Overview of
Dimethipin Risk Assessment

Introduction

This document summarizes EPA's human health, environmental fate and transport, and ecological risk findings for the pesticide dimethipin [2,3-dihydro-5,6-dimethyl-1,4-dithiin 1,1,4,4-tetraoxide]. This information is presented in greater detail in the following documents: "Dimethipin HED Chapter for Reregistration Eligibility Decision Document (RED)" (dated 10/26/04), and "Environmental Fate and Effects Division Preliminary Risk Assessment for Dimethipin Reregistration Eligibility Document" dated (11/18/04). The purpose of this overview is to help the reader understand the conclusions reached in the risk assessments by identifying the key features and findings of the assessments. This overview was developed in response to comments and requests from the public that risk assessments were too complex, and that it was not easy to compare the assessments for different chemicals due to formatting differences. References to relevant sections in the complete documents are provided, allowing the reader to find the place in these assessments where a more detailed explanation is provided.

These dimethipin risk assessments and additional supporting documents are posted on EPA's Pesticide Docket website (http://www.epa.gov/edockets) under docket number OPP-2004-0380 for public viewing. Public comments on the risk assessments will be invited for 60 days. During the comment period, EPA will continue its ongoing efforts to consult with other government agencies and stakeholders on the pesticides' uses and risk management options. After the comment period closes, EPA will consider the comments received, continue dialogue with other government agencies and stakeholders as needed, and develop a risk management decision.

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to dimethipin and any other substances, and dimethipin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this risk assessment action, therefore, EPA has not assumed that dimethipin has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative.

Use Profile

- ***Use Sites:*** Dimethipin is registered for use as a pre-harvest defoliant on cotton, as a post-emergence herbicide in cotton fields, and as a post-emergence herbicide on non-bearing apple nursery stock. Dimethipin is a plant growth regulator which functions by stressing the plant's stomatal system causing it to lose water resulting in leaf abscission.

- ***Formulations:*** All current commercial dimethipin formulations are soluble concentrates (SC) or flowable concentrates (FC).

- ***Methods of Application:*** Dimethipin can be applied to cotton crops via ground rig and air early in the season, or by hand-held spray applicator for non-bearing apple nursery stock late in the season.

- ***Use Rates:*** The maximum single application rate is 0.56 lb ai /A for post-emergence herbicidal use on cotton. The maximum single application rate for cotton defoliation is 0.31 lb ai/A. Dimethipin may be used under a Special Local Need registration in Washington state as a defoliant on non-bearing apple nurseries prior to transplanting at a maximum single application rate of 0.077 lbs ai/A.

- ***Use Locations:***. Dimethipin is used in Alabama, Arkansas, Florida, Georgia, Kansas, Louisiana, Missouri, Mississippi, North Carolina, New Mexico, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington, and California.

- ***Tolerances in Use Profile:*** Currently there are 17 listed tolerances on cotton, and livestock commodities: cattle, goat, hog, horse, and sheep.

- ***Technical Registrants:*** Crompton Manufacturing Company, Inc.

Hazard Characterization

Dimethipin has moderate (Category II) acute toxicity via the oral and inhalation routes, and low (Category III) acute toxicity via the dermal route. It is not an eye or skin irritant or a dermal sensitizer. Sub-chronic studies in rats and mice showed no treatment-related effects on mortality, clinical signs, food consumption, hematology, clinical chemistry or pathology. Decreased body weight gains were observed in female rats administered dimethipin in the diet for 90 days. Data from long-term studies indicate that organ effects and decreased weight gain are the primary effects of exposure to dimethipin. Dimethipin is classified as a possible human carcinogen (Group C). Dimethipin is not considered to be

mutagenic.

Dimethipin has a chronic RfD (and cPAD) of 0.0218 mg/kg/day. The RfD is based on the NOAEL of 2.18 mg/kg from a combined chronic toxicity/carcinogenicity feeding study in the rat and a 100-fold inter-/intra-species uncertainty factor. No quantitative or qualitative sensitivity was observed in the rat and rabbit developmental studies or in the 2-generation reproduction study in the rat. Based on the lack of evidence of pre- and/or postnatal susceptibility resulting following exposure to dimethipin, and considering the lack of residual uncertainties for pre- and/or postnatal toxicity, no special FQPA safety factor is needed (i.e., 1X). There is no concern for developmental neurotoxicity resulting from exposure to dimethipin.

