Appendix J:

The HED Chapter of the Reregistration Eligibility Decision Document (RED)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: October 14, 2004

SUBJECT: **Mancozeb**. Health Effects Division (HED) Human Health Risk Assessment to Support Reregistration.
Chemical ID No. 014504. List A Reregistration Case No. 0643.
DP Barcode No. D305811

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The attached human health risk assessment for the active ingredient mancozeb summarizes human health risks associated with its use as a fungicide on raw agricultural commodities, and on turf and ornamentals. The risk assessment has been reviewed by the HED Risk Assessment Review Committee (RARC), while supporting documents and exposure assessments have been approved by HED peer review committees (e.g., MARC, HIARC, ExpoSAC, DE SAC and ChemSAC). This risk assessment has since been revised to incorporate error corrections by the Mancozeb Task Force. The Task Force also made a number of comments and suggestions which have not been incorporated into the risk assessment; these comments will be addressed at a later point.

Principal changes to the risk assessment include revision of the chronic PAD to 0.05 mg/kg/day, elimination of a database uncertainty factor, approval of a dermal toxicity study, and limitation of turf use to sod farms, golf courses and collegiate and professional athletic fields. There is no home use, except for transplanted sod.

Risk from mancozeb and its metabolite ethylene thiourea (ETU) in food are below HED's level of concern for acute and chronic (cancer and non-cancer) exposures. Risks from residential exposure to mancozeb and ETU residues in home gardens and on golf courses are not of concern, but risks for toddlers playing on treated turf are of concern at the existing pre-harvest interval.

Occupational handler risks for mancozeb and ETU are highest for mixer/loaders using wettable powders, and respiratory protection is required in some cases to mitigate these risks. Potato seed piece and seed treatment mixer/loader risks can be mitigated with respiratory protection. Postapplication risks are not of concern for most activities/crops based on re-entry in accordance with registered labels (i.e., after 24 hours). However, chronic ETU postapplication risks are of concern for high exposure activities on greenhouse-grown cut flowers. Postapplication ETU cancer risks are in the range of $1x10^{-4}$ to $1x10^{-5}$ on the day of application for most scenarios, but did not decline to $1x10^{-6}$ until 35 days after application.

Provided the risks for occupational workers and for adults and toddlers exposed to residues on turf can be mitigated, HED has no objection to reregistration of the active ingredient mancozeb. Recommendations for reassessed tolerances will be provided when modifications to all relevant sections of 40 CFR have been determined.

Supporting information for this risk assessment includes the following documents:

1) Report of the HIARC Committee, 05/01/03, K. Farwell, HED TXR No. 0051868.
2) Toxicology Chapter for the Mancozeb RED, 3/08/00, K. Farwell, DP Barcode D251408.
3) Mancozeb. Endpoint Selection and Error-Correction Comments from Mancozeb Task Force. October 14, 2004, Kit Farwell, D305812
4) Outcome of the HED Metabolism Assessment Review Committee Meeting of 1/16/02, C. Swartz, 12/3/02, TXR # 0050408.
5) Residue Chemistry Chapter of the HED RED, 8/19/04, C. Olinger, DP Barcode No. D251407.
6) Mancozeb: Anticipated Residues for Dietary Exposure Assessment to Support Reregistration, C. Olinger, 8/19/04, DP Barcode No. D283152.
7) Ethylene bisdithiocarbamates [Mancozeb, Maneb, and Metiram]. Summary of Percent Crop Treated (%CT), and Justification for Use of the 1990 EBDC Market Basket Survey in Dietary Exposure Assessments for Reregistration., C. Swartz, 09/04/03, DP Barcode Nos. D290137, D290139 and D290140.
8) Acute Probabilistic, Chronic, and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision, Felecia Fort, 10/14/04.
9) Mancozeb: Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document, Timothy Dole, 9/27/04, DP Barcode: D305813
10) Review of Mancozeb Incident Reports, 10/16/02, J. Blondell, DP Barcode No. D286184.
11) Revision No. 2: Estimated Drinking Water Concentrations of Ethylenebisdithiocarbamate (EBDC) Degradate Ethylenethiourea (ETU) for the Use in Human Health Risk Assessment. 8/26/2004, Ronald Parker and Mohammed Ruhman. DP Barcode: D290057
12) Quantitative Usage Analysis for Mancozeb, F. Hernandez, 12/2/02.

HED Team members who participated in the preparation of this document include Christine Olinger (Residue Chemistry/Anticipated Residues), Felecia Fort (Dietary Exposure), Timothy Dole (Occupational/Residential Exposure), Dr. Jerome Blondell (Incident Report), Dr. Kit Farwell (Toxicology and Risk Assessor), Christina Swartz (Risk Assessor), Dr. Whang Phang and Michael Metzger. Information related to exposure from drinking water was provided by the Environmental Fate and Effects Division (EFED), Ron Parker and Mohammad Ruhman. Use information was provided by the EBDC task forces and Frank Hernandez (OPP Biological and Economic Analysis Division.

1.0 Executive Summary

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the toxicity and exposure data bases for the pesticide active ingredient mancozeb, and has conducted a human health risk assessment to support the reregistration of products containing mancozeb. Mancozeb is a coordination product of zinc ion and maneb (manganese ethylenebisdithiocarbamate), and is a member of the ethylene bisdithiocarbamate (EBDC) group of fungicides, which includes the related active ingredients metiram and maneb. Mancozeb is the common name of the fungicide.

Use and Usage Information

Mancozeb is a widely used fungicide in agriculture, professional turf management, horticulture, and home gardening. Mancozeb formulations include wettable powders (WP), dry flowables (DF), flowables (F) and dusts (D). Agricultural uses include pome fruit crops (e.g., apples, pears), fruits and vegetables (e.g., cucumbers, onions, tomatoes, and grapes), some high acre row crops (e.g., corn and potatoes), seed piece treatment (e.g. potatoes) and seed treatment (e.g. rice, wheat and cotton). Horticultural uses include ornamental plants in nurseries and greenhouses, sod farms, residential lawns and golf courses.

Approximately 7½ million pounds of mancozeb are used in agricultural settings on an annual basis. Agricultural uses are concentrated in (but not limited to) the following states: FL, ME, MI, MN, ND, NY, VA, VT, WA, and WI. In terms of pounds active ingredient applied annually in the US, mancozeb usage is allocated to potatoes (30%), fresh tomatoes (13%), apples (13%), watermelons (5%), grapes (4%) and fresh sweet corn (3%); crops with a high percentage of the total U.S. planted acres treated include fresh market tomatoes (56%), squash (51%), onions (42%), potatoes (35%), and pears (31%). Crops with less than 1 percent of the crop treated are barley, corn, cotton, oats, rice, soybeans, and wheat.

Regulatory Background

The EBDCs have been the subject of several Special Reviews. In 1977, the Agency initiated a Special Review and Continued Registration of Pesticide Products containing EBDCs based on evidence suggesting that the EBDCs and ethylenethiourea (ETU), a contaminant, metabolite and degradation product of these pesticides, posed potential risks to human health and the environment. In 1982, the Agency concluded this Special Review by issuing a Final Determination (PD 4) which required risk reduction measures to prevent unreasonable adverse effects pending development and submission of additional data needed for improved risk assessment.

In 1987, EPA issued a second Notice of Initiation of Special Review of the EBDC pesticides because of health concerns caused by ETU, including potential carcinogenic, developmental and thyroid effects. The Special Review's Preliminary Determination (PD 2/3) was published on 12/20/89 (54 FR 52158) and the Final Determination (PD 4) on 3/2/92 (57 FR 7484). The Agency concluded that

the dietary risks of EBDCs exceeded the benefits for the following food/feed uses for which one or more of the EBDC pesticides were registered: apricots, carrots, celery, collards, mustard greens, nectarines, peaches, rhubarb, spinach, succulent beans, and turnips. Accordingly, EPA canceled all mancozeb and other EBDC products registered on the above-listed food/feed crops.

Recently, EPA received requests for amendments to several mancozeb product registrations and a petition to amend the 1992 cancellation order to allow for limited use of mancozeb on carrots and celery. Specifically, applicants have requested amendments to include use of mancozeb on carrots in Michigan and Wisconsin to control Cercospora leaf blight or leaf spot and Alternaria leaf blight or leaf spot. Additional amendments have been requested to allow use on celery in Florida to control Cercospora early blight and Septoria late blight. EPA has not determined whether the petition warrants a hearing under 40 C.F.R. §164 nor has it determined whether it will grant the attendant registration amendment requests. Although EPA has not reached any conclusions on the merits of the petition or the amendment requests, it has considered in this risk assessment the additional risks that would result from the requested uses on carrots and celery. That consideration is for informational purposes only and cannot be interpreted as an indication of the Agency's position on the petition or amendment requests.

In addition to the product cancellations listed above, the Special Review initially set the pre-harvest interval for use on potatoes at 14 days for most states. The only exceptions to the 14-day PHI were CT, FL, ME, MA, NH, NY, PA, VT and WI, where EPA determined that disease pressures caused by late blight justified a 3-day PHI. Subsequently, presented with evidence of late blight in additional states, EPA extended the 3-day PHI to DE, MI, and OH. Recently, EPA received requests for amendments to several EBDC product registrations and petitions to amend the 1992 cancellation order to allow for a 3-day PHI in all states due to an alleged increase in the occurrence of late blight nationwide. EPA has not determined whether the petition warrants a hearing under 40 CFR §164, nor has it determined whether it will grant the attendant registration amendment requests. Although EPA has not reached any conclusions on the merits of the petition or the amendment requests, HED has considered in this risk assessment the additional risks that would result from a nationwide reduction in the PHI for potatoes to 3 days. This consideration is for informational purposes only, and cannot be interpreted as an indication of the Agency's position on the petition or amendment requests.

In the 1992 Special Review, and in the current risk assessment for mancozeb, exposure to both the parent EBDC, mancozeb, and its metabolite/degradate ETU have been considered, both for dietary (food and water) residential (dermal) and occupational (dermal and inhalation) risk assessments. Crops treated with mancozeb may contain both mancozeb and ETU residues; in addition, cooking and/or processing may result in conversion of mancozeb residues to ETU, or in concentration or reduction of existing ETU residues. Therefore, both parent mancozeb and ETU residues may be consumed in the diet. During application of products containing mancozeb, workers may be exposed to ETU residues which form during degradation of the tank mix over a typical workday, and the Agency has data to reflect these potential exposures. Additional exposure to both mancozeb and ETU may occur during activities conducted in and around growing crops following treatment with

mancozeb, including residential exposures following contact with treated turf. Finally, for both occupational and dietary exposures, including oral, dermal and inhalation routes of exposure, a 7.5% *in vivo* metabolic conversion of absorbed mancozeb to ETU has been used based on rat metabolism data, and has been accounted for in estimating exposure to ETU.

A separate risk assessment document is under preparation for each of the three EBDCs and ETU. The ETU risk assessment contains more detailed discussions of ETU hazard characterization, FQPA considerations, endpoint selection, and dose-response assessment. Relevant information is presented in the mancozeb risk assessment (see Appendix 1), in order to appropriately address potential exposure to ETU resulting from mancozeb uses. The other EBDCs, with their different use profiles, also have chemical-specific assessments of exposure to ETU, along with associated risks. The ETU risk assessment document discusses potential exposure to ETU from all sources, and characterizes such exposures in a broader sense.

Mancozeb *Hazard Profile and Food Quality Protection Act (FQPA) Decision*

The mancozeb toxicology database is incomplete; data gaps include an acute neurotoxicity study in rats and a comparative study for thyroid toxicity in adults and offspring. Once submitted, these studies may be used to refine exposure and risk assessments.

Mancozeb is not acutely toxic *via* the oral, dermal, or inhalation routes of exposure (Tox Category IV). Mancozeb is not a skin irritant (Tox Category IV) nor is it a skin sensitizer although it did cause eye irritation (Tox Category III). The findings in multiple studies demonstrate that the thyroid is a target organ for mancozeb. Thyroid toxicity was manifested as alterations in thyroid hormones, increased thyroid weight, and microscopic thyroid lesions (mainly thyroid follicular cell hyperplasia). In a subchronic study with rat, neuropathology was seen (injury to peripheral nerves) microscopically with associated clinical signs (abnormal gait and limited use of rear legs) and loss of muscle mass.

Mancozeb is rapidly absorbed and eliminated in the urine. In oral rat metabolism studies with radiolabelled mancozeb and other EBDCs, an average 7.5% *in vivo* metabolic conversion of EBDC to ETU occurred, on a weight-to-weight basis. While this metabolic conversion has been included in the mancozeb exposure and risk assessments, there is inherent uncertainty in assuming the metabolic conversion occurs following dermal and inhalation dosing because absorption after dermal and inhalation dosing bypasses the liver. Metabolism data indicate mancozeb does not bio-accumulate. Mancozeb has been tested in a series of *in vitro* and *in vivo* genotoxicity assays, which have shown that it exhibits weak genotoxic potential.

Thyroid follicular cell adenomas and carcinomas were increased in high-dose males and females in the combined rat toxicity/carcinogenicity study with mancozeb. Doses in a mouse study were too low to assess carcinogenicity, and there were no treatment-related changes in tumor rates. Historically, mancozeb's potential for carcinogenicity has been based on its metabolite ETU, which is classified as Group B2, with a cancer potency factor [Q_1*, 0.0601 $(mg/kg/day)^{-1}$] for risk assessment. Because

mancozeb is known to be converted to ETU, it has also been classified as Group B2 for carcinogenicity, and after applying the metabolic conversion factor for EBDC to ETU (0.075), the ETU cancer potency factor has been used in past and current risk assessments for assessing cancer risk associated with mancozeb uses.

Developmental defects in the rat developmental toxicity study were numerous and severe, including hydrocephaly, skeletal system defects, and other gross defects, but they occurred at a dose which caused maternal mortality and did not indicate increased susceptibility of offspring. Abortions occurred in the rabbit developmental toxicity study at the high dose which also caused maternal mortality, and there was no indication of enhanced susceptibility of offspring in the rabbit. There was no evidence of reproductive toxicity in the 2-generation reproduction study in rats. Based on the lack of evidence of pre- and/or postnatal susceptibility resulting from exposure to mancozeb, and considering the lack of residual uncertainties, the Special FQPA Safety Factor (FQPA SF) was removed, or reduced to 1X.

There is concern for developmental neurotoxicity resulting from exposure to mancozeb, due to the developmental effects observed following dosing with mancozeb and its metabolite ETU. Since the developmental effects are believed to be due to ETU, a developmental neurotoxicity study with ETU was required. For mancozeb, a comparative assessment of thyroid toxicity with young and adult animals is required to address potential thyroid effects in the young animal. Because there is a lack of regulatory experience with comparative thyroid studies, a database uncertainty factor was not required for this study.

***ETU** Hazard Profile and Food Quality Protection Act (FQPA) Decision*

The database for ETU is limited based on guideline studies, and HED has relied on a combination of guideline data and several studies in the open literature to assess hazard for ETU. The thyroid is a target organ for ETU as it is for the EBDCs fungicides; thyroid toxicity in subchronic and chronic rat, mouse, and dog studies included decreased levels of T_4, increases or decreases in T_3, compensatory increases in levels of TSH, increased thyroid weight, and microscopic thyroid changes, chiefly hyperplasia. Overt liver toxicity was observed in one chronic dog study.

Developmental defects in the rat developmental study were similar to those seen with mancozeb, and included hydrocephaly and related lesions, skeletal system defects, and other gross defects. These defects showed increased susceptibility to fetuses because they occurred at a dose which only caused decreased maternal food consumption and body weight gain. Although the data provided evidence for increased susceptibility to fetuses following dosing with ETU, HED removed (reduced to1X) the Special FQPA Safety Factor because the teratogenic effects were well characterized in numerous studies in the published literature, as well as in a guideline study submitted by the registrant. In addition, the dose-response relationship was well characterized, and doses selected for overall risk assessments addressed concerns for developmental and thyroid toxicity. However, due to the lack of several guideline studies, HED retained a 10X database uncertainty factor for dietary, residential and

aggregate risk assessments for ETU.

Mancozeb *Doses and Endpoints Selected for Risk Assessment*

The studies/doses/endpoints selected for mancozeb and ETU risk assessments are summarized below. For mancozeb, HED has selected thyroid effects as the endpoint for most risk assessments.

