µg]}}$

No monitoring data for ziram residues in ground and surface water are available for estimating environmental concentrations (EECs) for the aggregate dietary (food and water) risk assessment. Therefore, computer modeling was used to estimate surface (PRZM 3.12 and

EXAMS 2.97.7) and ground (SCI-GROW) water concentrations expected from normal agricultural use. These model estimates were compared to human drinking water levels of concern (DWLOCs), the theoretical concentration of pesticide in drinking water that would be an acceptable upper limit in light of the aggregate exposure to that pesticide from other sources (food and residential use). The Agency uses DWLOCs in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

Aggregate chronic risks resulting from chronic exposure to ziram via dietary (food and drinking water) exposures were assessed (given the current use patterns, no chronic residential exposure scenarios are anticipated). According to the water models, the ziram drinking water residue contribution to the chronic aggregate risk is not expected to be significant. As noted previously, the chronic food-source risks were estimated to be #28% of the cPAD.

Cancer Aggregate Risk. An aggregate cancer risk assessment for dietary (food and water) and residential dermal or inhalation exposures for various population subgroups was not conducted at this time since the potential cancer risks to U.S. population from food exposure alone is of concern. Any aggregation of drinking water and food exposure levels would only increase the calculated risks.

Occupational Risk

Occupational handlers may be exposed to a pesticide through such tasks as mixing, loading, or applying a pesticide. Handler non-cancer risk is measured by a Margin of Exposure (MOE) which determines how close the occupational handler exposure comes to a No Observed Adverse Effect Level (NOAEL). For workers entering a treated site, restricted entry intervals (REIs) are calculated to determine the minimum length of time required before workers or others are allowed to enter. REIs are calculated in hours or days. The restricted entry interval for ziram is currently set at 48 hours. See Table 1 for a summary of the toxicological endpoints and doses that were used to complete the occupational risk assessment.

The following general assumptions and factors were used in order to complete the occupational exposure and risk assessments:

- Maximum application rates and daily acreage were used to evaluate non-cancer occupational risk. Average application rates and daily acreage were used to evaluate cancer occupational risk.
- A body weight of 60 kg was assumed for short-term exposures because the short-term endpoint relates to females 13-50 years of age. A body weight of 70 kg was assumed for intermediate-term exposures because the intermediate-term endpoint is not gender specific. A body weight of 70 kg was assumed for cancer scenarios.

Antimicrobial Occupational Use Risk. Vancide MZ-96 (EPA Reg. No. 1965-79) is an industrial preservative containing 96 percent ziram as a wettable powder formulation. The

product is incorporated as a preservative additive at 0.185 to 0.5 percent during the initial phase of the manufacturing process in adhesives, caulks, sealants, and wallboard and 1 to 3 percent as a mold inhibitor for exterior latex paint. Based on the label directions, ziram is added to dry starch and synthetic latex adhesives because they are *"subject to bacterial degradation when water is added by the end user"*. It is added to dried films because they are *"subject to defacement by mold and mildew including wall and ceiling textures, wallpaper paste, wallboard joint compounds, spackles, wood fillers, caulks and sealants"*. Finally, ziram is added to paints as an in-can preservative. Although there is potential exposure during the application of the other treated materials (e.g., caulks and sealants), they are not included because no data are available to assess the uses. It is the Agency's professional judgement that the painting scenarios represent the high end exposures for ziram antimicrobial secondary uses.

According to the manufacturer, the antimicrobial users mix commercial products with ziram every other week at a frequency of 5 days per week. This type of intermittent exposure frequency is not considered a chronic exposure scenario for ziram (i.e., greater then 180 days) because ziram is not used continuously for at least 180 days and urinary and fecal excretion of ziram is nearly complete within 72 hours at low-dose groups and within 96 hours within high-dose groups in the rat metabolism study.