Summary of Toxicological Doses and Endpoints for Dimethipin for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Chronic Dietary (all populations)	NOAEL = 2.18 mg/kg/day UF = 100 (10x for intraspecies variation, 10x for interspecies extrapolation) Chronic RfD = 0.0218 mg/kg/day	1X cPAD = 0.0218 mg/kg/day (cRfD/FQPA SF = cPAD = 0.0218/1 = 0.0218)	ChronicToxicity/Carcinogenicity Study in the Rat LOAEL = 50.3 mg/kg/day , based on toxicity in the kidney, lungs, duodenum, and testes of male rats and depressed body weight gain and toxicity in the liver, kidney, glandular stomach, heart, and aortic artery of female rats.
Inhalation Short-Term (1 - 30 days) Occupational	NOAEL = 20 mg/kg/day	1X LOC: MOE = 100 (10x for intraspecies variation, 10x for interspecies extrapolation)	Developmental Study in the Rabbit LOAEL = 40 mg/kg/day, based on decreased body weight gain.

Summary of Toxicological Doses and Endpoints for Dimethipin for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Intermediate-Term (1 - 6 months) Occupational	NOAEL = 11.8 mg/kg/day	1X LOC: MOE = 100 (10x for intraspecies variation, 10x for interspecies extrapolation)	Two-generation reproduction study in the rat LOAEL = 31.2-120.3 mg/kg/day, based on decreased bodyweight/bodyweight gain in F0 & F1 females.
Cancer (oral, inhalation)	Classification: Class C - quantification not recommended.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern

Human Health Risk Assessment

Dietary Risk (Food)

(For a complete discussion, see Section 6.1 of the Dimethipin Human Health Risk Assessment)

Dietary risk assessment incorporates both exposure to and toxicity of a given pesticide. The risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the Reference Dose (RfD) divided by the special FQPA Safety Factor. EPA is concerned when estimated dietary risk exceeds 100% of the PAD.

The magnitude of the residue data for processed commodities of food/feed crops that are from presently registered use sites have been evaluated and deemed adequate by the Agency. Based on these data, the Agency intends to revise some tolerances and revoke livestock fat tolerances.

The residue of concern for purposes of this risk assessment is dimethipin *per se* in cotton and livestock commodities, except the liver of cattle, goats, hogs and sheep. The residues of concern for

liver are dimethipin and its metabolite acetyl dithiane tetraoxide. Human exposure to dimethipin is very limited.

Acute Dietary Risk (Food)

An endpoint attributable to a single exposure was not identified for dimethipin. Therefore, no acute dietary assessment was performed.

Chronic Dietary Risk (Food)

For the chronic dietary exposure assessment, an estimate of the residue level in each food or food-form on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form. The resulting residue consumption estimate is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and risk is expressed as a percent of the chronic PAD (cPAD).

The dimethipin chronic dietary exposure assessment was conducted using the Lifeline Model Version 2.0 and the Dietary Exposure Evaluation Model (DEEM-FCID™), Version 2.03, which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. In this analysis the chronic dietary exposure and risk estimates resulting from food intake were determined for the general U.S. population and various population subgroups.

The resulting food exposure estimates using the Lifeline™ software were less than 1% of the cPAD for the U.S. population and all population subgroups. Dimethipin food exposure was less than 1% of the cPAD even among the most highly exposed population subgroup (children, 3-5 years old). DEEM-FCID yielded similar results.

Drinking Water Dietary Risk

(For a complete discussion, see section 6.2 of the Dimethipin Human Health Risk Assessment)

Exposure to pesticides through drinking water can occur as a result of groundwater or surface water contamination. EPA considers both acute (one day) and chronic (multiple year) drinking water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. Modeling is carried out in tiers of increasing refinement, but is designed to provide high-end estimates of exposure. To determine the maximum allowable contribution from water allowed in the diet, EPA first looks at how much of the overall risk is contributed by food, then determines a "drinking water level of

comparison" (DWLOC). The DWLOC represents the maximum allowable contribution to the human diet (in ppb or μg/L) 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 DWLOC to the estimated drinking water concentrations (EDWCs) in surface water and groundwater. The Agency generally has no risk concerns when the EDWCs are below the DWLOC.