Exposure Route, Duration	Mancozeb Dose in mg/kg/day (study/effects)
Acute dietary (females 13-49)	NOAEL of 30 (Developmental rabbit/abortions)
Acute dietary (gen. US pop.)	No applicable endpoint/dose identified
Chronic dietary (gen. US pop.)	NOAEL of 4.83 (Rat chronic/thyroid effects)
Incidental oral, any duration	NOAEL of 9.24 (Subchronic oral rat/decreased thyroxine)
Dermal, Short-, Intermediate-term	Quantitation not required (no toxicity at limit dose in dermal tox study)
Dermal, Long term	NOAEL of 4.83 (Rat oral chronic/carcinogenicity/thyroid effects)
Inhalation, any duration	NOAEL of 21 (Subchronic inhalation rat/thyroid hyperplasia and decreased thyroxine in females)

[Combined Uncertainty factors (UFs) for mancozeb occupational and residential assessments are 100x. Mancozeb dermal absorption is 1%. Inhalation absorption is 100%.]

ETU *Doses and Endpoints Selected for Risk Assessment*

For ETU risk assessments, HED has selected developmental effects as the most sensitive endpoint for short- and intermediate-term risks, based on a registrant-submitted guideline developmental rat study and on a developmental rat study from the open literature.

Exposure Route, Duration	ETU Dose in mg/kg/day (study/effects)
Acute dietary (females 13-49)	NOAEL of 5 (Developmental rat/developmental brain defects)
Acute dietary (gen. US pop)	No applicable endpoint/dose identified
Chronic dietary (gen. US pop.)	NOAEL of 0.18 (Chronic dog/thyroid toxicity)
Incidental oral, any duration	NOAEL of 7 (4-week Dog/thyroid toxicity)
Dermal, Short/Int-Term	NOAEL of 5 (Developmental rat/developmental brain defects)
Dermal, Long-Term	NOAEL of 0.18 (Chronic dog/thyroid toxicity)
Inhalation, Short/Int-Term	NOAEL of 5 (Developmental rat/developmental brain defects)
Inhalation, Long-Term	NOAEL of 0.18 (Chronic dog/thyroid toxicity)

[Combined Uncertainty factors (UFs) for ETU occupational assessments are 100x; combined UFs for residential and dietary assessments are 1000x. Dermal absorption for ETU is 26%, while inhalation absorption is 100%. Dermal and inhalation exposures can be combined, since the toxic effects from these two routes of exposure are similar for similar durations.]

Exposure Assessment

The use pattern for mancozeb is expected to result in exposure to mancozeb and ETU for the general population, through food and drinking water. The uses in home gardens and on turf result in residential handler and postapplication exposure. Exposures can occur for occupational handlers mixing, loading or applying mancozeb formulations, both in agricultural settings and in greenhouses. In addition, potato seed piece treatment and other seed treatment uses result in handler exposure during treatment as well as during planting of treated seed pieces and seed. Postapplication exposure is expected when workers perform crop maintenance activities or during harvest, as well as in greenhouse settings.

Mancozeb and ETU Dietary (Food) Exposure and Risk

The residue chemistry database for mancozeb is generally adequate for risk assessment purposes, but additional field trial data, a ruminant feeding study, and some processing studies are needed (see data gaps). In general, the data are acceptable for tolerance reassessment purposes. The nature of mancozeb residues is adequately understood, both for tolerance enforcement and risk assessment purposes. The HED Metabolism Assessment Review Committee (MARC) has concluded that residues of concern for risk assessment include mancozeb [and metabolites converted to carbon disulfide (CS_2)] and the metabolite ETU; residues of concern for tolerance enforcement (i.e., to be included in the tolerance expression) are mancozeb and metabolites converted to CS_2.

HED has recommended a change to the existing tolerance expression (40 CFR §180.176) for mancozeb, and for similar changes in other EBDC tolerances. Reassessed tolerances for all three EBDCs will be calculated in terms of CS_2, rather than in terms of zineb, an EBDC that is no longer registered. Recommended changes to EBDC tolerance expressions will be made after the preliminary risk assessments have been reviewed. The previous requirement for analytical methods capable of distinguishing between the three parent EBDCs has been waived. Adequate analytical methods are available for tolerance enforcement.

Highly refined acute and chronic dietary exposure and risk assessments were conducted for mancozeb and mancozeb-derived ETU using anticipated residues based on field trial residue data and monitoring data from the EBDC/ETU Market Basket Survey. In addition, processing factors derived from extensive processing and cooking and consumer practices studies and estimated percent crop treated (%CT) information were used. Anticipated residue estimates for ETU include (1) ETU present in commodities analyzed in field trial and market basket survey data, (2) ETU formed from mancozeb during processing, and (3) ETU formed based on 7.5% *in vivo* mammalian metabolic conversion of mancozeb to ETU residues.

Acute dietary exposure and risk from mancozeb and ETU are below HED's level of concern for females 13-49. Estimated dietary exposure to mancozeb *per se* is 2% of the acute population adjusted dose (aPAD). For ETU, estimated exposure of is 18 %aPAD. No acute effects associated with a

single exposure to either mancozeb or ETU were identified that are applicable to other population subgroups.

Chronic dietary exposure and risk from mancozeb and ETU are below HED's level of concern for the general US population and various population subgroups. For both mancozeb *per se* and ETU, the most highly exposed population subgroup is children 1-2 years old with <1% of the chronic population adjusted dose (cPAD). For ETU, children 1-2 years old have an estimated exposure of 33% cPAD.

The estimated dietary exposure for the general US population corresponds to a cancer risk of 1.3×10^{-6}, which is not of concern. The commodity contribution analysis indicates that mango and milk are the major contributors to the risk estimate.

Mancozeb and ETU Residential Exposure

Residential exposures to mancozeb and mancozeb-derived ETU are likely to occur based on registered uses. Products containing mancozeb are intended for use on home gardens (vegetables) and ornamentals. Potential residential exposures occur for those who apply these products (residential handlers), and for adults and youth who re-enter gardens to harvest crops (postapplication). There is also a potential for golfer, athlete, and toddler post application exposure on golf course turf, athletic fields, and transplanted lawns. As a result, risk assessments have been completed for both residential handler and postapplication scenarios.

Residential handler exposures were assessed assuming application with a low pressure sprayer or backpack sprayer at an application rate of 2.4 lbs ai/acre to a 1000 square foot garden. The residential handler MOEs for both mancozeb and ETU are not of concern because they greatly exceed the target MOEs of 100 and 1000, respectively. The cancer risks are also not of concern because they are less than $1x10^{-6}$.

The post application risks were also assessed for adult and youth-aged home gardeners working in gardens following mancozeb treatment. The MOEs for both mancozeb and ETU exceed the target MOEs on day 0 for all of the post application scenarios considered. The cancer risks for adult home gardeners are less than $1x10^{-6}$.

The turf exposures were assessed for toddlers by assuming that the turf would be installed in a residential setting no sooner than three days after application. The MOEs were calculated for Mancozeb and ETU using the residential SOPs. The total MOE for mancozeb is below 100 (93). The total MOEs for mancozeb rise to 100 with a PHI of 2 days while the total MOE for ETU rises to 1000 with a PHI of 3 days.

The turf exposures were assessed for golfers and athletes by using the day 0 TTR for short term exposures and the 7 day average TTR for lifetime exposures. The ETU MOE for golfers exceeds the

target MOE of 1000 while the ETU MOE for athletes (450) does not exceed the target MOE. The golfer cancer risk is 2×10^{-7} assuming that golfers played an average of 19 days per year as indicated by data from the National Golf Federation. The cancer risk for athletes is 6×10^{-7} assuming 10 days exposure per year and 10 years exposure per lifetime.

Drinking Water Assessment

The OPP Environmental Fate and Effects Division (EFED) prepared the drinking water assessment for mancozeb reregistration. The parent EBDC fungicides are very short-lived in soil and water, and would not reach water used for human consumption whether from surface water or ground water. However, ETU is highly water soluble, and may reach both surface and ground water under some conditions. The drinking water exposure assessment for mancozeb (and for maneb and metiram) addresses concentrations of ETU only.

Estimated drinking water concentrations (EDWCs) for surface water were derived using a combined modeling/monitoring approach. The monitoring data were from a targeted surface water monitoring study conducted by the ETU Task Force, in which none of the tested water samples had concentrations above the limit of detection of 0.1 ppb. A ground water EDWC was selected from a targeted ground water monitoring study conducted in FL in a known EBDC use area. Acute surface water estimates were reported as a range of 0.1 ppb (monitoring) to 25.2 ppb (modeling) and chronic/cancer surface water estimates were 0.1 ppb (monitoring). Acute/chronic/cancer ground water estimates were 0.21 ppb (monitoring).

Aggregate Exposure from Food, Drinking Water and Residential Sources

A variety of aggregate exposure and risk assessments were conducted for mancozeb *per se* and ETU (cancer and non-cancer). Toddlers' exposures to mancozeb and ETU on treated turf exceed HED's level of concern, and therefore aggregate risks were not calculated; any additional exposure from food and drinking water would only add to HED's level of concern.

Mancozeb residues are not expected in drinking water, so aggregate risks for mancozeb *per se* include only food and residential (inhalation) exposures. Dermal risk was not quantified for residential exposure because no toxicity occurred at the limit dose in the dermal toxicity study. Since ETU residues are expected in drinking water, ETU aggregate risks are based on food, water and residential (dermal and inhalation) exposures. For calculating ETU acute aggregate risk, the DWLOC approach was used, while for ETU short-term and chronic aggregate risks, quantitative exposure estimates for drinking water from ground water sources were added to dermal and inhalation exposures. Aggregate ETU exposure and risk calculated using ground water are protective of aggregate risk from surface water sources, since chronic ground water residues are twice those of surface water.

Mancozeb and ETU exposure and risk from food and water are not of concern; these exposures,

combined with residential exposures that were also below the level of concern, resulted in aggregate risks below HED's level of concern for acute, short-term, and chronic (cancer and non-cancer) exposures.

Mancozeb and ETU Occupational Exposure and Risk

Occupational populations (handlers) are potentially exposed to mancozeb and ETU while making applications to a variety of tree fruits, fruits, vegetables, row crops, sod, turf, ornamentals (including in greenhouses) potatoes (foliar and seed piece), and during seed treatments. In addition, potential exposure to mancozeb and ETU occurs after application, when workers contact foliage or harvest treated crops or ornamentals (postapplication). In both handler and postapplication exposure assessments, risks for both mancozeb *per se* and ETU were calculated. For both handler and postapplication assessments, the mancozeb dose was multiplied by 0.075 to take into account the 7.5 % in vivo metabolic conversion of mancozeb to ETU. This "metabolic" ETU was added to the ETU exposure from handler and postapplication activities to obtain the total ETU exposure. Handler assessments addressed combined dermal and inhalation exposures, but postapplication risks were derived solely from dermal exposure.

Mancozeb labels require double layer personal protective equipment (PPE) and a chemical resistant apron for mixing/loading and double layer PPE without the apron for application. Double layer PPE consists of a long-sleeved shirt, long pants, shoes, socks, gloves, and coveralls. The labels do not require respiratory protection.

Mancozeb and ETU Handler Assessments

Risks for occupational handlers addressed the following scenarios: mixer/loader, applicator, mixer/loader/applicator, and flagger, potato seed piece treatment and planting, and seed treatment (including a variety of individual and combined tasks). These scenarios were used to estimate exposures based on application of a variety of formulations (wettable powder, dry flowables, liquid flowables, liquid dips and dusts), and using a variety of application methods, such as groundboom, aerial, chemigation, and high- and low-pressure handheld equipment, as well as seed and seed piece treatment equipment.

There were no chemical-specific handler data, so unit exposures from the Pesticide Handlers Exposure Database (PHED) were used to estimate exposures for a variety of clothing scenarios and combinations of PPE and engineering controls. Standard assumptions were used for the number of acres treated, body weight, hours worked, etc., for most handler scenarios. For the potato seed piece use, assumptions were based on labels and on conversations with experts in the potato industry. For seed treatment scenarios, unit exposures were derived from the recently published Seed Treatment SOP; the amount of seed treated was estimated based on seed planting rates on a per acre basis, and assuming 80 acres planted per day. Overall, medium to high quality data were used to generate unit exposures for mancozeb handler assessments, although there were no data available to assess several

scenarios. The target MOE for occupational risk is 100.

Mancozeb Risks (Ag and Greenhouse Uses)

Only inhalation MOEs were calculated for short/intermediate term mancozeb exposures because no effects were observed in the mancozeb 28 day dermal toxicity study at the limit dose. For some of the mixer loader scenarios involving wettable powder, the risks are of concern and respiratory protection is required to achieve HED risk targets. The risks for mixing and loading dry flowable and liquid flowable formulations are much lower and respiratory protection is not needed. The risks for the remaining scenarios are not of concern. The labels typically require that mixers and loaders wear an apron with double layer PPE (i.e. coveralls and gloves over long pants and long-sleeved shirts) while applicators are required to wear double layer PPE without the apron. Most of the labels do not require respiratory protection. Chronic MOEs were calculated for greenhouse scenarios and exceed the target MOE of 100 if single layer PPE is worn.

The non-cancer mancozeb risks for seed treatment are of concern only when mixing or loading the wettable powder formulations and require respiratory protection or engineering controls to achieve the target MOE. The risks for loading the dry flowable or liquid flowable formulations are not of concern and do not require respiratory protection. The risks of applying the seed treatment and handling the treated seed are not of concern. The risks for loading dusts for potato seed piece treatment are also of concern and require respiratory protection. The risks of applying the dusts to potato seed pieces could not be evaluated because there is no exposure data for this scenario.

Risk calculations were also performed to assess the risk of ETU that is contaminant in the mancozeb spray mix and that is metabolized from absorbed mancozeb. The short/intermediate term ETU MOEs are of concern for some high volume mix/load wettable powder scenarios and require respiratory protection or engineering control to achieve the target MOE. The chronic risks for ETU are of concern for a few scenarios such as mix/load/apply wettable powders to pachysandra, however, these risks can be mitigated with respiratory protection. The cancer risks were also calculated for ETU exposure assuming 30 days of mancozeb use per year. Most of the risks were below $1x10^{-4}$ without mitigation and all of the cancer risks are below $1x10^{-4}$ with the mitigation recommended to address the non-cancer risks. Many of the risks are also below $1x10^{-5}$ with mitigation and some are below $1x10^{-6}$. Some of the high volume commercial mixer/loader scenarios, however, remain above $1x10^{-6}$ with engineering controls and might be of concern if $1x10^{-6}$ is chosen as a risk mitigation goal.

Mancozeb and ETU Postapplication Assessments

Current mancozeb labels specify 24 hour Restricted Entry Intervals (REIs). A variety of postapplication exposure scenarios were identified by the type of activity involved, and by the range of exposure expected, i.e., low, medium and high exposure activities. Examples of low exposure activities include irrigation and scouting; medium exposure activities may involve scouting of mature plants, or, in greenhouses, hand pinching chrysanthemums. Potential high exposure activities are hand-harvesting sweet corn or flowers.

Eight chemical-specific dislodgeable foliar residue (DFR) studies were submitted for mancozeb on apples, grapes and tomatoes. These data show that mancozeb residues are much higher than ETU residues, which were often low or nondetectable. The best available DFR data were translated to all other crops based on the region and crop type, and were adjusted proportionally for application rate. These data were used with standard HED transfer coefficients and assumptions to estimate postapplication exposure and risk for all crops/ornamentals potentially treated with mancozeb. A mancozeb turf transferable residue (TTR) study was used to estimate postapplication residues of mancozeb and ETU on turf.

Non-Cancer Postapplication Risks

Mancozeb risks were not assessed for short and intermediate term exposures because no toxicity was observed in the subchronic dermal toxicity with mancozeb at the limit dose. All of the ETU short- and intermediate-term MOEs meet or exceed the required uncertainty factor of 100 at the currently labeled REI of 24 hours.

Of the fifteen crop groups evaluated for short- and intermediate-term risk, only 3 groups were thought to have chronic exposures. These include greenhouse cut flowers, greenhouse ornamental plants and greenhouse tomatoes. The mancozeb MOEs for all of the scenarios associated with these crops are greater than 100 on day 0 and are not of concern. With the exception of the high exposure cut flower scenario (which includes hand harvesting, pruning, thinning and pinching), most of the ETU MOEs are greater than 100 on day 0. The ETU MOE of 67 for the cut flower scenario rises to above 100 by day 6.

The cancer risks for field workers are less than $1x10^{-4}$ on the day of application for all of the scenarios and some are less than $1x10^{-5}$. The risks for many of the scenarios, however, do not decline to less than $1x10^{-6}$ until 2 to more than 35 days (for deciduous tree fruit) after application.

Data Gaps:

Toxicology:

870.6200	Acute neurotoxicity [870.6200]
870.3200	Comparative thyroid assay between young and adult animals [Special Study].