The MOE results of the antimicrobial assessment are presented below in Table 8. For the general preservative use, the short- and intermediate-term total MOEs for the primary handlers wearing long pants, long sleeved shirts, chemical resistant gloves, and a dust/mist respirator at the 0.5 percent Vancide concentration range from a high of 670,000 for the product with the lowest density and percent solids (i.e., CBP Patch-N-Paint at 3 pounds per gallon with a 7.3 percent solid) and as low as 1,100 for the product with the highest density and percent solids (i.e., texture coating 16 pounds per gallon with 84 percent solids). The intermediate-term total MOEs for the handlers adding ziram to paint during the manufacturing process at the maximum Vancide concentration (i.e., 0.5 percent) are 2,500 for 100 gallon paint batches and 250 for 1,000 gallon paint batches. Although the MOEs are sufficiently above the target MOE of 100 to remove some of the PPE, the CMA data do not accommodate exposure estimates for lower levels of PPE. The short- and intermediate-term total MOEs for the commercial painters while wearing long pants and long sleeved shirts are 30 for commercial painters using airless sprayers and 170 for commercial painters using paint brushes. No mitigation measures are available for the secondary exposures because the individuals that are being exposed to paint containing ziram are exposed to products with no pesticide labels (i.e., in-can preservative use).

Table 8. Non-Cancer Combined MOEs for Occupational Exposure to Ziram

Endpoint	Clothing/Attire	MOEs
Short-and Intermediate-term antimicrobial	long pants, long sleeved shirt (baseline)	**30**-170
	baseline + gloves, dust/mist respirator	250 - 670,000
Short-and Intermediate-term agricultural	long pants, long sleeved shirt (baseline)	**2.5**-18,000
	baseline + gloves, dust/mist respirator	**24** -56,000

Postapplication Exposure from Antimicrobial Use. Postapplication dermal and inhalation exposures may occur in the industrial settings around open vats of processing material while maintaining industrial equipment. No postapplication exposure data have been submitted to determine the extent of postapplication exposures in the industrial settings. Nonetheless, inhalation exposures are expected to be minimal because of the low vapor pressure of ziram (1.4×10^{-7} mmHg at 25 °C) and aerosols are not expected. Dermal postapplication exposures are expected to be lower than when handling/loading the 96 percent formulated product. Postapplication inhalation and dermal exposures in the residential settings, as a result of commercial applications of products such as paints, are also expected to be minimal because of the low vapor pressure of ziram and low dermal contact potential to the treated surfaces and/or adhesives. Therefore, postapplication exposures in the residential (as a result of commercial applications) and industrial settings are expected to be minimal and not of concern.

Handler Exposures for Agricultural Uses. The results of the agricultural occupational handler assessments from agricultural use indicate that for the *dry flowable formulation* all of the potential exposure scenarios provide dermal and inhalation MOE(s) greater than or equal to 100 at the baseline clothing attire of long pants, long sleeved shirts, no gloves, and no respirator while using open systems. The incident data do, however, indirectly support the retention of respirator requirements. Because most current labels require a dust/mist respirator, incidents may increase if the respirator were to be removed. The use of a respirator is consistent with some of the current dry flowable labels, but some do not require a respirator. For the ***liquid formulation***, risks indicate that in order for the MOEs to be 100 for the mixer/loader scenario for all uses at both the short- and intermediate-term exposure durations, minimum PPE are needed (i.e., long pants, long sleeved shirts, chemical resistant gloves, and a dust/mist respirator while using open systems). This is consistent with the current label except for the need in some scenarios to add a dust/mist respirator. Finally, for the ***wettable powder formulation***, for the MOEs to be 100 for the mixer/loader scenario for all uses at both the short- and intermediate-term durations, the wettable powder must be packaged in water soluble packets (clothing attire of long pants, long sleeved shirts, water proof gloves, and no respirator). The current wettable powder formulation is not packaged in water soluble packets.

Postapplication Exposure for Agricultural Uses. Several levels of postapplication exposure activities have been identified ranging from "low" activities such as weeding and scouting in immature plants to very high activities such as harvesting or thinning fruit from trees. The short- and intermediate-term postapplication assessments indicate that the potential restricted entry interval (REI) (i.e., the day after treatment that the MOEs reaches 100), based on the toxicity of the active ingredient, is 0 days for all crops and all activities. Although MOEs are at 100 for all crops and all activities on day 0, ziram is an acute Tox I category for eye irritation, and therefore, the REI will be a minimum of 48 hours.