Available data indicate that dimethipin is both mobile and persistent, and has high potential to leach to groundwater. No monitoring data for dimethipin were available to the Agency; therefore, EDWCs were derived from Tier 1 modeling done with FIRST (for surface water) and SCI-GROW (for ground water). Estimates were run using the maximum seasonal use rate of 0.56 lb ai/A, a Koc of 10, and a half-life of 408 days. The SCI-GROW model depicts areas in which groundwater is exceptionally vulnerable to contamination, resulting in highly conservative estimates.

Dimethipin Chronic (non-cancer) DWLOC Values Compared to EDWCs

Population Subgroup	*DWLOC (ug/L)*	*EDWC (Surface Water) (ug/L)*	*EDWC (Ground Water) (ug/L)*
General U.S. Population	762	7.3	99
Infants <1	218	7.3	99

Since the ground water EDWC is the higher residue value, it should be used as a protective estimate for dietary risk from drinking water. Based on the conservative, screening nature of the SCI-GROW model, the Agency believes the EEC of 99 ppb is a reliable estimate of dimethipin residues in ground water and should therefore be used for determining risk from consumption of dimethipin-contaminated water.

Cancer Dietary Risk

Dimethipin has been classified as a Group C (possible human carcinogen). The classification was based on evidence of lung adenomas and carcinomas in male CD-1 mouse. The original rat study was not conducted at a high enough dose and recommended that a new study be conducted. The results of the new study indicated no evidence of carcinogenicity in the rat. Calculation of a q* was not recommended for dimethipin, based on the weight-of-evidence (ie., tumors at the HDT in only one sex, strain, species and only one experiment; weak mutagenicity of dimethipin; and lack of structural congener information). Thus, a cancer dietary risk assessment was not conducted for dimethipin.

Residential Risk

There are no residential uses for dimethipin, as a result a residential risk assessment was not conducted.

Aggregate Risk

(For a complete discussion, see section 7.0 of the Human Health Risk Assessment.)

Aggregate exposure to a pesticide combines exposure from food, drinking water, and if applicable, residential exposure to homeowners. For aggregate risk, EPA typically considers combined exposures from food and residential sources and calculates a drinking water level of comparison (DWLOC), which represent the maximum allowable exposure through drinking water after considering food and residential exposures. If the estimated drinking water concentrations (EDWCs) are less than the DWLOCs, EPA does not have a concern for aggregate exposure. If EDWCs are greater than the DWLOCs, EPA will conduct further analysis to characterize the potential or aggregate risk of concern.

In the case of dimethipin, an acute aggregate assessment was not conducted because an endpoint of concern attributable to a single dose was not identified. In addition as there are no residential uses, the aggregate assessments include exposures via food and drinking water only. The EDWCs for the U.S. population are 99 ppb for ground water and 7.3 ppb for surface water, while the DWLOC is 762 ppb. For the most sensitive sub-population, all infants (<1 year old), the EDWCs are 99 ppb for ground water and 7.3 ppb for surface water, while the DWLOC is 218 ppb. The EPA concludes with reasonable certainty that residues of dimethipin in drinking water and food will not contribute to aggregate chronic risks of concern.

Occupational Risk

(For a complete discussion, see section 9.0 of the Dimethipin Human Health Risk Assessment)

People can be exposed to a pesticide while working through handling, mixing, loading, or applying a pesticide, and reentering a treated site. Handler and worker risks are measured by a Margin of Exposure (MOE) which determines how close the occupational exposure comes to a No Observed Adverse Effect Level (NOAEL) taken from animal studies. Generally, MOEs greater than 100 do not exceed the Agency's level of concern. For workers entering a treated site, Restricted Entry Intervals (REIs) are calculated to determine the minimum length of time required until MOEs exceed 100 and workers can safely re-enter.

Handler and worker risks were assessed via the inhalation route only, as there was no dermal risk concern. Dimethipin has a Re-entry Interval (REI) of 48 hours for all application scenarios. Short

and intermediate inhalation exposure was assessed for dimethipin, as chronic exposure is not applicable. The target MOEs for occupational exposure risk assessments are 100 for both short and intermediate-term exposure.