Residue Chemistry:

860.1200	Directions for Use [potato, sugar beet, apple, field corn, wheat, barley, oats]
860.1340	Enforcement Analytical Method - Livestock Commodities
860.1380	Storage Stability Data [carrot, onion (dry bulb)]
860.1500	Crop Field Trials [celery, wheat hay (will be translated to barley and oat hay), tobacco, cottonseed, cotton gin by-products, seed or propagation stock treatments (safflower)]
860.1520	Processing Studies [wheat (middlings and germ), cottonseed, potato, barley (pearled), and oats (rolled)]
860.1480	Ruminant Feeding Study
860.1850	Confined Rotational Crop

Occupational/Residential:

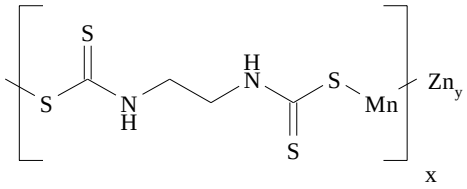
- Information regarding preferred formulation types, if any. This information is critical because the wettable powder formulations create the highest exposures particularly when used at high rates. These exposures can be greatly reduced by using the other formulations or by using the wettable powder in water soluble bags.
- There are no data to evaluate the mix/load/apply scenarios for high pressure handwand application of WP and DF formulations. The PHED data for both high and low pressure handwand application of liquids (mix/load/apply and apply only) is of low quality. These data gaps make it difficult to accurately assess the risks of the handwand method of application which is commonly used in horticulture. There are data gaps for loading and applying dust formulations for seed treatments; the degree of dustiness is also not known. There are data gaps for seed piece treatment with liquids and dusts.
- Additional TTR data using different dislodging techniques such as the wet hand press could be used to refine the hand-to-mouth and object-to-mouth turf exposures for toddlers.

2.0 Physical/Chemical Properties

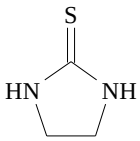
Mancozeb is a coordination product of zinc ion and maneb (manganese ethylene-bisdithiocarbamate), which contains 20% manganese and 2.5% zinc. Technical mancozeb is a yellowish powder which decomposes at 150 C, and has a density of 0.4 g/mL, an octanol/water partition coefficient (K_{ow}) of 1.8, and negligible vapor pressure at 20 C. Mancozeb is practically insoluble in water (13.6 µg/mL), and most organic solvents. Mancozeb decomposes in acid and alkaline conditions, with heat, and upon exposure to moisture and air. Other identifying codes and characteristics include:

Empirical Formula:	$(C_4H_6MnN_2S_4)_x\ (Zn)_y$
Molecular Weight:	$(265.3)_x + (65.4)_y$
CAS Registry No.:	8018-01-7
PC Code:	014504

The structures of mancozeb and its metabolite/degradate ethylenethiourea (ETU) are as follows:



mancozeb



ethylenethiourea

3.0 Hazard Characterization

The mancozeb toxicology database is incomplete; however, the available data were adequate to select dietary, incidental oral, dermal and inhalation endpoints for risk assessment. Data gaps are an acute neurotoxicity study in rats and a comparative study for thyroid toxicity in adults and offspring in rats. Once submitted, these studies may be used to refine the risk assessments.

3.1 Hazard Profile

Mancozeb is a fungicide in the class of ethylenebis dithiocarbamates, which also includes maneb and metiram; all of these compounds have a common metabolite/degradation product/contaminant, ethylenethiourea (ETU). The findings in multiple studies demonstrate that the thyroid is a target organ for mancozeb.

Mancozeb is not acutely toxic *via* the oral, dermal, or inhalation routes of exposure (Tox Category

IV). Mancozeb is not a skin irritant (Tox Category IV) nor is it a skin sensitizer although it did cause eye irritation (Tox Category III).

Thyroid toxicity in chronic and subchronic rat and dog studies with mancozeb was manifested as alterations in thyroid hormones (decreased thyroxine and increased or decreased triiodothyronine), increased thyroid weight, and microscopic thyroid lesions (mainly thyroid follicular cell hyperplasia). Thyroid stimulating hormone (TSH) was also increased.

Developmental defects which occurred in the rat developmental toxicity study were numerous and severe. The effects included hydrocephaly and related lesions, skeletal system defects, and other gross defects. Although the developmental defects were of concern, they occurred at the same dose which caused maternal mortality and did not indicate increased susceptibility of offspring. Abortions occurred in the rabbit developmental toxicity study at the high dose which also caused maternal mortality. No teratogenic effects were attributed to mancozeb in the rabbit developmental toxicity study and there was no indication of enhanced susceptibility of offspring in this study. No reproductive toxicity occurred in the 2-generation reproduction study in rats with mancozeb.

An acute neurotoxicity study with mancozeb was not available. Injury to peripheral nerves (demyelination, myelin phagocytosis, Schwann cell proliferation, thickened myelin sheath, intrasheath ellipsoids, neurofibrillary degeneration, and myelin ovoids, bubbles, and debris) was seen microscopically in the rat subchronic neurotoxicity study with associated clinical signs (abnormal gait and limited use of rear legs) and loss of muscle mass.

Other toxicity included increases in bilateral retinopathy in the chronic rat study. Elevated cholesterol and a mild, regenerative, anemia occurred in subchronic and chronic dog studies.

Mancozeb is rapidly absorbed and eliminated in the urine. There is no evidence of bioaccumulation. Mancozeb has been tested in a series of *in vitro* and *in vivo* genotoxicity assays, which have shown that mancozeb exhibits weak genotoxic potential.

Thyroid follicular cell adenomas and carcinomas were increased in high-dose males and females in the combined rat toxicity/carcinogenicity study with mancozeb. Doses in a mouse study were too low to assess carcinogenicity, and there were no treatment-related changes in tumor rates. The table below provides a comparison of tumor data for ETU, mancozeb, maneb, and metiram.

Tumor Incidence in EBDC/ETU Carcinogenicity Studies in Rats and Mice.				
Species	ETU	Mancozeb	Maneb	Metiram
Rats	Thyroid follicular cell adenomas and carcinomas at 83 & 250 ppm	Thyroid follicular cell adenomas and carcinomas at 750 ppm (HDT) [56 ppm ETU]	No ↑in tumor of any type at 1000 ppm (HDT) [75 ppm ETU]	No ↑in tumor of any type at 320 ppm (HDT) [24 ppm ETU]
Mice	Thyroid follicular cell adenomas and carcinomas, pituitary adenomas, hepatocellular adenomas and carcinomas at 1000 ppm	No ↑in tumor of any type at 1000 ppm (HDT) [75 ppm ETU]	↑ incidence of hepatocellular adenomas and alveogenic adenomas in the lungs at 2400 ppm [180 ppm ETU]	No ↑in tumor of any type at 1000 ppm [75 ppm ETU]

[Numbers in brackets represent ETU "dose" levels based on a 7.5% conversion of parent EBDC to ETU]

Historically, it has been assumed that mancozeb's potential for carcinogenicity (as well as that of the other EBDCs, maneb and metiram) is due to the formation of the metabolite ETU, which is classified as a probable human carcinogen (B2), with a cancer potency factor (Q_1^*) of 0.0601 $(mg/kg/day)^{-1}$ for risk assessment. On this basis, mancozeb cancer risk has been calculated by estimating exposure to mancozeb-derived ETU (including the metabolic conversion) and using the ETU cancer potency factor to provide a quantitative estimate of risk. In a 1999 *ad hoc* meeting of the Cancer Assessment Review Committee, HED concluded that cancer risk for mancozeb and the other EBDCs should continue to be evaluated in this way.

The results of acute toxicity testing for mancozeb are shown in Table 1. A toxicity profile for mancozeb technical is shown in Table 2.

Table 1. Acute Toxicity Data for Mancozeb

Guideline No.	Study Type	MRID #	Results	Tox. Category
870.1100	Acute Oral	00142522	LD_{50} > 5000 mg/kg	IV
870.1200	Acute Dermal	00142522	LD_{50} > 5000 mg/kg	IV
870.1300	Acute Inhalation	00142522	LC_{50} > 5.14 mg/L	IV
870.2400	Eye Irritation	00142522	corneal damage < 7 days	III
870.2500	Skin Irritation	00142522	Negative	IV
870.2600	Dermal Sensitization	40469501	Negative	N/A
870.6100	acute delayed neurotox (hen)	none		
870.6200	acute neurotoxicity	none		

Table 2. Toxicity Profile for Mancozeb Technical

Study Type [Guideline #] Doses	MRID No.	Results
Subchronic feeding - rat [870.3100] [males: 1.78, 3.49, 7.42, 14.98, 57.34 mg/kg/day] [females: 0, 2.20, 4.38, 9.24, 17.82, 74.64 mg/kg/day]	00261536/ Acceptable	NOAEL=9.24/14.98 mg/kg/day in females/males LOAEL=17.82 in females/males based on decreased serum thyroxine. In males, body weight decrements, changes in thyroid hormones and liver enzymes, microscopic changes in liver and thyroids, increased absolute and relative thyroid weights, and increased relative liver weights were observed at the LOAEL of 57.34 mg/kg/day.
Subchronic Feeding - mouse [870.3100] [males: 0, 1.78, 18.13, 166.9, or 1662.5 mg/kg/day] [females: 0, 2.34, 21.68, 233.8, or 2160.2 mg/kg/day]	00259888	NOAEL=18.13/21.68 mg/kg/day in males/females LOAEL=166.9/233.8 mg/kg/day in males/females, based on microscopic lesions of thyroid follicular cell hypertrophy or hyperplasia in females and decreased liver MFO enzyme activity in males.
Subchronic Feeding - dog [870.3150] [males: 0, 0.29, 2.98, 28.62, 101.53 mg/kg/day] [females: 0, 0.32, 3.35, 28.91, 108.67 mg/kg/day]	00261537	NOAEL=2.98/3.35 mg/kg/day in males/females. LOAEL =28.62/28.91 mg/kg/day in males/females, based on dehydration, decreased body weights and food consumption, anemia, lymphoid depletion of the thymic cortex, elevated cholesterol and prostate hypogenesis.
28-Day Dermal Toxicity - rabbit [870.3200] [0, 10, 100, or 1000 mg/kg/day]	40588201	NOAEL ≥ 1000 mg/kg/day [HDT] in males and females.

Table 2. Toxicity Profile for Mancozeb Technical

Study Type [Guideline #] Doses	MRID No.	Results
90-Day Inhalation Toxicity - rat [870.3465] [0, 0.018, 0.079, or 0.326 mg/L]	00159471	NOAEL=0.079 mg/L LOAEL=0.326 mg/L based upon body weight decrements in males, thyroid hyperplasia in females, and decreased thyroxine in females.
Subchronic Neuropathology - rat [870.6100] [males: 0, 1.35, 8.21, 49.7, or 339 mg/kg/day] [females: 0, 1.67, 10.5, 63.3, or 412 mg/kg/day]	42034101	NOAEL=8.21/10.5 mg/kg/day in males/females. LOAEL=49.7/63.3 mg/kg/day in males/females, based on microscopic evidence of peripheral nerve damage and decreased body weight gain in females.
Chronic Oral Toxicity - rat [870.4100] [males: 0, 0.77, 2.33, 4.83, or 30.9 mg/kg/day] [females: 0, 1.06, 3.06, 6.72, or 40.2 mg/kg/day]	41903601	NOAEL=4.83/6.72 mg/kg/day in males/females. LOAEL =30.9/40.2 mg/kg/day in males/females, based on changes in thyroid hormone levels, microscopic thyroid changes, changes in thyroid weights and bilateral retinopathy.
Chronic Oral Toxicity - dog [870.4100] [males: 0, 1.75, 7.26, 27.26, 53.52 mg/kg/day] [females: 0, 1.84, 7.02, 29.24, or 59.72 mg/kg/day]	41810501	NOAEL in males=1.75 mg/kg/day; LOAEL in males=7.26 mg/kg/day, based on decreased body weight gain. NOAEL in females=7.02 mg/kg/day, LOAEL in females=29.24 mg/kg/day, based on anemia.
Carcinogenicity - mouse [870.4200] 0, 30, 100, or 1000 ppm [males: 0, 4, 13, or 131 mg/kg/day] [females: 0, 5, 18, or 180 mg/kg/day] Much of the mancozeb degraded to ETU by weeks 52-80.	41981801	NOAEL for systemic toxicity=100 ppm. LOAEL=1000 ppm based on minor body weight decrements and changes in thyroid hormone levels. Instability of test material from weeks 52-80, when much of the mancozeb had degraded to ethylenethiourea (ETU). No treatment-related increase in tumors occurred. Dosing considered inadequate for assessing the carcinogenic potential due to minimal toxicity in the study. Classified unacceptable.
Developmental Toxicity - rat [870.3700] 0, 2, 8, 32, 128, or 512 mg/kg/day	00246663	Maternal NOAEL=32 mg/kg/day. Maternal LOAEL=128 mg/kg/day, based on decreased food consumption, body weight, and body weight gains. Developmental NOAEL=128 mg/kg/day. Developmental LOAEL=512 mg/kg/day, based on hydrocephaly, gross developmental defects, skeletal defects, cryptorchidism, abortions, increased resorptions, and decreased fetal weight.

Table 2. Toxicity Profile for Mancozeb Technical

Study Type [Guideline #] Doses	MRID No.	Results
Developmental Toxicity - rabbit [870.3700] 0, 10, 30, or 80 mg/kg/day	40433001	Maternal NOAEL=30 mg/kg/day. Maternal LOAEL=80 mg/kg/day, based on abortions, mortality, and clinical signs. Developmental NOAEL=30 mg/kg/day. Developmental LOAEL=80 mg/kg/day, based on abortions.
2-Generation Reproduction - rat [870.3800] [males: 0, 1.73, 6.95, 68.90 mg/kg/day] [females: 0, 1.83, 7.47, or 79.37 mg/kg/day]	41365201	Parental NOAEL=6.95/7.47 mg/kg/day males/females Parental LOAEL=68.90/79.37 mg/kg/day males/females, based on body weight decrements, increased relative thyroid weights, and increased incidence of thyroid follicular cell hyperplasia. Reproductive NOAEL ≥ 69.90/79.37 mg/kg/day [HDT] males/females. No adverse reproductive or offspring effects were attributed to mancozeb.
Chronic Toxicity/Carcinogenicity - rat [870.4100]	41903601	See chronic toxicity in rats, above.
Developmental Neurotoxicity - rat [870.6300]	none	N/A
Gene Mutation [870.5100, 870.5300] - Mutagenicity: *Salmonella* - *in vitro* mammalian: CHO/HGPRT - mouse host-mediated	 00259044 00259044 00259044	 Negative with and without activation Negative with and without activation Negative
Cytogenetics/Structural Chromosomal Aberrations [870.5900, 870.5385] - CHO cells - *in vivo* bone marrow cytogenetics - Mouse micronucleus assay	 40810202 00259044 40788901	 Positive (stronger response without activation) Negative Negative
Other Genotoxic Effects [870.5550] - Unscheduled DNA Synthesis- hepatocytes - Unscheduled DNA Synthesis- HeLa cells - SCE in CHO cells - *in vitro* transformation 10T1/2 cell - *in vitro* transformation/promotion10T1/2 cell - DNA damage in *E. coli* pol A	 40611701 40810205 00259044 00259044 00259044 40810201	 Negative Pos with/without activation, not concentration dependent Positive without activation, negative with activation Negative Negative Positive (stronger response without activation)
Metabolism [870.7485]	00262834 00262835 41656301	Rapidly absorbed after oral administration, highest accumulations in thyroid. No significant overall accumulation in the body in either rat or mouse study.

Table 2. Toxicity Profile for Mancozeb Technical

Study Type [Guideline #] Doses	MRID No.	Results
Dermal Penetration 870.7600	40955401 00250063	Dermal absorption = 1%
Domestic Animal Safety 870.7200	None	

3.2 FQPA Considerations

The potential for increased susceptibility of infants and children from exposure to mancozeb was evaluated by the Health Effects Division Hazard Identification Assessment Review Committee (HIARC) on February 20, 2003). HIARC evaluated mancozeb in accordance with the February, 2002 OPP FQPA 10X Safety Factor guidance document. The potential for susceptibility was re-evaluated by the EBDC team on July 30, 2004 (October 14, 2004 memo, D305812) to follow the policy outlined in a new guidance document, Clarification on the Application of Database Uncertainty Factors as Described in the 2002 OPP FQPA 10x Guidance (September, 2003). This risk assessment follows the most recent guidance document (September, 2003).