Cancer Risk Estimates for Antimicrobial and Agricultural Occupational Handlers. There are three populations of workers exposed to ziram. These consist of industrial workers that handle technical ziram or formulate products with it; users of paints, caulks and adhesives; and agricultural workers (in which both applicators and field workers may also be exposed). The

Agency closely examines occupational cancer risks in the 1×10^{-4} to 1×10^{-6} range and seeks ways to reduce occupational cancer risks to the greatest extent feasible, preferably 10^{-6} or less.

The estimated antimicrobial occupational use cancer risks are presented in Table 9. For the general preservative use, the estimated cancer risks for the primary handlers at the 0.5 percent Vancide concentration range from 1.2×10^{-7} for the product with the lowest density and percent solids and as high as 7.0×10^{-5} for the product with the highest density and percent solids. The estimated cancer risks for the handlers adding ziram to paint during the manufacturing process at the maximum Vancide concentration (i.e., 0.5 percent) are 3.1×10^{-5} for 100 gallon paint batches and 3.1×10^{-4} for 1,000 gallon paint batches. The estimated cancer risks for the secondary handlers (i.e.commercial painters) are 1.0×10^{-4} for airless sprayers and 1.8×10^{-4} for paint brushes.

Table 9. Ziram Cancer Assessment for Antimicrobial Uses

Exposure Scenario	Population Targeted (frequency days/year)	Clothing Attire	Dermal Unit Exposure (mg/lb ai) [1]	Inhalation Unit Exposure (µg/lb ai) [2]	Appl. Rate [3] (lb ai/gal)	Amount Treated [4]	Total Absorbed Dose (mg/kg/day) [5]	LADD (mg/kg/day) [6]	Risk [7]
Primary Handlers: Short- and Intermediate-term Exposure Duration									
Loaders of WP for General Preservatives	Occupational (125 day/year	Open pour, long pants, long-sleeved shirt, chemical resistant gloves, and a 5-fold PF dust/mist type respirator	0.466	2.5	0.0011 min rate	100 gal	1.1×10^{-5}	1.9×10^{-6}	1.2×10^{-7}
						1,000 gal	1.1×10^{-4}	1.9×10^{-5}	1.2×10^{-6}
					0.065 max rate	100 gal	6.6×10^{-4}	1.1×10^{-4}	7.0×10^{-6}
						1,000 gal	6.6×10^{-3}	1.1×10^{-3}	7.0×10^{-5}
Loaders of WP for Paint Manufacturers	Occupational (125 day/year		0.466	2.5	0.29 max rate	100 gallons	3.0×10^{-3}	5.1×10^{-4}	3.1×10^{-5}
						1,000 gal	3.0×10^{-2}	5.1×10^{-3}	3.1×10^{-4}
Secondary Handlers: Short- and Intermediate-term Commercial Exposure Durations									
Airless Sprayers	Commercial (50 day/year)	Long pants, long sleeved shirt	38	830	0.29 max rate	50 gallons	0.25	0.017	1.0×10^{-3}
Paint Brush	Commercial (50 day/year)	Long pants, long sleeved shirt	180	280	0.29 max rate	5 gallons	0.043	0.0030	1.8×10^{-4}

[1,2] Dermal and inhalation unit exposures are from the CMA study and PHED V1.1.
[3] Application rates are from the ziram label (Vancide MZ-96 EPA Reg. No. 1965-79)) along with density and % solid information from Vanderbilt Co.
[4] Amount treated is based on assumptions from EPA's Antimicrobial Division and HED's Residential SOPs.
[5] Total daily absorbed dose (mg/kg/day) = [((dermal unit exposure (mg/lb ai) * 1 percent dermal absorption) + (inhalation unit exposure (mg/lb ai) * 100 % inhalation absorption)) * Appl. rate (lb ai/gallon) * gallons] / body weight (70 kg).
[6] LADD (Lifetime average daily dose) mg/kg/day = Total daily absorbed dose (mg/kg/day) * (days worked per year/365 days per year) * (35 years worked/70 year lifetime). Days worked per year are estimates. Standard assumptions for residential uses are 50 years worked over a 75 year lifetime.
[7] Risk = LADD (mg/kg/day) * Q_1^* = 6.11E-2 $(mg/kg/day)^{-1}$.