Occupational Handler Summary

- Exposure analyses were performed using the Pesticide Handlers Exposure Database (PHED).
- The target MOE for occupational populations is 100, which includes the standard safety factors of 10X for intraspecies variability (i.e. differences among humans) and 10X for interspecies variability (differences between humans and animals).
- The results of the short and intermediate-term handler inhalation assessments indicate that all potential exposure scenarios provide MOEs greater than 100 at either the baseline (i.e., no respirator) using open systems or using engineering controls (i.e., closed systems for fixed wing aircraft). Short-term inhalation MOEs range from 1,500 (mixing/loading liquid for aerial applications) to 1,300,000 (mixing/loading liquid for high pressure handwand applications). Intermediate-term inhalation exposures range from 880 (mixing/loading liquids for aerial applications) to 770,000 (mixing/loading liquids for high pressure handwand application).

Post-Application Occupational Risk

EPA did not quantify occupational post-application risks to agricultural workers following cotton or apple treatments because there were no dermal endpoints of concern identified.

Ecological Risk Assessment

To estimate potential ecological risk, EPA integrates the results of exposure and ecotoxicity using the quotient method. Risk quotients (RQs) are calculated by dividing exposure estimates by ecotoxicity values, both acute and chronic, for various wildlife species. RQs are then compared to levels of concern (LOCs). Generally, the higher the RQ, the greater the potential risk. Risk characterization provides further information on the likelihood of adverse effects occurring by considering the fate of the chemical in the environment, communities and species potentially at risk, their spatial and temporal distributions, and the nature of the effects observed in studies.

Environmental Fate and Transport

(For a complete discussion, see section III of the Environmental Risk Assessment)

Dimethipin is persistent in most environmental conditions, with biodegradation, hydrolysis, and photolysis all occurring slowly with a range of half-lives from a few weeks to several months. Dimethipin is not expected to absorb in solids and sediments, and therefore may be available for leaching to groundwater or run-off to surface water. Dimethipin does not bioaccumulate in aquatic organisms. No major degradates were identified in the environmental fate studies.

Terrestrial Risk

Terrestrial wildlife exposure estimates are typically calculated for bird and mammals, emphasizing a dietary exposure route for uptake of pesticide active ingredients. These exposures are considered as surrogates for terrestrial-phase amphibians as well as reptiles. For exposure to terrestrial organisms, such as birds and small mammals, pesticide residues on food items are estimated, based on application rate for acute exposures. Degradation is factored into chronic exposure calculations. Maximum residue levels and application rates are assumed for the terrestrial assessments:

- No mammalian LOCs (acute or chronic) were exceeded for non-bearing apple nursery stock
- For applications to cotton, the mammalian acute RQs range from (0.0001-0.2). The acute restricted use criteria (LOC 0.2) is exceeded for a 15g mammal feeding on short grass.
- All chronic RQs for mammals are below the LOC of 1 for the application of dimethipin to cotton.
- No avian acute risks are predicted for cotton and non-bearing apple nursery stock.
- Avian chronic RQs could not be calculated due to a lack of chronic data on birds; therefore chronic risk cannot be precluded.
- Despite the lack of plant toxicity data, there is an assumption that dimethipin may be harmful to terrestrial plants, due to its herbicidal properties.

Aquatic Organism Risk

- No acute or chronic risks are predicted for freshwater fish, estuarine fish, and aquatic invertebrates.
- Acute RQ values for aquatic plants are well below the LOC for acute risk for both cotton and apples/non-bearing nursery stock crop applications.

Risk to Endangered Species

The preliminary risk assessment for endangered species indicates that dimethipin has the potential for causing acute risk to endangered small mammals that forage on grasses and broadleaf

plants. The LOC for acute endangered risk (LOC 0.1) is exceeded for a 15g mammal feeding on short grass, tall grass, and broadleaf plants/small insects, and for a 35g mammal feeding on short grass and broadleaf plants/small insects. Due to a lack of plant toxicity data, there is also an assumption that dimethipin may be harmful to endangered terrestrial plants. These findings are based solely on EPA's screening level assessment and do not constitute "may affect" findings under the Endangered Species Act.

Status of Data

The following data requirements have been initially identified by the Agency:

Environmental Fate and Ecological Effects Data Gaps for OPPTS Guidelines:

835.7100 Small Scale Prospective Ground Water Monitoring Study: Due to the extreme mobility and persistence of dimethipin in the environment, a small-scale prospective groundwater monitoring study will provide additional fate information for the better understanding of this chemical in the environment and improve the certainty of the risk assessment.