Studies available for FQPA consideration include acceptable developmental toxicity studies in rats and rabbits and an acceptable reproduction study in rats. Data gaps for mancozeb include an acute neurotoxicity study and a comparative thyroid toxicity study in adults and offspring.

There was no indication of increased susceptibility to fetuses or offspring in the developmental and reproduction studies. In the rat developmental study, developmental effects were observed in the presence of severe maternal effects, including maternal mortality and clinical signs. In the rabbit developmental study, developmental effects (abortions) were observed at the same dose (80 mg/kg/day) at which maternal effects included mortality and clinical signs. In the reproduction study, no effects were observed in offspring, while thyroid effects and body weight gain decrements occurred in adults.

Based on the lack of evidence of pre- and/or postnatal susceptibility resulting from exposure to mancozeb, and considering the lack of residual uncertainties, the Special FQPA Safety Factor (FQPA SF) was removed, or reduced to 1X.

There is concern for developmental neurotoxicity resulting from exposure to mancozeb, due to the developmental effects observed following dosing with mancozeb and its metabolite ETU. Since similar toxicity was identified in the developmental toxicity study with ETU, and the hydrocephaly which occurred after mancozeb treatment was believed to be due to ETU, toxicity to the developing nervous system will be addressed by a developmental neurotoxicity study with ETU, which has been

identified as a data gap for ETU. A comparative assessment of thyroid toxicity with mancozeb treatment in young and adult animals is required in order to assess potential thyroid effects in the young animal.

Regarding the required comparative thyroid study, thyroid effects in offspring are not well established in the scientific literature; 2) experience with these studies is lacking to show lowered regulatory values or greater sensitivity in children; 3) scientific peer review of the study protocol has not been made; and 4) there is no standard evaluation procedure or general consensus available for the comparative thyroid studies. In accordance with the September, 2003 guidance document described above, it is more likely that the available database provide reliable data to assign a protective safety factor, and a database uncertainty factor should not be applied for lack of a comparative thyroid study.

Regarding the datagap for an acute neurotoxicity study, this endpoint will be applied to the general population, and will not affect the endpoint for Females 13-50 years. Furthermore, the NOAEL from the acute neurotoxicity study with maneb was 1000 mg/kg/day. If an endpoint from the required developmental neurotoxicity study is developed, that endpoint will be applied to ETU residues and will not affect the mancozeb endpoints. Therefore, a database uncertainty factor is not required for mancozeb.

3.3 Dose Response Assessment

The HIARC evaluated the toxicology database of mancozeb on February 20, 2003 and selected the doses and endpoints for risk assessment. Subsequent to that meeting, the EBDC team re-evaluated the endpoints because of new information submitted by the EBDC Task Force. It was determined that the NOAEL for chronic exposure is 4.83 mg/kg/day, rather than 4.38 mg/kg/day. Because the database uncertainty factor was removed (see FQPA considerations above), the chronic PAD is now 0.05 mg/kg/day. The Task Force also provided information about the subchronic dermal toxicity study; since the thyroids were evaluated microscopically in that study, it provides an appropriate endpoint for short- and intermediate-term dermal exposure.

Since exposure to the metabolite and degradate ETU occurs in conjunction with the use of mancozeb, endpoints and doses for ETU selected at the February 18, 2003 HIARC meeting are included in Appendix 1.

Mancozeb Acute Dietary Endpoint (Females 13-49 years old): The rabbit developmental toxicity study was used to establish an acute reference dose for females 13-50 years old, based on abortions at the LOAEL of 80 mg/kg/day. Application of the standard 100X combined uncertainty factors (UFs) for interspecies extrapolation and intraspecies variability results in an acute reference dose (aRfD) of 0.3 mg/kg/day. Since the Special FQPA SF was reduced to 1X, the acute population adjusted dose (aPAD) is the same as the acute RfD, 0.3 mg/kg/day. The endpoint is relevant for acute dietary risk

assessment as defined in OPP, since the toxic effect (abortions) may occur following a single exposure.

Mancozeb Acute Dietary Endpoint (General US Population): An endpoint attributable to a single exposure was not available from oral studies, including the developmental toxicity studies.

Mancozeb Chronic Dietary Endpoint: The chronic reference dose (cRfD) for the general population was selected from a combined chronic toxicity/carcinogenicity feeding study in the rat. The endpoint selected was thyroid toxicity, including microscopic changes, increased thyroid weights and alterations in thyroid hormones, observed at the LOAEL of 30.9 mg/kg/day. After application of the standard 100X combined uncertainty factors (UFs) to the study NOAEL of 4.83 mg/kg/day, the cRfD is 0.05 mg/kg/day. With a Special FQPA SF of 1X, the chronic population adjusted dose (cPAD) of 0.05 mg/kg/day is equivalent to the chronic RfD. The duration of the study is appropriate for chronic (long-term) dietary exposure assessment, and the thyroid toxicity observed in the study is consistent with the findings in other studies with mancozeb.

Mancozeb Incidental Oral (Short- and Intermediate-Term) Endpoints: For incidental oral exposures occurring over 1 to 30 days (short-term) or for 30 days to 6 months (intermediate-term), the endpoint selected was thyroid effects, i.e. decreased serum thyroxine in females, observed at the LOAEL of 17.8 mg/kg/day in the 90-day rat study. Although this 13-week rat study was selected for exposures from 1 to 30 days, HIARC concluded that the effects observed in the study could have occurred earlier. The endpoint is supported by the fact that thyroid lesions were seen in the 21-day dermal toxicity study for the related active ingredient maneb, and since the thyroid is the target organ in a number of species and studies. The standard 100X UFS are considered applicable to the selected dose for risk assessment.

Mancozeb Dermal Penetration: 1%. This value is from a rat dermal absorption study.

Mancozeb Dermal Endpoints (Short- and Intermediate-Term): Quantitation of short-term dermal exposure to mancozeb should not be conducted. In the 28-day dermal toxicity study, there were no effects on body weight, food consumption, clinical signs, hematology, clinical chemistry (including thyroid hormones), organ weights, and gross or microscopic pathology of organs (including liver and thyroid) at 1000 mg/kg/day, the highest dose tested and the limit dose for dermal toxicity. There are no developmental toxicity concerns for short/intermediate-term dermal exposure. This is because developmental toxicity in rats only occurred at doses four fold greater than those causing maternal toxicity, and no systemic toxicity occurred in the dermal study with mancozeb. Furthermore, developmental toxicity in rats only occurred at a dose that was lethal to the dams. In rabbits, abortions were the only developmental endpoint and occurred at a dose that was lethal to does.

Mancozeb Dermal Endpoint (Long-Term): The combined chronic toxicity/carcinogenicity feeding study in the rat was used to select the endpoint and dose for long-term dermal exposure. The endpoint selected was thyroid toxicity, including microscopic changes, increased thyroid weights and

alterations in thyroid hormones, observed at the LOAEL of 30.9 mg/kg/day. The study NOAEL is 4.83 mg/kg/day. The duration of exposure in this study was considered relevant for long-term dermal exposures. Because an oral study was chosen, the 1% dermal absorption factor for mancozeb must be used in estimating dermal exposure and risk.

Mancozeb Inhalation Endpoints (Any Duration): A subchronic inhalation toxicity study conducted in rats was used to select endpoints to assess risks from inhalation exposures lasting from 1 day to more than 6 months. The NOAEL was 21 mg/kg/day, based on thyroid hyperplasia and decreased thyroxine in females at the LOAEL of 88 mg/kg/day. The route-specific study endpoint of thyroid effects is considered appropriate for all durations of exposure.

The standard 100X UFS are considered applicable to the selected doses for risk assessment for inhalation exposure to mancozeb (any duration). The target MOE for residential and occupational exposure is 100.

The doses and endpoints selected for risk assessment for mancozeb are presented in Table 3.

Table 3. Toxicological Doses and Endpoints for Mancozeb for Use in Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment and UFS	Special FQPA SF and Dose for Risk Assessment	Study and Toxicological Effects
Mancozeb Dietary Exposures			
Acute Dietary **Females 13+**	NOAEL = 30 mg/kg/day UF=100X (inter and intraspecies) $UF_{database}$=1X Total UF=100X Acute RfD = 0.3 mg/kg/day	FQPA SF = 1 aPAD = Acute RfD / FQPA SF aPAD = 0.3 mg/kg/day	Developmental Toxicity, rabbit LOAEL = 80 mg/kg/day based on abortions.
Acute Dietary **General Population**	N/A	No appropriate endpoint was identified from oral toxicity studies.	
Chronic Dietary **General Population**	NOAEL= 4.83 mg/kg/day UF=100X (inter and intraspecies) $UF_{database}$=1X Total UF=100X Chronic RfD=0.05 mg/kg/day	FQPA SF = 1 cPAD = Chronic RfD / FQPA SF cPAD = 0.05 mg/kg/day	Toxicity/Carcinogenicity, rat LOAEL = 30.9 mg/kg/day based on thyroid toxicity.
Carcinogenic Risk [oral/dermal/inhalation]	Q_1* = 6.01×10^{-2} $(mg/kg/day)^{-1}$	Mancozeb is classified as a **Group B2** carcinogen; use low-dose extrapolation for human risk assessment, based on ETU.	
Mancozeb Incidental Oral Exposures			
Any Duration [1 day to 6 mos.]	NOAEL = 9.24 mg/kg/day UF=100X (inter and intraspecies) $UF_{database}$=1X Total UF=100X	FQPA=1X Residential MOE=100 Occupational MOE=100	Subchronic toxicity, rat LOAEL = 17.82 mg/kg/day based on decreased thyroxine.
Mancozeb Dermal Exposures			
Short-Term [1-30 days] Intermediate-Term [>30 days to 6 mos.]	None	N/A	Quantitation not conducted. No systemic toxicity via the dermal route at 1000 mg/kg/day and there are no developmental concerns.
Long-Term [> 6 months]	NOAEL = 4.83 mg/kg/day UF=100X (inter and intraspecies) $UF_{database}$=1X DA = 1%	FQPA=1X Residential MOE=100 Occupational MOE=100	Toxicity/Carcinogenicity, rat LOAEL = 30.9 mg/kg/day based on thyroid toxicity.
Mancozeb Inhalation Exposures			
Any Duration [1day to > 6 mos.]	NOAEL = 0.079 mg/L [equivalent to 21 mg/kg/day] UF=100X (inter and intraspecies) $UF_{database}$=1X	FQPA=1X Residential MOE=100 Occupational MOE=100	Subchronic Inhalation, rat LOAEL = 0.326 mg/L based on thyroid hyperplasia and ↓ thyroxine (females)

3.4 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, mancozeb and ETU may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption. Mancozeb and ETU have demonstrated effects on thyroid hormones.

4.0 Exposure Assessment and Characterization

4.1 Summary of Registered Uses

Mancozeb is a widely used contact fungicide in agriculture, professional turf management, horticulture, and home gardening; some of the fungi and diseases controlled by mancozeb include spots, blights, rots, downy mildew, rusts, scabs, seed piece decay in potatoes and smuts on seed. Mancozeb formulations include wettable powders, dry flowables, liquid flowables and dusts. Agricultural uses include pome fruit crops (e.g., apples, pears), fruits and vegetables (e.g., cucumbers, onions, tomatoes, and grapes), some row crops (e.g., corn and potatoes), seed piece treatment (e.g. potatoes) and seed treatment (e.g. rice, wheat and cotton). Horticultural uses include ornamental plants in nurseries and greenhouses, sod farms, residential lawns and golf courses.

There are currently 47 active Section 3 mancozeb labels and 63 Section 24C registrations. The application rates in agriculture range from 1.2 lb ai/acre for corn to 4.8 lb ai/acre for pome fruits. The allowable number of applications per season ranges from 3 for cranberries to 15 for sweet corn and the application intervals range from 7 to 14 days. Some of the uses, such as grapes, have separate rates for eastern and western regions. The application rates in horticulture range from 1.2 lb ai/acre for most ornamentals (except pachysandra which has a rate of 14.0 lb ai/acre) to 17.4 lb ai/acre for turf. Horticulture and turf applications are allowed as much as twice weekly with no annual limit.

Usage information was derived from meetings with the registrants, end-use labels, the Mancozeb Use-Closure Memo of April 21, 1999, and on a use profile report (quantitative usage analysis, QUA) provided by BEAD in 1998 and updated in 2002.

The application methods were derived from the labels and/or Agency knowledge of typical use practices and include aerial, airblast, groundboom, chemigation, and hand application methods such as handwand and backpack sprayers. The daily acres treated are those typically used by the Agency for risk assessment (e.g. 80 to 200 acres/day for groundboom, 350 to 1200 acres/day for aerial and 40 acres/day for airblast). The application methods for seed and seed piece treatment include commercial stationary equipment, on-farm stationary equipment and tractor drawn planter boxes.

Due to the large number of mancozeb uses, and considering the complexity of the assessment for occupational exposure, representative crops or targets were selected as the basis for the assessment. A broad range of rates were used to ensure that use scenarios would be addressed in the range of values selected. Uses in agricultural/horticultural settings are presented in Table 4, while Tables 5 and 6 indicate rates for potato seed piece and seed treatments, respectively. Seed and seed pieces are treated once before being planted.

Table 4. Mancozeb Agricultural Application Rates

Crop Group	Specific Crop	Label Application Rates			Average Application Rates (lb ai/A)	
		Max. Rate (lb ai/A)	Min. Rate (lb ai/A)	Max lb ai Per Season	Per Application	Per Year
Berry, Small	Cranberries	4.8	2.4	14.4	3.0[1]	ND
Bunch, Bundle	Bananas, Plantains	2.4	2	24	ND	ND
	tobacco seedlings	2	1.1	None	ND	ND
	tobacco fields	1.5	0.3	6	ND	ND
Field/Row Crop, Low/Medium	Barley, Oats, Rye, Triticale, Wheat	1.6	NA	4.8	NU[2]	NU[2]
	Cotton	1.6	1.07	6.4	NU[2]	NU[2]
	Peanuts	1.6	0.8	12.8	ND	ND
	Sugar Beets	1.6	1.24	11.2	1.4[3]	1.5[3]
Field/Row Crop, Tall (Corn)	sweet/pop/seed: East of Miss.	1.2	NA	18	1.0[4]	4.5[4]
	sweet/ pop/seed: West of Miss.	1.2	NA	6	ND	ND
	field and hybrid seed corn	1.2	NA	12	ND	ND
Ornamentals	Variety	1.2 - 1.6	0.8	NA	1.3[5]	ND
	Pachysandra	13 -14	NA	NA	ND	ND
Pome fruits	Apples, Pears, Crabapples, Quince	2.4	NA	16.8	3.1 = Apples and Pears (West)[4] 2.1 = Apples (East)[4]	
Turf	Golf Course, Sod Farm	16.3 - 19	6	NA	ND	ND
Tree, "Fruit", Evergreen	Christmas Trees (Conifer) Douglas Fir	3.2	NA	NA	1.3[5]	ND
	Papayas	2	1.65	28	ND	ND
Vegetables, Cucurbits	Cucumbers	2.4	1.6	19.2	1.3[4]	4.9[4]
	Gourds: Edible	2.4	1.6	19.2	ND	ND
	Melons	2.4	1.6	19.2	ND	ND
	Squash (summer)	2.4	1.6	19.2	ND	ND
	Watermelons	2.4	1.6	19.2	1.3[4]	4.8[4]
Vegetable, Fruiting (Tomatoes)	East of Miss.	2.4	1.2	16.8	1.4[3]	14.6[3]
	West of Miss.	1.6	NA	6.4	1.4[3]	2.8[3]
Vegetables, Leafy	Fennel	1.6	NA	12.8	ND	ND
Vegetable, Root	Onions: Dry Bulb, Garlic, Shallots	2.4	NA	24	1.4[4]	4.7[4]
	Potatoes	1.6	0.51	11.2	1.2[4]	3.9[4]
Vegetables, Stem/Stalk	Asparagus	1.6	NA	6.4	1.4[4]	3.0[4]
Vine/Trellis(Grapes)	East of Rockies	3.2	1.2	19.2	2.2[6]	5.1[6]
	West of Rockies	2	1.2	6	1.5[7]	ND

1 - National Cranberry Institute data.
2 - NU = Insufficient data to publish per NASS Data 1996 - 2001.
3 - EPA QUA Report for Mancozeb, December 2, 2002
4 - NASS Data 1992 -2000 for Vegetables, 1991-2001 for Field Crops and 1993 -2001 for Apples and Pears.
5 - NASS Data for All Nursery and Floriculture 2000.
6 - NASS Data 1991 - 2001 for Grapes in MI, NY and PA.
7 - CA DPR Data 1993 - 2001.