The estimated cancer risks for the agricultural occupational handlers (see Table 10) range from 1.1×10^{-4} to 1.0×10^{-6} at baseline for mixing/loading the dry flowable formulation, 3.6×10^{-5} to 3.4×10^{-7} at minimum PPE for mixing/loading the liquid formulation, 2.6×10^{-5} to 2.4×10^{-7} using water soluble packets for mixing/loading the wettable powder formulation, and 1.1×10^{-5} to 7.7×10^{-6} at baseline for applicators/flaggers.

Table 10. Ziram Agricultural Handler Baseline and Max PPE Cancer (Q*) Risks

Exposure Scenario	Crop	Baseline Total Daily Dose	Base-line Daily LADD	Base-line Risk	PPE Total Daily Dose	PPE LADD	PPE Risk
Mixer/Loader							
Dry Flowables for Airblast application	Dormant Peaches Only	0.0062	2.55×10^{-4}	1.56×10^{-5}	0.0024	9.76×10^{-5}	5.96×10^{-6}
Dry Flowables for Groundboom application	Tomatoes	0.0050	2.04×10^{-4}	1.25×10^{-5}	0.0019	7.81×10^{-5}	4.77×10^{-6}
Dry Flowables for High-Pressure HandWand application	Ornamentals	0.00041	1.68×10^{-5}	1.03×10^{-6}	0.00016	6.42×10^{-6}	3.92×10^{-7}
Mixing/Loading Liquids for Aerial application	Dormant Peaches Only	1.1	4.72×10^{-2}	2.88×10^{-3}	0.011	4.53×10^{-4}	2.77×10^{-5}
Mixing/Loading Liquids for High-Pressure HandWand application	Ornamentals	0.0086	3.55×10^{-4}	2.17×10^{-5}	0.000083	3.41×10^{-6}	2.08×10^{-7}
Wettable Powders for Aerial application	Dormant Peaches Only	3.0	0.125	7.63×10^{-3}	0.21	8.75×10^{-3}	5.34×10^{-4}
Wettable Powders for Airblast application	Dormant Peaches Only	0.35	1.43×10^{-2}	8.72×10^{-4}	0.024	9.99×10^{-4}	6.11×10^{-5}
Wettable Powders for High-Pressure HandWand application	Ornamentals	0.023	9.39×10^{-4}	5.74×10^{-5}	0.0016	6.58E-5	4.02×10^{-5}
Applicator							
Sprays for Airblast application	Dormant Peaches Only	0.035	1.45×10^{-3}	8.83×10^{-5}	0.012	4.73×10^{-4}	2.89×10^{-5}
Sprays for Groundboom application	Tomatoes	0.0031	1.26×10^{-4}	7.68E-6	0.00064	2.63×10^{-5}	1.61×10^{-6}
Sprays for High-Pressure HandWand application	Ornamentals	0.028	1.14×10^{-3}	6.96×10^{-5}	0.0033	1.35×10^{-4}	8.25×10^{-6}
Flagger							
Flagging for Sprays application	Dormant Peaches Only	0.017	7.18×10^{-4}	4.39×10^{-5}	0.0051	2.11×10^{-4}	1.29×10^{-5}

Post Antimicrobial and Agricultural Application Cancer Risk Estimates

Postapplication dermal and inhalation exposures may occur in the industrial settings around open vats of processing material while maintaining industrial equipment. No postapplication exposure data have been submitted to determine the extent of postapplication exposures in the industrial settings. Nonetheless, inhalation exposures are expected to be minimal because of the low vapor pressure of ziram (1.4×10^{-7} mmHg at 25 °C) and aerosols are not expected. Dermal postapplication exposures are expected to be lower than when handling/loading the 96 percent formulated product. Postapplication inhalation and dermal exposures in the residential settings, as a result of commercial applications of products such as paints, are also expected to be minimal because of the low vapor pressure of ziram and low dermal contact potential to the treated surfaces and/or adhesives. Therefore, postapplication exposures in the residential (as a result of commercial applications) and industrial settings are expected to be minimal and not of concern.

For agricultural workers, based on the high exposure activity of hand harvesting, the estimated cancer risks are in the range of 10^{-4} to 10^{-5} on post-treatment day that the MOE reached 100 (i.e., day 0). Ziram foliar residues decline very slowly, and for hand harvesting, cancer risks reach 10^{-5} on day 1 to 94, depending on the crop scenario. Cancer risks do not reach 10^{-6} until day 81 to 178.