850.2300 Avian Reproduction Test (Bobwhite Quail and Mallard Duck): There are no chronic avian reproduction data available for dimethipin. These studies will enable a chronic risk assessment of this persistent chemical.

850.1300 Daphnid Chronic Toxicity Test (Early-Life Stage in Fish-Freshwater): Current aquatic modeling indicates the potential for chronic aquatic exposure to dimethipin. The current assessment is relying on Supplemental data. A Core study will enable reduced uncertainty in the chronic risk assessment for freshwater fish.

850.1300 Daphnid Chronic Toxicity Test (Early-Life Stage in Fish-Marine/Estuarine): Current aquatic modeling indicates the potential for chronic aquatic exposure to dimethipin. This study is *reserved* pending the submission and review of the early life-stage study with a freshwater fish species.

850.1350 Life Cycle Aquatic Invertebrates- Marine/Estuarine: Current aquatic modeling indicates the potential for chronic aquatic exposure to dimethipin. Although chronic freshwater invertebrate toxicity data does not indicate that these organisms would be at risk, marine/estuarine invertebrates may be more sensitive.

850.1500 Fish Life Cycle Study: This study is *reserved*, pending submission and review of early life-stage fish testing.

850.4225 Seedling Germination and Seedling Emergence, Tier II: Dimethipin is a plant growth regulator used as a defoliant, and thus may have an adverse effect on non-target plants. This study will enable the assessment of risk to non-target terrestrial plants off-site. The

current assessment does not have guideline data valid for calculating the needed risk quotients.

850.4250 Vegetative Vigor - Tier II: Dimethipin is a plant growth regulator used as a defoliant, and thus may have an adverse effect on nontarget plants. This study will enable the assessment of risk to non-target terrestrial plants off-site. The current assessment does not have guideline data valid for calculating the needed risk quotients.

Health Effects Data Gaps for OPPTS Guidelines:

Toxicology:

870.3700a Prenatal Developmental Toxicity (Teratogenicity), Rat: Data must be submitted on test material stability, homogeneity, and concentration in the dosing medium.

870.3700b Prenatal Developmental Toxicity (Teratogenicity), Rabbit: Data must be submitted on test material stability, homogeneity, and concentration in the dosing medium.

870.4100b Chronic Feeding Toxicity Study, Non-rodent: Data must be submitted on historical controls, and diet homogeneity and stability.

Residue Chemistry:

860.1500 Crop Field Trials (Cotton Gin Byproducts Group): Data must be submitted depicting dimethipin residues in cotton gin byproducts which include burrs, leaves, stem, lint, immature seeds and sand (dirt) obtained from ginning cotton.

860.1850 Confined Accumulation in Rotational Crops Study: To demonstrate the storage stability of the samples used in the supplemental confined rotational crop submission, the registrant must submit additional data/information comparing the chromatographic profiles of the stored samples with those of the original analyses (see D219060and D223855, DERs 4376801, 43768202,and 43931301).

860.1900 Field Accumulation in Rotational Crops Study: Additional storage stability data are required to support the limited field rotational crop studies (see D225417, DERs 43979102 and 43979101). HED notes that crop field trial data for cotton gin byproducts and extensive field rotational crop studies are required; storage stability data to support those studies will be required unless samples are analyzed within one month of collection.

860.1900 Field Accumulation in Rotational Crops Study: The available limited rotational crop studies indicate the potential for dimethipin residues in certain rotated crops at the established plantback interval (6 months). Extensive field rotational crop studies must be submitted for all crops, except leafy vegetables, for which the registrant wishes to allow a 6-month plantback interval. In the submitted studies, residues of dimethipin were below the LOQ (<0.02 ppm) to 0.031 ppm in lettuce, <0.02 ppm in carrot roots, 0.034-0.071 ppm in carrot tops, 0.027-0.039 ppm in wheat forage, <0.02 ppm in wheat grain, and <0.02-0.023 ppm in wheat straw planted one month after application

of dimethipin. Residues of dimethipin were below the LOQ (<0.02 ppm) in lettuce, <0.02-0.024 ppm in carrot roots, <0.02-0.180 ppm in carrot tops, <0.02 ppm in oat forage, <0.02 ppm in oat grain, and <0.02-0.021 ppm in oat straw planted six months after dimethipin application. At both plantback intervals, residues were highest in carrot tops.