ND - No data available
NA - Not applicable

Table 5. Mancozeb Application Rates For Seed Piece Treatment.		
Application Method	**Seed Piece Type**	**Label Rate**
Seed Piece Treatment Using WP, DF or Liquids	caprifig asparagus crown	0.032 lb ai/gal 0.008 lb ai/gal
Seed Piece Treatment Using Dust Formulations	potatoes	0.098 lb ai/cwt

Table 6: Mancozeb Application Rates For Seed Treatment.	
Seed Type	**Label Rate (lb ai per cwt of seed)**
barley, field corn	0.21, 0.27
cotton: acid delinted (adl), reginned (rg)	0.16 = adl, 0.32 = rg
flax, oats, shelled peanuts, rice, rye	0.35, 0.31, 0.80, 0.21, 0.18
safflower, sorghum, tomato, triticale, wheat	0.11, 0.23, 0.42, 0.16, 0.16

Note: 1 cwt = 100 pounds

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Mancozeb is included in a listing of dithiocarbamate pesticides under 40 CFR §180.3(e)(3). The following statement appears under 40 CFR §180.3(d)(5): Where tolerances are established for more than one member of the class of dithiocarbamates listed in paragraph (e)(3) on the same raw agricultural commodity, the total residue of such pesticides shall not exceed that permitted by the highest tolerance established for any one member of the class, calculated as zinc ethylenebisdithiocarbamate (zineb).

Tolerances for mancozeb residues, calculated as zineb, are established in/on numerous crops under 40 CFR §180.176. Currently established tolerances range from 0.1 ppm (asparagus and corn grain) to 65 ppm in sugar beet tops.

Maneb and metiram, the only other ethylenebisdithiocarbamate pesticides with current registrations, have tolerances for residues in apples and potatoes as does mancozeb. Additional tolerances in numerous other commodities have been established for residues of mancozeb.

The HED Metabolism Assessment Review Committee (MARC) has recommended a change in the tolerance expressions for mancozeb, maneb and metiram. The EBDC tolerance expressions will be revised at a later date to include residues of the parent EBDC (and metabolites converted to CS_2), calculated as CS_2, rather than as zineb, which no longer has active registrations. This change will serve to update the CFR to include only those EBDCs with registered uses or import tolerances, and

will also allow the Agency to harmonize its EBDC tolerance definitions with CODEX. Dietary exposure and risk assessments for each EBDC will include residues of the parent EBDC (and metabolites converted to CS_2) and the common metabolite and degradate, ethylenethiourea (ETU).

The proposed revised tolerance expression for mancozeb (40 CFR §180.176) is as follows:

> Tolerances are established for residues of a fungicide that is a coordination product of zinc and manganese ethylenebisdithiocarbamate *calculated as carbon disulfide, CS_2,* in or on raw agricultural commodities.

The qualitative nature of mancozeb residues in plants and livestock is adequately understood based on acceptable metabolism studies conducted on potato, soybean, sugar beet, tomato, and wheat, and in goats and hens. In plants and livestock, the terminal residues of concern for risk assessment are mancozeb (and metabolites converted to CS_2) and ETU; however, for tolerance reassessment, only the parent mancozeb (and metabolites converted to CS_2), calculated as CS_2, must be included in the tolerance expression. The metabolite ETU has been determined not to be a useful regulatory indicator of misuse. The plant and livestock metabolism studies indicate that the bulk of total radioactive residues (TRR) represents the incorporation of carbon fragments into natural products. The enforcement methods for dithiocarbamates in plants are listed in the Pesticide Analytical Manual [PAM, Vol. II, Methods I - IV]. These methods are based on the decomposition of dithiocarbamates with release of carbon disulfide (CS_2), which is determined colorimetrically as a measure of the original dithiocarbamate. The Keppel colorimetric method (Method III in PAM Vol. II) is currently the preferred enforcement method for residues of mancozeb *per se*. HED recommends that the data collection method for EBDC residues be included in PAM II as an alternate enforcement method.

Although enforcement methods that are specific to mancozeb (and maneb and metiram) are not available, no additional analytical methodologies are required for reregistration. The Agency has concluded (in the Maneb Update to the Registration Standard) that analytical methods converting all EBDCs and some metabolites to carbon disulfide are considered adequate for both data collection and enforcement of tolerances in plant and livestock commodities.

Although not necessary for tolerance enforcement, specific data collection methods are available for ETU. The Onley GC method (AOAC 14th Edition 29.119:554) provides acceptable results when properly validated with recovery and control data. An HPLC method with electrochemical detection (ECD) is available to analyze ETU in crop samples with an LOQ of 0.005 ppm.

Mancozeb and ETU are not recovered using any FDA Multiresidue Protocols (specifically, Multiresidue Protocol A-E and 232.3). The 10/99 FDA PESTDATA database (PAM Volume I, Appendix I) indicates ETU is not recovered using method Sections 303 (Mills, Onley, and Gaither method; Protocol E), and 304 (Mills method for fatty food); however, there is a small recovery (<50%) of ETU using multiresidue method Section 302 (Luke method; Protocol D).

Residue data submitted in support of reregistration, in combination with MBS data, are generally adequate for risk assessment purposes. However, the mancozeb reregistration data requirements for magnitude of the residue data are only partially fulfilled. Adequate field trial data depicting mancozeb and ETU residues in some commodities are available, have been evaluated, and support the use patterns eligible for reregistration as per the PD 4. The integrity of samples collected from the adequate field trials was generally maintained by appropriate storage procedures and supported by adequate storage stability data. Data gaps include directions for use, storage stability, magnitude of the residue studies, and processing studies. With a few exceptions, the basic registrants have complied with the label changes previously required by the Agency findings as per the EBDC PD 4.

In conjunction with the EBDC Special Review concluding in 1992, chemical-specific processing and cooking information for mancozeb (and for metiram and maneb) were submitted to the Agency. The results of these studies were incorporated into the 1991 dietary exposure assessment. These data have been reevaluated, along with any additional processing information requested under the Special Review and submitted after 1992, for use in the current EBDC risk assessments. The chemical specific washing, cooking, peeling, etc. studies for EBDCs and ETU have been used to calculate average processing factors (PFs) and cooking factors (CFs) for use in all three EBDC risk assessments. This is appropriate because of the similar structures and chemical properties of these compounds, and because average processing factors allow use of the best available data for all three actives. In general, these studies have demonstrated that parent and ETU residues are largely surface residues, but some translocation of ETU does occur through the skin of certain vegetables and fruits, generally those with thinner skins.

The processing studies indicate EBDC (and mancozeb *per se*) residues in vegetables and fruits are largely reduced through typical consumer and commercial practices such as washing, peeling, juicing, and canning. However, EBDC residues in grain concentrate in processed fractions such as bran, and are not reduced in other fractions, such as flour, meal and oil. In potatoes, EBDC residues concentrate in both flakes and flour. Available information for ETU, while limited, indicates reduction of existing residues during cooking or processing.

Processes that involve cooking certain commodities, such as processing potatoes into flakes, cooking, canning or drying, result in conversion of EBDC residues to ETU. This has been accounted for in the mancozeb (and metiram and maneb) dietary exposure and risk assessments by using empirical EBDC-to-ETU conversion factors from processing/cooking studies.

In oral rat metabolism studies conducted with radiolabelled parent EBDCs, there was an average 7.5% *in vivo* conversion of the EBDC to ETU, on a weight-to-weight basis. This 7.5% conversion was used in the risk assessments for the 1992 Special Review, and has also been used for mancozeb and the other EBDCs in the current exposure and risk assessments, in order to estimate total dietary exposure to ETU resulting from application of EBDCs to agricultural crops.

In order to include *in vivo* metabolic conversion, estimated mancozeb residues (including processing

or cooking factors, where appropriate) were multiplied by 0.075 to estimate ETU exposure from metabolic conversion. This "metabolic" ETU was added to anticipated residues of ETU in the raw agricultural commodities (including any cooking or processing), and the total ETU was compared to the relevant toxicological endpoints for risk assessment.

In addition to the field trial data submitted in support of registration and reregistration for mancozeb, maneb and metiram, the EBDC/ETU task forces conducted an extensive EBDC/ETU market basket survey (MBS) in conjunction with the 1989 - 1992 Special Review. Although the data are more than 10 years old, they have been incorporated into the current dietary exposure and risk assessments for EBDCs because the magnitude and frequency of detected residues in the survey are still considered either relevant to or protective for the current use pattern in terms of the percent crop treated (%CT) and the amount applied per acre. This assumption is based on assessment of trends in EBDC usage for a wide variety of crops; estimates of %CT for individual EBDCs; information the EBDC Task Force presented to the Agency in SMART meetings conducted 10/98; and information about application rates in effect at the time the survey data were collected, prior to the completion of the Special Review. The lack of significant changes in use patterns over time, for most commodities, is largely due to the restrictions placed on usage and rates at the conclusion of the Special Review in 1992. The rate restrictions included rate reductions for some crops, so the residue levels detected in the MBS are considered, in general, to be the same as or higher than those expected in the same foods under current usage, and therefore current exposure estimates are conservative.

The EBDC/ETU MBS was conducted during 1989 and 1990, and the results incorporated into an Agency dietary exposure and risk assessment (for parent EBDCs and the metabolite/degradate ETU) in 1991. The commodities surveyed included dry beans ("fresh" and canned); broccoli (fresh and frozen), sweet corn (fresh, frozen and canned); cucumber; head lettuce; meat; milk; onion; potato (fresh and frozen fries); and tomato (fresh, juice, ketchup, paste and puree). The EBDC/ETU MBS was the largest survey of its kind, reflecting analysis of close to 6,000 samples and 12,000 analyses (300 samples for each of 10 crops/19 food forms). The survey included a randomized probability design to estimate national annual mean residue levels found on foods in grocery stores. Although there were some problems with the timing of sampling for certain commodities, the Agency concluded that sampling was representative of regions and store volume categories. The sampling was not likely seasonally representative, but the Agency concluded this had little bearing on the estimated risks, noting that the peak usage months for the surveyed crops were May through June, and survey samples were collected May through July.

Samples collected for the EBDC/ETU MBS were analyzed for both EBDC (CS_2, calculated as zineb) and ETU, but the analyses did not distinguish between the EBDC active ingredients. Results for both EBDC and ETU were reported for all samples. For some commodities, such as potatoes, more than one EBDC is registered for use. In the current dietary exposure and risk assessments, individual parent EBDC risks (i.e., mancozeb, maneb, or metiram) were estimated assuming the EBDC residues in the MBS were attributable to use of each EBDC active ingredient individually, and that the corresponding ETU residues were also derived from that use. For estimating ETU risk resulting from

the individual active ingredients, it was assumed that all detected ETU was derived from the parent active ingredient. This approach considers residues to be from one EBDC active ingredient in one assessment, and another EBDC active ingredient in the next. While this will necessarily exaggerate risks for one or more of the actives, it is still the most refined assessment possible considering analytical constraints.

There are no EBDC monitoring data available from the USDA Pesticide Data Program. An evaluation of FDA and state Monitoring data in 1991 concluded that there were insufficient samples (S. Hummel, 10/24/91) for risk assessment purposes. In addition, very few samples were analyzed for both EBDC and ETU, so it would be difficult to ensure that both the ETU and EBDC residue distributions would be representative. HED has reviewed the FDA data for the years 1991-2000 and has concluded that the recommendation made in 1991 is still valid: insufficient FDA surveillance data are available for use in a quantitative exposure assessment. However, the FDA data are consistent with the market basket survey data in that residues found are generally much lower than the residues found in field trial studies.

4.2.2 Dietary Exposure and Risk

Mancozeb and ETU acute, chronic and cancer dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" are linked to EPA-defined food commodities using publicly available recipe translation files developed jointly by USDA/ARS and EPA. Consumption data are averaged for the entire U.S. population and within population subgroups for chronic and cancer exposure assessment, but are retained as individual consumption events for acute exposure assessment.

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic assessments, the risk is expressed as a percentage of the aPAD or cPAD, respectively. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD. For cancer risk, the estimated chronic exposure is multiplied by the cancer potency factor (Q_1^*) to yield a unitless risk number which represents the number of excess cancers potentially attributed to consumption of the pesticide over a lifetime. In general, HED is concerned when estimated cancer risk exceeds one in one million (i.e., $>1x10^{-6}$).

4.2.2.1 Acute Dietary Exposure and Risk

HED typically uses two types of monitoring data in its probabilistic acute dietary exposure assessments. For commodities considered to be partially blended, such as juices or small fruits, composite samples consisting of 2 to 5 lbs are expected to have similar residues to smaller quantities that would be consumed as a single serving. However, for non-blended commodities, such as apples,

residues in a 2 to 5 lb composite are not considered representative of the highest residue that might be present in a single fruit (single unit). Use of composite sample residues for non-blended commodities in an acute probabilistic analysis would underestimate potential dietary exposure and risk. If available, single unit (often referred to as single-serving) residue data are used in acute assessments. In the absence of single unit monitoring data (e.g., from USDA/PDP or registrants), and in order to conduct a more refined dietary exposure assessment, HED typically uses a statistical procedure known as 'decompositing' to better estimate the maximum potential residue levels (e.g., theoretical single unit residues) from composite monitoring samples.

The EBDC/ETU MBS data for non-blended commodities were not decomposited for the EBDC acute dietary exposure assessments. Although this may underestimate acute dietary exposure to some extent, HED has opted to use the composite data directly considering that: (1) the samples taken for the MBS were of a smaller size than those collected for most other monitoring studies, and the shoppers were instructed to take samples from the same lot, both of which should lead to a more homogeneous residue distribution within the sample; (2) shoppers were instructed to choose blemish-free fruit or vegetables (for fresh commodities), increasing the likelihood that treated commodities were selected; and (3) acute risks do not reflect the most sensitive toxic effect; rather, the cancer risks are of primary concern, and use of composite residue values is appropriate for cancer exposure and risk assessment. Although acute dietary exposure and risk from monitored commodities may be slightly underestimated because the MBS samples were not decomposited, the risk from other (non-monitored) commodities is likely to be greatly overestimated because field trial data were used, and because, in some instances, an assumption of 100 %CT was used.

Mancozeb per se Data Sources and Assumptions

To estimate mancozeb acute dietary exposure and risk, a refined probabilistic assessment was conducted using a distribution of either field trial data or monitoring data for commodities considered to be either nonblended or partially blended. Average field trial or monitoring residues were used for blended commodities. For all RACs and associated commodities, the estimated maximum %CT (if available) and relevant processing factors were included in the assessment.

ETU (from Mancozeb) Data Sources and Assumptions

To estimate mancozeb-derived ETU acute dietary exposure and risk, the full distribution of field trial or monitoring residues was used for nonblended and partially blended commodities; for blended commodities, the average field trial or monitoring residue value was used. The estimated maximum %CT, relevant processing and cooking factors, conversion of EBDC to ETU for certain cooked commodities, and the 7.5% *in vivo* metabolic conversion of EBDC residues to ETU were incorporated into the total ETU anticipated residues.

Acute Dietary Results - See Table 7

The results of the acute dietary exposure assessments for mancozeb *per se* and ETU are shown in Table 7. For mancozeb, acute dietary exposures were compared to the aPAD of 0.3 mg/kg/day for females 13-49. For ETU, exposures were compared to the aPAD of 0.005 mg/kg/day selected for females 13-49 years old.

Mancozeb per se
For mancozeb *per se*, estimated acute dietary risk at the 99.9th percentile of exposure is below the Agency's level of concern for females 13-49 year old; an estimated mancozeb exposure of 0.00584 mg/kg/day corresponds to 2% of the aPAD.

ETU (from Mancozeb)
The mancozeb-derived ETU acute dietary exposure and risk at the 99.9th percentile for females 13-49 years old are below the Agency's level of concern; an estimated ETU exposure of 0.000898 mg/kg/day corresponds to 18% aPAD.

Table 7. Mancozeb and ETU Acute Dietary Exposure and Risk.

Population Subgroup	aPAD (mg/kg/day)	99.9th Percentile Exposure (mg/kg/day)	% aPAD
Mancozeb Acute Risk			
Females 13-49 years	0.3	0.005844	2
ETU Acute Risk			
Females 13-49 years	0.005	0.000898	18

4.2.2.2 Chronic and Cancer Dietary Exposure and Risk

Mancozeb per se Data Sources and Assumptions

To estimate mancozeb *per se* chronic dietary exposure and risk, a refined assessment was conducted using average field trial residues or average monitoring residues. In addition, the average %CT (when available) and relevant processing factors were included.