Incidents. According to California and Poison Control Center data, it appears that a majority of cases involved skin and eye illnesses (e.g., skin rashes, conjunctivitis, and red, irritated, and itchy eyes and skin). Of the 23 Poison Center cases, six were non-occupational including one child under six years of age. A large proportion of cases resulted after field workers were exposed to ziram due to failure to wear, or use properly, their personal protective equipment. Appropriate personal protective equipment such as the use of skin and eye protection would protect workers who may have extensive exposure to ziram. Only one "other non-occupational" activity category incident was reported by California from 1982 to 1999.

Ecological Risk Assessment

EPA uses the quotient method to evaluate potential risk to nontarget organisms. Applying this method, risk quotients (RQs) are calculated by dividing the estimated concentrations of a pesticide in the environment by results from ecotoxicity studies in various organisms. A risk concern results when an RQ exceeds a Level of Concern (LOC). An LOC is a value calculated based on the category of nontarget organism and category of concern. EPA further characterizes ecological risk based on any reported aquatic or terrestrial incidents to nontarget organisms in the field (e.g., fish or bird kills).

Ziram is acutely very highly toxic and poses acute and chronic risk to most endangered and non-endangered aquatic organisms, should the compound enter aquatic habitats. The major sites considered in this risk assessment include terrestrial food and non-food uses. Acute terrestrial risk (and chronic risk for mammals) in endangered and non-endangered avian and mammalian species may occur from the application of ziram to foliage or other wildlife food items mainly due to the compound's higher application rates and multiple applications, rather than the compound's toxicity. Avian chronic reproductive effects could not be assessed due to a lack of toxicity data. A proper assessment for risks to terrestrial and aquatic plants could not be conducted due to a lack of toxicity data. Ziram's susceptibility to degradation, especially in neutral and acidic environments, reduces the probability of prolonged exposure to the chemical.

The chemical is expected to dissipate relatively quickly under many conditions, hydrolyzing rapidly under neutral to acidic conditions in a matter of hours. In acidic soils, ziram degraded with half-lives that were typically in hours; in water, the compound also photolyzed rapidly. In addition, ziram degraded much faster under aerobic than anaerobic conditions during soil metabolism studies. While ziram can reach surface water by spray drift or runoff (it is relatively soluble and does not bind to most soils), it is not likely to persist. The main degradates are volatiles such as carbon dioxide, carbon disulfide, and carbonyl sulfide, and are not expected to persist in soil and water.

However, ziram may pose ecological risk to aquatic organisms through pulse dosing, due to the compound's high application rates, multiple applications and short intervals between those applications. The compound can be available following rain events during the growing season

and especially on days following application. In addition, since ziram is relatively soluble and is very highly toxic to aquatic organisms, there is a possibility of acute risk to amphibians and their larval stages through dermal exposure from terrestrial broadcast spray applications and through aquatic exposures, respectively.

Major Conclusions

Terrestrial Risks

- Low acute risk to avian species. However, endangered birds may be adversely affected.
- Chronic risk to avian species could not be assessed due to a lack of toxicity data.
- High acute risk to endangered and non-endangered mammals (other than granivores) from both single and multiple applications.
- Chronic risk to endangered and non-endangered mammals (other than granivores) with either single and multiple applications.
- As Ziram is practically non-toxic to honeybees (LD_{50} >100 ug/bee), low risk is assumed.
- There were no ecological incidents involving terrestrial organisms found in the Agency's incidents database for Ziram.

Aquatic Risks

- Using a Tier II model for refinement (PRZM/EXAMS), the present assessment suggests potential acute risk to endangered and non-endangered freshwater fish, freshwater invertebrates and estuarine invertebrates. The Acute Risk Quotients (RQs) were 3.4 and 0.5 for fish and invertebrates, respectively. Acute RQs of greater than 0.1 are of concern.
- Chronic risk could not be assessed due to a lack of toxicity data.
- Low risks to aquatic plants, however more data is needed.
- There were no ecological incidents involving aquatic organisms found in the Agency's incidents database for ziram.

Water Resources

- The compound can be available following rain events during the growing season and especially on days following application. It does not appear to be likely to substantially leach into soils, because it is highly labile.