ETU (from Mancozeb) Data Sources and Assumptions

The mancozeb-derived ETU chronic dietary exposure (for both non-cancer and cancer risk assessments) was estimated using average ETU residues from field trials or monitoring, along with the average %CT, relevant processing and cooking factors, potential conversion of EBDC to ETU in certain cooked commodities, and the 7.5% metabolic conversion of mancozeb *per se* to ETU.

Chronic (Non-Cancer) Dietary Results - See Table 8

For mancozeb, chronic dietary exposures were compared to the cPAD of 0.05 mg/kg/day for the general US population (and various population subgroups including infants and children). For ETU, exposures were compared to the cPAD of 0.0002 mg/kg/day.

Mancozeb per se and ETU

Mancozeb *per se* chronic (non-cancer) dietary exposure and risk are below HED's level of concern (i.e., <100% cPAD). For mancozeb *per se*, the highest exposed population subgroup is children 1-2 years old, with an exposure of 0.000175 mg/kg/day, or <1% cPAD. Results for this population and other population subgroups are shown in Table 8.

ETU chronic (non-cancer) exposure and risk are below HED's level of concern (i.e., <100% cPAD). For the general US population, an estimated exposure of 0.000022 mg/kg/day corresponds to 11 %cPAD. The highest exposed population subgroup is children 1-2 years old, with an exposure of 0.000065 mg/kg/day, which corresponds to 33% cPAD.

Table 8. Mancozeb and ETU Chronic Dietary Exposure and Risk.

Population Subgroup	**Mancozeb** Chronic Exposure/Risk			**ETU** Chronic Exposure/Risk		
	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
General U.S. Population	0.05	0.000053	<1	0.0002	0.000022	11
All Infants (< 1 year)	0.05	0.000064	<1	0.0002	0.000027	14
Children 1-2 years old	**0.05**	**0.000175**	**<1**	**0.0002**	**0.000065**	**33**
Children 3-5 years	0.05	0.000137	<1	0.0002	0.000051	26
Children 6-12 years	0.05	0.000070	<1	0.0002	0.000029	15
Youth 13-19 years	0.05	0.000031	<1	0.0002	0.000015	8
Adults 20-49 years	0.05	0.000040	<1	0.0002	0.000017	9
Adults 50+ years	0.05	0.000045	<1	0.0002	0.000017	9
Females 13-49 years	0.05	0.000046	<1	0.0002	0.000018	9

Cancer Dietary Results (ETU)

The estimated chronic dietary exposure to ETU of 0.000022 mg/kg/day for the general U.S. population corresponds to a cancer risk estimate of 1.3×10^{-6}, which is not of concern. The commodity contribution analysis indicates that mango and milk are the major contributors to the risk estimate.

4.3 Water Exposure/Risk Pathway

The OPP Environmental Fate and Effects Division (EFED) prepared a drinking water exposure assessment for ETU, which is applicable for mancozeb, as well as the other EBDCs. The EBDC fungicides, Metiram, Maneb and Mancozeb are very short lived in soil and in water and would not themselves be expected to remain in surface water long enough to reach a location that would supply water for human consumption whether from surface or groundwater. However, ETU is highly water soluble, and may reach both surface and ground water under some conditions. The drinking water exposure assessment for mancozeb, maneb and metiram addresses concentrations of ETU only.

The ETU estimated drinking water concentrations (EDWCs) were generated using data from monitoring and modeling. See sections 4.3.2 and 4.3.3 below, for more details.

ETU Surface Water EDWCs (from PRZM-EXAMS modeling and from monitoring data):
acute (peak) surface water = range of 0.1 (monitoring) to 25.2 ppb (modeling)
chronic/cancer surface water = 0.1 ppb (from monitoring)

ETU Ground Water EDWC (from a Targeted Monitoring Study in FL):
acute/chronic/cancer ground water = 0.21 ppb (from monitoring)

4.3.1 Environmental Fate

The EBDC metabolite/degradate ETU has an aerobic soil half-life of about 3 days; in the absence of data, the aquatic aerobic metabolism half-life was assumed to be about 6 days, or double the soil half life. The measured anaerobic aquatic metabolism half-life, however, is substantially longer (149 days) possibly leading to the periodic detections in ground water. ETU is highly soluble in water (20,000 ppm); highly vulnerable to indirect photolysis (half-life= 1 day), and moderately mobile (288 L/kg). It also has a relatively high vapor pressure but high solubility reduces the possibility of losses from surface water due to volatilization.

4.3.2 Surface Water

Water Monitoring: The EBDC/ETU Task Force conducted a national surface water monitoring survey from 2001-2003. A total of 22 sites were chosen to represent vulnerable and high EBDC-use sites. Surface water sites were sampled twice monthly for three months during each application season and quarterly for the three remaining quarters of each year for a period of 2 years. There were no detections of ETU in surface water during this period. The limit of quantitation for the study was 0.1 ppb.

The Agency has been unable to locate any other surface water monitoring data for the EBDC fungicides or for ETU. The EBDCs and ETU were not included in the US Geological Survey (USGS) National Water Quality Assessment (NAWQA) sampling program because EBDC/ETU test methods were incompatible with NAWQA test methods. The USGS is currently planning to begin method development and limited EBDC/ETU monitoring in late 2004.

Water Modeling: The ETU surface water estimates were calculated using the linked USEPA PRZM (Pesticide Root Zone Model) and EXAMS (Exposure Analysis Model System) simulation models. This type of modeling provide high-end estimates for surface water pesticide concentrations. Calculation includes pesticide-specific properties, multiple years of actual weather variations, and crop-specific information. In addition to runoff from the field, the model takes into account surface water residues resulting from spray drift (aerial or ground). Conservative assumptions included the use of a vulnerable drinking water reservoir surrounded by a runoff-prone watershed, maximum use rate, lowest application intervals, and no buffer zone. Modeling was done for 22 crop scenarios.

The highest one-in-ten year acute surface water EDWC was 25.2 ppb and the lowest value was 4.5 ppb. These values were calculated using the national percent cropped area (PCA) value of 0.87. It the maximum regional PCA value (0.56 California PCA) is used, then the highest acute surface water EDWC was 13.9 ppb and the lowest is 1.4 ppb.

The highest chronic concentration value was 1.9 ppb and the lowest value was 0.2 ppb. This was calculated using the national maximum PCA.

Acute Surface Water EDWCs: The ETU surface water estimated drinking water concentrations (EDWCs) were generated using a combined monitoring/modeling approach. The targeted ETU monitoring found no surface water concentrations above the detection limit of 0.1 ppb. Because samples were taken every 14 days during the application season and acute values may have been missed, a range of acute surface EDWCs was established with a lower limit based on monitoring and an upper limit based on PRZM/EXAMS modeling.

The range of acute EDWCs was 0.1 ppb (monitoring) and the upper limit was 25.2 ppb. The values were adjusted by the national maximum default percent cropped area (PCA) value of 0.87.

Chronic Surface Water EDWC: The chronic EDWC is 0.1 ppb from the targeted ETU monitoring program mentioned above. No surface water concentrations were found above the detection limit of 0.1 ppb and the Agency believes that monitoring demonstrates that long-term average chronic values would not exceed the detection limit.

4.3.3 Ground Water

Water Monitoring: A monitoring program of community ground water systems was conducted by the EBDC Task Force from 2001-2003. Untreated and associated treated ground water were sampled for a period of two years in 84 sites chosen to represent high EBDC-use sites. ETU was detected above the detection limit intermittently in untreated water from two ground water sites. The highest concentration was 0.21 ppb in untreated water in Florida. There were no detections in treated water in any of the 84 community water sites; including those two sites where ETU was detected in the untreated water.

A monitoring program of private wells was conducted by the EBDC Task Force from 2001-2003. Raw ground water was sampled monthly for a period of two years in 125 sites chosen to represent high EBDC-use sites. ETU was detected in the range of 0.10 to 0.25 ppb continuously at 2 sites in Florida and intermittently at six sites: three in Florida and one each in New York, Illinois and Maine (Figure 3). The highest detected ETU concentration measured for a private well near an EBDC treated field was 0.57 ppb in an apple growing region of New York. No detection of ETU was observed in all the other 117 sites. Such higher groundwater concentration values, found in private areas in rural areas, are very rare and are unlikely to represent ground water ETU concentrations expected in drinking water relevant for use in a national assessment.

In 25 years of monitoring in California, there has been only one ETU detection (0.75 ppb). Additionally, ground water monitoring in Holland, resulted in only 8 positive samples with a maximum concentration of 1.5 ppb.

Water Modeling: The ETU EDWCs in ground water, derived from the industry's targeted ground water monitoring study, were evaluated by comparing them to concentrations predicted by the SCI-GROW model. This is a screening model used to estimate pesticide concentrations in vulnerable ground water. The SCI-GROW estimate is based on environmental fate properties of the pesticide, maximum application rate, and existing data from small-scale prospective ground water monitoring studies at sites with sandy soils and shallow ground water (i.e., exceptionally vulnerable ground water). Pesticide concentrations estimated by SCI-GROW represent conservative or high-end exposure values and in most cases, use areas will have groundwater that is less vulnerable to contamination than the areas used to derive the SCIGROW estimate. The SCI-GROW modeling indicates that the upper level ETU concentrations from the targeted monitoring study are unlikely to be exceeded even under the most vulnerable conditions.

Ground Water EDWCs (acute and chronic): For ETU, the EDWC value for both acute and chronic exposure is 0.21 ppb. This value is from monitoring untreated water in Florida.

4.4 Residential Exposure/Risk Pathway

The agricultural and horticultural labels have statements such as "Not for Homeowner Use" and "Not for Use on Fruit Trees by Homeowners" that prevent homeowner applications of mancozeb to turf and fruit trees. The registrants have also agreed to limit turf applications to sod farms, golf courses and athletic fields. There are two home garden labels (Dragon #707-156-16 and Bonide #707-78-4) that were based upon the Rohm and Haas agricultural labels. Although these labels were cancelled on 9/21/01, they are still available in local garden centers and Dow AgroSciences, LLC has indicated that they will be re-instated; therefore they are considered in this assessment.

Based upon the above information it has been determined there is a potential for home gardener exposure during and after applications to home garden vegetables. The is also a potential for golfer and toddler post application exposure on golf course turf and transplanted lawns. As a result, risk assessments have been completed for both residential handler and postapplication scenarios.

Residential labels currently indicate homeowners must wear long pants, long sleeve shirts and water proof gloves during application of products containing mancozeb. These label recommendations were required at the conclusion of the 1992 Special Review, but are inconsistent with current labeling policies. Therefore, the current residential exposure assessment is based on the standard homeowner clothing scenario, which consists of shorts and a short-sleeve shirt.

The target Margin of Exposures (MOE) for residential risk are 100 for mancozeb and 1000 for ETU, based on the combined uncertainty factors (UFs) associated with endpoint selection for dermal, inhalation and nondietary risk assessments.

4.4.1 Home Garden Uses

Uses considered include application to vegetable gardens and ornamentals. Because there were discrepancies in the label rates on products likely to be used by homeowners, the residential exposure assessment used the agricultural application rates. Exposures were estimated based on application to a selection of home garden vegetables (cucurbits, corn and tomatoes) and ornamentals, which represent the full range of application rates, and also represent commodities commonly grown in home gardens. An application rate of 2.4 lb ai/A was used for all crops considered, and is the maximum rate for the representative crops.

4.4.1.1 Handler Data and Assumptions

For home gardens, the area treated per day was assumed to be 1000 sq. feet, and is typical Agency practice based on the National Home Garden Survey. Application methods considered include backpack and low pressure handwand sprayers. As stated above, the application rate was assumed to be 2.4 lb ai/A for a representative selection of crops.

Exposure data used to estimate risks for residential handlers applying mancozeb with a low pressure handwand were based on a study submitted for the active ingredient carbaryl. Only the hand held pump spray data were used. For the backpack sprayer scenario, the unit exposure data from The Pesticide Handlers Exposure Database (PHED v. 1.1) were used as a surrogate. Because the study evaluated exposures with gloves, a unit exposure value was estimated for residential exposures assuming no gloves, leading to less confidence in exposure and risk estimates for residential handlers using a backpack sprayer.

For mancozeb *per se* and ETU, only short-term risks were estimated for home gardeners. Dermal and inhalation exposures were combined for ETU, since the toxic effects assumed to result from these two routes of exposure were identical (developmental effects for ETU). For mancozeb, exposure was by the inhalation route only because a dermal endpoint was not selected (dermal NOAEL = 1000 mg/kg/day). For estimating cancer risks, a 70-year life-span was assumed, with 50 years of gardening, five exposure days per year, and the standard 70 kg body weight for applicators.

4.4.1.2 Summary of Residential Handler Risks

Handler risks for home gardeners applying products containing mancozeb to vegetables are below the level of concern for short-term risk for mancozeb *per se* and mancozeb-derived ETU; in addition, cancer risks associated with ETU exposure are below the level of concern. Short-term MOEs for mancozeb and ETU are significantly higher than the target MOEs of 100 and 1000. Cancer risks are well below the target of 1×10^{-6}. A summary of mancozeb and ETU risk for home gardeners is presented in Table 9.

Table 9. Home Gardener Handler Exposure and Risks for Mancozeb and ETU.

Exposure Scenario	Appl. Rate (lb ai/acre)	Area Treated (Acre/Day)	Mancozeb (non cancer)		ETU (non-cancer)		ETU (Cancer)	
			Absorbed Dose (mg/kg/day)	Inhal. MOE	Absorbed Dose (mg/kg/day)	MOE	LADD	Risk
1) Backpack Sprayer	2.4	0.023 (1000 ft^2)	2.4×10^{-5}	890000	8.1×10^{-6}	620000	6.8×10^{-8}	4×10^{-9}
2) Low Pressure Handwand			7.1×10^{-6}	3000000	4.5×10^{-5}	110000	3.8×10^{-7}	2×10^{-8}

Notes:
Absorbed Dose = inhalation for Mancozeb, combined dermal and inhalation for ETU.
MOE = Margin of Exposure = NOAEL/Absorbed Dose [NOAEL for mancozeb = 21 mg/kg/day; NOAEL for ETU = 5 mg/kg/day]
LADD = Lifetime Average Daily Dose (the average daily dose x (5 exposure days/365 days)*(50 years/70 years)
Cancer Risk = LADD x 0.0601 $(mg/kg/day)^{-1}$

4.4.1.3 Postapplication (Includes Recreational)

Mancozeb can be used in areas that can be frequented by the general population including residential areas (e.g., home gardens and transplanted turf), athletic fields, and golf courses. As a result, individuals can be exposed by entering these areas if the areas have been previously treated. To address these exposures the following scenarios were evaluated:

1) Adult and youth gardeners, following application to a variety of vegetable crops;
2) Adults golfing on treated turf;
3) Toddlers playing on transplanted turf that was treated at the sod farm; and
4) Adults playing on collegiate or professional athletic fields.

Residential postapplication exposures for adult and youth gardeners are considered to be dermal only, and short-term in nature. Toddlers' postapplication exposure to residues on transplanted turf consist of the combined estimates of dermal exposure from playing on treated turf and incidental nondietary ingestion. The three types of nondietary ingestion considered include (1) hand-to-mouth (occurs when children touch treated turf and then put their hands in their mouths); (2) object-to-mouth (results from children mouthing a handful of treated turf); and (3) soil ingestion (occurs when children ingest soil that has been treated with a pesticide). These exposures are considered to be short-term in duration, and are also considered likely to co-occur.

In accordance with HED policy, a cancer assessment was completed for adults exposed to mancozeb-derived ETU but not for children (toddlers).

4.4.1.4 Postapplication Data and Assumptions

In general, the approach used to estimate postapplication exposure to mancozeb and ETU encompassed typical Agency policies and assumptions, and have been summarized in Standard Operating Procedures (guidance documents), or SOPs.

A total of 8 chemical-specific dislodgeable foliar residue (DFR) studies were submitted for conducting mancozeb and mancozeb-derived ETU postapplication exposures. In addition, the registrants submitted one turf transferrable residue (TTR) study. The DFR studies were conducted on apples, grapes and tomatoes using a DF formulation. Mancozeb dislodgeable residues were considerably higher than ETU residues on the day of application; mancozeb residues ranged from 3X to 500X the LOQ, while ETU residues were typically at or just above the LOQ. Mancozeb half-lives ranged from 4.9 (FL tomatoes) to 35.4 (CA grapes) days. The ETU half-lives ranged from 3.2 (FL tomatoes) to 28 (WA apples) days.

The results of the DFR studies were extrapolated to other crop types based first on the region, followed by application method and crop type. Some of the studies were of higher quality than others, so the best available DFR data were used to calculate dissipation rates on crops for estimating postapplication exposures.

For postapplication exposure to youth and adults in home gardens, the same application parameters (representative crops, application rates, area treated, etc.) described for handlers were used. For turf, the maximum application rate of 17.4 lb ai/A was used, based on labels.

The mancozeb TTR study was conducted at 3 separate sites on several turf varieties, in CA, PA and NC, in which mancozeb was applied with a groundboom sprayer. Turf was treated at 0.6X to 0.9X the maximum label rate. Turf samples were analyzed up to 14 days after applications were made. The mancozeb half-life on turf ranged from 2.3 to 6.6 days; an ETU half-life could not be calculated since ETU residues were very low or nondetectable. To estimate exposure from residues on turf, the mancozeb residues were assumed to be 5% of the application rate on the day of application, and subsequent values were calculated based on residue decline kinetics. The concomitant ETU residues were assumed to be 0.61% of the mancozeb residues, and this was based on DFR studies in which both mancozeb and ETU were measured.

The half life for the California site, where irrigation occurred, was used to represent the dissipation rate for transplanted turf because transplanted turf must be kept wet to become established. It was assumed that sod farm turf would be harvested on the day after application in accordance with the REI of 24 hours and that it would take to two additional days to transport and install the turf. The average half life from the all three sites included in the TTR study was used to calculate seven day average TTRs to be used in assessing golfer and athlete cancer risk.

Other relevant assumptions include:

- Youth are considered to be ages 10-12 and weigh 39.1 kg; transfer coefficients for youth are 50% of those established for adults;
- The typical exposure duration for home gardeners is 40 minutes;
- Soil residues are found in the top centimeter, and soil density is 0.67 mg/L;
- Three-year-old toddlers weigh 15 kg;
- Hand-to-mouth events occur 20 times/hour;
- Saliva extraction is 50% (i.e., half the residue on the hand is removed by saliva);
- Typical transfer coefficients for turf were used (SOP for Residential Exposure Assessment); for golfers, the transfer coefficient was 500 cm^2/hour (typically used, and a policy is under development);
- Toddler contact with treated turf lasts for 2 hours per day.
- Golfer contact with treated turf lasts for fours per day for short term exposures and 1 hour per day for lifetime exposures.
- Golfers play an average of 19 days per year.
- Adult athletes were exposed to treated fields for 2 hours per day, 10 days per year, for 10 years out of a 70 year lifetime.

The transfer coefficients used to calculate postapplication risks for adult home gardeners are shown in Table 10, and are based on SOPs.

Table 10. Home Gardener Post Application Exposure Scenarios and Transfer Coefficients

Crop Type (Specific Crops)	Post Application Exposure Scenarios	Transfer Coefficient (cm^2/hr)
Cut Flowers	Low - Irrigation, scouting, thinning weeding immature low foliage plants Medium - Irrigation, scouting mature/high foliage plants High - Hand harvesting, pruning, thinning, pinching	2500 4000 7000
Field/row crop, tall (Corn)	Medium - Scouting, weeding more mature plants High - Scouting, weeding, irrigation mature plants Very High - Sweet corn hand harvest	400 1000 17000
Vegetable, cucurbit (Cucumbers, squash, melons)	Low - Irrigation, scouting, thinning weeding immature plants Medium - Irrigation and scouting mature plants High - Hand harvesting, pulling, leaf thinning, thinning, turning	500 1500 2500
Vegetable, fruiting (Tomato)	Low - Irrigation, scouting, thinning, weeding immature plants Medium - Irrigation and scouting mature plants High - Hand harvesting, pruning, staking, tying	500 700 1000

Note - Transfer coefficients shown are for adults; youth transfer coefficients are 50% of those shown in the table.

4.4.1.5 Postapplication Risks for Home Gardeners

Short-term dermal postapplication risks for adult and youth home gardeners are below the level of concern (i.e., MOEs exceed 1000) for ETU. A postapplication assessment was not conducted for mancozeb because no effects were observed at the limit dose in the 28 day dermal toxicity study.

Cancer risks were calculated for adults only, and were all below $5x10^{-7}$, the risk associated with hand harvesting sweet corn on the day of application.

A summary of postapplication exposure and risk is provided in Table 11. Only the risks associated with the very high exposure activities are shown for the purpose of calculating aggregate exposure and risk for ETU (food + residential + water). Provided aggregate risks for these very high activities are not of concern, then risks for lower exposure activities are also not of concern.

Table 11. Home Gardener Postapplication Risks for ETU.

Exposure Scenario	ETU (non-cancer)		ETU (Cancer), Adults only		
	Absorbed Dose (mg/kg/day)	MOE	Average Daily Dose (mg/kg/day	LADD	Cancer Risk
Youth	0.00081	8600	N/A	NA	NA
Adults	0.00106	4700	0.00091	8.8×10^{-6}	5.3×10^{-7}

Notes:
Risks are for hand-harvesting sweet corn, on the day of application. All other postapplication risks for home gardeners were lower.
Absorbed Dose = Dermal only
MOE = NOAEL/Absorbed Dose [NOAEL for ETU = 5 mg/kg/day for adults and 7 mg/day for youth]
LADD = Lifetime Average Daily Dose (the average daily dose x (5 exposure days per year/365 days per year)*(50 years of exposure/70 years of life)
Cancer Risk = LADD x 0.0601 $(mg/kg/day)^{-1}$

4.4.1.6 Postapplication Risks for Adults on Turf

The MOEs and cancer risks for the golfer and athlete turf scenarios are summarized in Table 12. The MOEs were calculated using day zero residues and the cancer risk was calculated using seven day average residues. The MOE for golfers exceeds the target MOE of 1000 and the MOE for athletes (450) does not exceed the target MOE. The cancer risks for ETU are not of concern for either golfers or athletes.

Table 12. ETU Postapplication Risks for Adults Exposed to Turf.

	ETU (non-cancer)		ETU (Cancer), Adults				
Exposure Scenario	**Absorbed Dose (mg/kg/day)**	**MOE**	**Average Daily Dose (mg/kg/day)**	**Days per Year Exposure**	**Years Exposure**	**LADD (mg/kg/day)**	**Cancer Risk**
Golfing	0.00076	6600	0.000078	19	50	$3.3x10^{-6}$	$2.0x10^{-7}$
Athletics	0.011	450	0.011	10	10	$1.0x10^{-5}$	$6.0x10^{-7}$

Notes:
Absorbed Dose = Dermal only
MOE = Margin of Exposure = NOAEL/Absorbed Dose [NOAEL for ETU = 5 mg/kg/day]
LADD = Lifetime Average Daily Dose (average daily dose x (days per year exposure /365 days)*(years exposure/70 years)
Cancer Risk = LADD x 0.0601 $(mg/kg/day)^{-1}$.

4.4.1.7 Postapplication Risks for Toddlers on Turf

A summary of postapplication risks for toddlers is shown in Table 13. The mancozeb MOEs from all the individual pathways are above the target MOE of 100. The total MOE of 93, which includes all of the individual pathways, is below 100. The individual mancozeb MOEs rise to 100 with a PHI of 0 to 1 days while the total MOE rises to 100 with a PHI of 2 days. The ETU MOEs for all the individual pathways were above the target MOE of 1000. The total ETU MOEs which included dermal, hand-to-mouth, object to mouth and soil ingestion were below 1000. The total ETU MOE is above 1000 with a PHI of 3 days.

Table 13: Mancozeb and ETU Postapplication Risks for Toddlers Exposed to Turf.

Exposure Pathway	Mancozeb		ETU	
	MOE on Day 3 (PHI = 1 day)	PHI Needed to Reach an MOE of 100	MOE on Day 3 (PHI = 1 day)	PHI Needed to Reach an MOE of 1000
Dermal	N/A	N/A	1400	1
Hand-to-Mouth	110	1	1100	1
Object-to-Mouth	460	0	4300	0
Soil Ingestion	34000	0	320000	0
Total	93	2	530	3

* The current "PHI" is one day because the REI is 24 hours.

5.0 Aggregate Risk Assessments and Risk Characterizations

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources or pathways: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposure and risk from various sources, HED considers both the route and duration of exposure. However, if exposure and risk from any one pathway exceed the level of concern, an aggregate assessment is not conducted.

Exposure to mancozeb and mancozeb-derived ETU can occur in residential settings. The mancozeb uses in home gardens result in handler exposure, and postapplication exposure can occur for adults or youth harvesting home garden vegetables, adults contacting professionally-treated turf during athletic activity or golfing, and for children contacting treated turf. Short-term postapplication risks for toddlers from mancozeb *per se* and ETU were below the target MOE for residential exposure, are of concern, and therefore could not be added to exposure through food or drinking water.

Exposure to mancozeb *per se* is not expected from the water pathway, so aggregate exposure and risk for mancozeb *per se* are limited to combined food and residential pathways. For ETU, aggregate risks include dietary food and water and residential pathways of exposure. The following aggregate risk assessments have been completed:

(1) ETU acute aggregate (food + water)
(2) ETU non-cancer chronic aggregate (food + water)
(3) Mancozeb short-term handler, home garden (food + residential)
(4) ETU short-term handler (food + water + residential)
(5) ETU short-term postapplication, home garden (food + water + residential)
(6) ETU short-term postapplication, golfing (food + water + residential)

(7) ETU cancer handler, home garden (food + water + residential)
(8) ETU cancer postapplication, home garden (food + water + residential)
(9) ETU cancer postapplication, golfing (food + water + residential)

These aggregate risk assessments are representative exposures that are expected to co-occur. HED did not add handler and postapplication activities for adults, since they are not considered likely to co-occur, and addition of these two types of exposure, along with food and water, would be overly conservative. Aggregate postapplication risks for mancozeb *per se* were not calculated because no dermal toxicity occurred at the limit dose in the subchronic dermal toxicity study and because inhalation exposure is not expected in a postapplication scenario.

The ETU surface and ground water monitoring data are considered adequate to generate quantitative surface and ground water drinking water chronic exposure estimates. The surface water monitoring data indicate a concentration of 0.1 ppb should be used to calculate aggregate chronic non-cancer and cancer exposure and risk. The ETU ground water concentration (0.21 ppb) was taken from a targeted monitoring study; use of this value to calculate aggregate risk provides an upper bound estimate of exposure through drinking water from ground water sources.

Estimated chronic exposure and risk from ETU in surface and ground water were calculated by using the monitored residue values for surface and ground water for water (all sources) in the dietary exposure assessment conducted using DEEM™-FCID. The exposure from ground water was then added to food and residential exposures to determine chronic and short-term aggregate risk. Aggregate risks calculated using exposure from ground water are protective of exposure and risk from surface water, since ground water residues/exposures/risks are approximately 2X those of surface water.

In order to determine if acute aggregate risks are of concern, HED has calculated drinking water levels of comparison, or DWLOCs. The DWLOC is the maximum amount of a pesticide in drinking water that would be acceptable in light of combined exposure from food and residential pathways. The calculated DWLOCs are then compared to the EDWCs provided by EFED; if model-derived EDWCs exceed the DWLOCs for surface or ground water, there may be a concern for dietary exposure to residues in drinking water, and monitoring data may be required.

5.1 ETU Acute Aggregate Risk Assessment (Food + Water)

Acute dietary exposure and risk from ETU in food is below HED's level of concern for females 13 - 49, the only population subgroup for which an acute endpoint was identified for ETU. A body weight of 60 kg and 2 L/day water consumption were assumed.

The estimated food exposure at the 99.9th percentile is 0.000898 mg/kg/day. The surface water EDWCs range from 0.1 ppb (monitoring) to 25.2 ppb (modeling). The ground water EDWC is 0.21 ppb (from monitoring). See Table 14, below.

Potential exposure to ETU from both ground and surface water sources of drinking water, when combined with exposure through food, is below HED's level of concern for acute risk. According to calculations for surface water, ETU combined food and water exposures are not of concern provided surface and ground water residues are less than 123 ppb (the DWLOC). The upper-bound ETU estimates are 25.2 ppb in surface water and 0.21 ppb in ground water, both of which are significantly less than the DWLOC.

5.1.1 ETU Acute DWLOC Calculations

Table 14. ETU Acute DWLOC Calculations

Population Subgroup	aPAD mg/kg/day	Acute Food Exp mg/kg/day	Max Acute Water Exp. mg/kg/day[2]	Acute DWLOC (µg/L)[4]	Surface Water EDWC (ppb)[3]	Ground Water EDWC (ppb)[3]
Females 13-49[1]	0.005	0.000898	0.00410	123	25.2	0.21

[1] For females 13-49, the body weight assumption is 60 kg.
[2] Maximum acute water exposure (mg/kg/day) = [(aPAD - acute food exposure]
[3] For surface water, modeling/monitoring data were used; for ground water, targeted monitoring data were used.
[4] Acute DWLOC(µg/L) = $\frac{\text{[max. acute water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x 10-3 mg/µg]}}$

5.2 ETU Chronic Aggregate Risk Assessment (food + water)

The chronic dietary exposure and risk from mancozeb-derived ETU in food is below HED's level of concern for the General US Population and various population subgroups. The ETU surface water and ground water residues of 0.1 and 0.21 ppb, respectively, were incorporated into a dietary (water only) exposure assessment using the DEEM-FCID™ model. The resulting exposures were then added to exposure from food.

5.2.1 ETU Chronic (Non-Cancer) Aggregate Risks

Aggregate ETU chronic non-cancer risks are below HED's level of concern (100 %cPAD) for the general US population and all other population subgroups. The most highly exposed population subgroup is children 1-2 years old, with chronic (non-cancer) aggregate risks of 34-36 %cPAD. Exposure from food was significantly higher than exposure from ground or surface water sources of drinking water. Table 15 summarizes food exposure, water exposure from DEEM-FCID™, based on estimated concentrations of ETU in surface and ground water, and total (aggregate) chronic (non-cancer) exposure and risk.

Table 15. ETU Chronic Non-Cancer Aggregate Risk Calculations - Surface Water and Ground Water.

Population Subgroup	ETU Chronic Food Exp. mg/kg/day	Surface Water			Ground Water		
		Chronic Water Exp mg/kg/day	Chronic (Food + Water) Exp mg/kg/day	Aggregate Risk (%cPAD)[a]	Chronic Water Exp mg/kg/day	Chronic (Food + Water) Exp mg/kg/day	Aggregate Risk (%cPAD)[a]
General US Pop.	0.000022	0.000002	0.000024	12	0.000004	0.000026	13
All infants	0.000027	0.000007	0.000034	17	0.000015	0.000042	21
Children 1-2 yr	**0.000065**	**0.000003**	**0.000068**	**34**	**0.000007**	**0.000072**	**36**
Children 3-5 yr	0.000051	0.000003	0.000054	27	0.000006	0.000057	29
Children 6-12 yr	0.000029	0.000002	0.000031	16	0.000004	0.000033	16
Youth, 13-19 yr	0.000015	0.000002	0.000017	8	0.000003	0.000018	9
Adults, 20-49 yr	0.000017	0.000002	0.000019	10	0.000004	0.000021	10
Females, 13-49	0.000017	0.000002	0.000019	10	0.000004	0.000021	10
Adults 50+ yr	0.000020	0.000002	0.000022	12	0.000004	0.000024	12

a ETU cPAD = 0.0002 mg/kg/day

5.2.2 ETU Chronic (Cancer) Aggregate Risk

The ETU chronic exposure estimate of 0.000027 mg/kg/day from combined food and ground water exposures for the general US population corresponds to a cancer risk of 1.6×10^{-6}, which is not of concern. Most of the estimated exposure was from residues in food.

5.3 Short-Term Aggregate Exposure and Risk

5.3.1 Mancozeb Short-Term Aggregate, Handler, Home Garden

Aggregate short-term exposure and risk for residential handlers applying mancozeb are below HED's level of concern.

Exposure pathways considered include food and residential handler (inhalation) exposures. Residential handler risks are only assessed for adults, so the mancozeb aggregate short-term handler risks also apply to adults. Residential handler exposures are considered short-term in nature; exposure estimates shown in Table 9 were used with chronic food exposure for the general US population (Table 8) to calculate aggregate exposure using the 1/MOE approach. Chronic food exposure for the General US population was used because it was higher than exposures estimated for any of the adult population subgroups.

Aggregate MOEs were significantly higher than the target MOE of 100 and are not of concern. Mancozeb short-term aggregate handler risks are shown in Table 16.

Table 16. Mancozeb Short-Term Aggregate Handler Risk, Home Garden.

Exposure Scenario	Residential Handler Absorbed Dose (mg/kg/day)	MOE	Dietary (Food) Exposure (mg/kg/day)	MOE	Aggregate MOE
1) Backpack Sprayer	2.4×10^{-5}	890000	0.000053	170000	140000
2) Low Pressure Handwand	7.1×10^{-6}	3000000			160000

Notes:
Absorbed Dose = inhalation exposure (Table 9). Inhalation NOAEL = 21 mg/kg/day
Dietary Exposure = chronic food exposure for General U.S. Population (Table 8). ST dietary NOAEL = 9.24 mg/kg/day

Aggregate MOE (Margin of Exposure) = $\dfrac{1}{1/MOE_{handler} + 1/MOE_{food}}$

5.3.2 ETU Short-Term Aggregate, Handler, Home Garden

ETU short-term aggregate risk for residential handlers applying mancozeb is below HED's level of concern.

Exposure pathways considered include dietary food and water and residential dermal and inhalation. Residential handler risks are only assessed for adults, so the ETU aggregate short-term handler risks also apply to adults. A developmental endpoint was chosen for short-term risks, so non-cancer handler risks were calculated assuming a body weight of 60 kg, for females. Short-term combined dermal and inhalation exposure estimates (Table 9) were added to chronic food exposure for females 13-49 (Table 8) and chronic ground water exposure for females 13-49 (Table 15) to calculate aggregate exposure.

Combined food, water and residential exposures were compared to the short-term NOAEL of 5 mg/kg/day; the endpoint selected for short-term exposures was developmental defects of the brain. Short-term MOEs are significantly higher than the target MOE of 1000. ETU short-term aggregate handler risks are shown in Table 17.

Table 17. ETU Short-Term Aggregate Handler Exposure/Risk, Home Garden.

Exposure Scenario	Residential Handler Absorbed Dose	Dietary Exposure		Aggregate Exposure/Risk	
		Food	Water	Exposure	MOE
1) Backpack Sprayer	8.1×10^{-6}	0.000018	0.000004	3.1×10^{-5}	161000
2) Low Pressure Handwand	4.5×10^{-5}			6.7×10^{-5}	75000

Notes:
Absorbed Dose = combined dermal and inhalation, mg/kg/day. (Table 9)
Food Exposure = chronic food exposure for females 13-49, mg/kg/day (Table 8)
Water Exposure = chronic ground water exposure for females 13-49, mg/kg/day (Table 15)
Aggregate Exposure = Absorbed dose + food exposure + water exposure (mg/kg/day)
Aggregate MOE (Margin of Exposure) = NOAEL/Aggregate Exposure [NOAEL for ETU = 5 mg/kg/day]

5.3.3 ETU Short-Term Aggregate, Postapplication, Home Garden

ETU aggregate short-term postapplication exposure and risk for youth and adult home gardeners are below HED's level of concern, with MOEs significantly higher than the target MOE of 1000.

Exposure pathways considered include dietary food and water and residential dermal from postapplication activities in the home garden. Residential postapplication exposure and risk have been assessed for both youth and adults, so both youth and adult aggregate postapplication exposure and risk for ETU have been calculated. Postapplication exposures are considered short-term in nature, and have been calculated assuming people re-enter the garden on the day of application. The highest postapplication exposure estimates were for hand harvesting sweet corn grown in the West on the day of application; these exposure estimates have been aggregated with ETU exposure from food and water, and are protective for all other lower exposure postapplication activities.

Postapplication exposures for adults and youth (Table 11) were added to chronic food and ground water exposures (Table 15) for females 13-49 (adults), and to the chronic food and ground water exposures (Table 15) for children 6-12 (youth), respectively, to calculate aggregate exposure. The food exposure for children ages 6-12 was chosen because youth gardeners are assumed to be aged 10-12. Chronic food and water exposure for females 13-49 were used for adults because a developmental endpoint was selected for short-term risk assessments for ETU.

Combined food, water and postapplication exposures to ETU were compared to the short-term NOAEL of 5 mg/kg/day for females 13-49, and to the short-term NOAEL of 7 mg/kg/day for youth; the endpoint selected for aggregate risk assessment for youth and toddlers was thyroid effects. ETU short-term aggregate postapplication risks for home gardeners are shown in Table 18.

Table 18. ETU Short-Term Aggregate Postapplication Risk, Home Garden.

Population	Residential Postapplication Absorbed Dose	Dietary Exposure		Aggregate Exposure/Risk	
		Food	Water	Exposure	MOE
Youth	0.00081	0.000031	0.000004	0.000845	8300
Adults	0.00106	0.000018	0.000004	0.00108	4600

Notes:
Absorbed Dose = Dermal, mg/kg/day. (Table 11)
Dietary Exposure = Food exposure + water exposure
Food Exposure = chronic food exposure for children 6-12/Females 13-49, mg/kg/day (Table 15)
Water Exposure = chronic water exposure, children 6-12/Females 13-49, mg/kg/day (Table 15)
Aggregate Exposure = Absorbed dose + food exposure + water exposure, (mg/kg/day)
Aggregate MOE (Margin of Exposure) = NOAEL/Aggregate Exposure
[Short-term NOAEL for youth = 7 mg/kg/day; short-term NOAEL for adults = 5 mg/kg/day]

5.3.4 ETU Short-Term Aggregate, Postapplication, Golfing

ETU aggregate short-term postapplication risk for adult golfers is below HED's level of concern.

Exposure pathways considered include dietary food and water and residential postapplication dermal exposure from golfing on treated turf. Postapplication exposures are considered short-term in nature, and have been calculated assuming people spend up to 4 hours on the golf course. ETU postapplication exposure estimates for adult golfers (Table 12) were added to the ETU chronic food and ground water exposure (Table 15) for females 13-49 to calculate aggregate exposure.

Chronic food and water exposure for females 13-49 were used for adults because a developmental endpoint was chosen for assessing short-term risks for ETU. Short-term ETU risks were calculated assuming a female body weight of 60 kg. Combined food, water and dermal exposures to ETU were compared to the short-term NOAEL of 5 mg/kg/day. ETU short-term aggregate postapplication risk for adult golfers is shown in Table 19.

Table 19. ETU Short-Term Aggregate Postapplication Risk, Golfing.

Scenario	Residential Postapplication Absorbed Dose	Dietary Exposure		Aggregate Exposure/Risk	
		Food	Water	Exposure	MOE
Golfing	0.00076	0.000031	0.000004	0.00080	6300

Notes:
Absorbed Dose = Dermal, mg/kg/day. (Table 12)
Dietary Exposure = Food exposure + chronic ground water exposure
Food exposure = chronic food exposure females 13-49, mg/kg/day (Table 15)
Water exposure = chronic ground water exposure, females 13-49, mg/kg/day (Table 15)
Aggregate Exposure = Absorbed dose + food exposure (mg/kg/day)
Aggregate MOE (Margin of Exposure) = NOAEL/Aggregate Exposure
[Short-term NOAEL for ETU = 5 mg/kg/day]

5.4 ETU Aggregate Cancer Risk

5.4.1 ETU Cancer Aggregate, Handler, Home Garden

ETU aggregate cancer risk for residential handlers applying mancozeb is 1.6×10^{-6}, which is not of concern.

Exposure pathways include dietary food and water and residential dermal and inhalation. Residential handler cancer risks are only assessed for adults. The combined dermal and inhalation exposure lifetime average daily dose (LADD) estimates (Table 9) were added to chronic food and ground water exposure for the general US population (Table 15) to calculate aggregate cancer exposure.

Combined food, water and residential handler exposures for ETU were multiplied by the cancer potency factor for ETU, 0.0601 $(mg/kg/day)^{-1}$. ETU aggregate cancer risks for residential handlers are shown in Table 20. The most significant source of exposure is from the dietary food pathway.

Table 20. ETU Cancer Aggregate Handler Exposure/Risk, Home Garden.

Exposure Scenario	Residential Handler LADD	Dietary Exposure		Aggregate Exposure	
		Food	Water	Exposure	Cancer Risk
1) Backpack Sprayer	6.8×10^{-8}	0.000023	0.000004	0.000027	1.6×10^{-6}
2) Low Pressure Handwand	3.8×10^{-7}			0.000027	1.6×10^{-6}

Notes:
LADD = Lifetime Average Daily Dose = combined dermal and inhalation, mg/kg/day (Table 9)
Dietary Exposure = Food exposure + ground water exposure
Food Exposure = chronic food exposure for the general US population, mg/kg/day (Table 15)
Water Exposure = chronic ground water exposure for the general US population, mg/kg/day (Table 15)
Aggregate Exposure = LADD + food exposure + water exposure (mg/kg/day)
Cancer risk = Aggregate exposure x 0.0601 $(mg/kg/day)^{-1}$ [cancer potency factor for ETU]

5.4.2 ETU Cancer Aggregate, Postapplication, Home Garden

ETU aggregate postapplication cancer risk for adult home gardeners is 2.2×10^{-6}, which is not of concern. Exposure from postapplication activities in the home garden and from water are significantly lower than exposure from food.

Exposure pathways considered include dietary food and water and residential dermal from postapplication activities in the home garden. Residential postapplication exposure and cancer risk have been assessed for adults only. The highest dermal postapplication exposure estimates were associated with hand harvesting sweet corn grown in the West on the day of application; these exposure estimates have been aggregated with ETU exposure from food and water, and are protective for all other lower exposure postapplication activities in the home garden.

Postapplication exposures for adults (Table 11) were added to chronic food and ground water exposures (Table 15) for the general US population to calculate aggregate exposure. Combined food, water and postapplication exposures to ETU were multiplied by the cancer potency factor for ETU, 0.0601 $(mg/kg/day)^{-1}$. ETU aggregate cancer risk for residential postapplication exposure in the home garden is shown in Table 21.

Table 21. ETU Cancer Aggregate Postapplication Risk, Home Garden.

Population	Residential Postapplication LADD	Dietary Exposure		Aggregate Exposure	
		Food	Water	Exposure	Cancer Risk
Adults	8.8×10^{-6}	0.000023	0.000004	0.000036	2.2×10^{-6}

Notes:
LADD = Lifetime Average Daily Dose, mg/kg/day. (Table 11)
Dietary Exposure = Food exposure + ground water exposure
Food Exposure = chronic food exposure for the general US population, mg/kg/day (Table 15)
Water Exposure = chronic ground water exposure, general US population, mg/kg/day (Table 15)
Aggregate Exposure =LADD + food exposure + water exposure, (mg/kg/day)
Cancer risk = Aggregate exposure x 0.0601 $(mg/kg/day)^{-1}$ [cancer potency factor for ETU]

5.4.3 ETU Cancer Aggregate, Postapplication, Golfing

ETU aggregate postapplication cancer risk for adult golfers is 1.8×10^{-6}, which is not of concern. Exposure from golfing on treated turf and from water are significantly lower than exposure from food.

Exposure pathways considered include dietary food and water and residential postapplication dermal exposure from golfing on treated turf. ETU postapplication exposure estimates for adult golfers (Table 12) were added to the ETU chronic food and ground water exposure (Table 15) for the general US population to calculate aggregate exposure and cancer risk.

Combined food, water and postapplication exposures to ETU were multiplied by the cancer potency factor for ETU, $0.0601\ (mg/kg/day)^{-1}$. ETU aggregate cancer risk for residential postapplication exposure to golfers is shown in Table 22.

Table 22. ETU Short-Term Aggregate Postapplication Risk, Golfing.

Scenario	Residential Postapplication LADD	Dietary Exposure		Aggregate Exposure	
		Food	Water	Exposure	Cancer Risk
Golfing	3.3×10^{-6}	0.000022	0.000004	0.000030	1.8×10^{-6}

Notes:
LADD = Lifetime Average Daily Dose, mg/kg/day. (Table 12)
Dietary Exposure = Food exposure + chronic ground water exposure
Food exposure = chronic food exposure, general US population, mg/kg/day (Table 15)
Water exposure = chronic ground water exposure, general US population, mg/kg/day (Table 15)
Aggregate Exposure =LADD + food exposure + water exposure (mg/kg/day)
Cancer risk = Aggregate exposure x $0.0601\ (mg/kg/day)^{-1}$ [cancer potency factor for ETU]

6.0 Cumulative Exposure and Risk

Section 408(b)(2)(D)(v) of the FFDCA 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."

The Agency has concluded that N-methyl carbamates subgroup should be designated as a common mechanism group (CMG) based on their shared structural characteristics and similarity, and on their shared ability to inhibit acetylcholinesterase (Report of 9/22/99 SAP Meeting). Thiocarbamates and dithiocarbamates (which include the EBDCs) have not been included in the CMG because they do not share cholinesterase inhibition as a common principal mechanism of toxicity.

During previous Special Review of the EBDCs (metiram, maneb and mancozeb), the Agency considered the three active ingredients to be related due to the common effect, thyroid cancer, resulting from formation of the common metabolite, ETU; exposure to residues in and on crops as well as *in vivo* conversion of EBDCs to ETU was included in the assessments. Previous and current mancozeb risk assessments (from food and water, and in residential and occupational settings) are based on combined ETU exposure associated with mancozeb. The current series of EBDC risk assessments (including maneb) consider formation of ETU from each active ingredient individually, and aggregate risks from exposure to ETU from all three EBDCs are characterized in a companion ETU risk assessment document.

In 2001, the Agency proposed a common mechanism of toxicity for all dithiocarbamates based on neuropathology related to CS_2 formation. However, following public comment and SAP review of the data, OPP concluded there was no support for grouping dithiocarbamates, including EBDCs, based on a common mechanism for neuropathology. The panel did not find a link between carbon disulfide and neuropathy with mancozeb or other EBDC pesticides. No determination of a common toxic effect or mechanism of toxicity has been made for acute or chronic non-cancer risks from EBDCs. No other dithiocarbamates are included in the risk assessment because they do not produce the metabolite ETU.

7.0 Occupational Exposure

Occupational populations (handlers) are potentially exposed to mancozeb and ETU while making applications to vegetables, fruits, field crops, ornamentals and turf, including golf courses. Some of these exposures are expected to occur in greenhouses, such as greenhouse tomatoes and ornamentals. In addition, potential exposure to mancozeb and ETU occurs after application, when workers contact foliage or harvest treated crops or ornamentals (postapplication). Exposures are defined by the type of activity involved. Workers defined as "handlers" may prepare spray solutions (mixer/loader) for application, they may apply the pesticide (applicator), or they may combine these tasks (mixer/loader/applicator). The Agency typically conducts an assessment for flaggers, who may be exposed during aerial application.

For mancozeb and ETU handler risk assessments, 5 mixer/loader scenarios were identified for each formulation - wettable powder, liquid and dry flowable - including mixing/loading sprays for aerial, chemigation, groundboom, airblast and high pressure handwand applications. For applicators, 4 scenarios include airblast, groundboom, aerial and high-pressure handwand applications. For each formulation type, 3 mixer/loader/applicator scenarios were identified - low pressure handwand, backpack sprayer and turf gun; a single flagger scenario was identified for aerial sprays.

Although labels permit seed piece treatment of asparagus and caprifigs, there were no data to indicate the daily amount treated. Potato seed piece scenarios include both commercial and on-farm treatments. Mixer/loader scenarios include WP, DF and liquids for commercial treatment, and liquids for on-farm treatment. For dust formulations, scenarios include loading and applying for commercial and on-farm treatments; applicator scenarios were identified for liquid dips. Secondary handler scenarios involve loading treated seed pieces for tractor planting, and planting seed pieces with a tractor. Finally, a scenario for hand planting treated seed pieces was identified. For seed treatments, 9 handler scenarios were identified - mixer/loader for commercial seed treatment (WP, DF and liquid), loader/applicator, bagger, sewer, multiple activities, on-farm planter box treatment, and seed planter.

A variety of postapplication exposure scenarios were identified by the type of activity involved, and by the range of exposure expected, i.e., low, medium and high exposure activities. Examples of low exposure activities include irrigation and scouting; medium exposure activities may involve scouting of mature plants, or in greenhouses, hand pinching chrysanthemums. Potential high exposure activities include hand harvesting cut flowers and thinning and pruning apples. Both handler and postapplication risks were calculated for agricultural and greenhouse scenarios.

Handler and postapplication exposure and risk were estimated for mancozeb *per se* and its metabolite/degradate ETU. For handlers, most exposures were considered to be short- or intermediate-term in duration, with the exception of greenhouse uses (such as tomatoes or cut flowers), which may result in chronic (i.e., >180 days) exposure. For both handler and postapplication assessments, the mancozeb dermal exposure (including a 1% dermal absorption

factor) was multiplied by 0.075 to take into account the 7.5 % *in vivo* metabolic conversion of mancozeb to ETU. This "metabolic" ETU was added to the ETU exposure from handler and postapplication activities to obtain the total ETU exposure.

For mancozeb non-cancer handler assessments, the short- and intermediate-term risks were the same, because the same endpoints (thyroid effects) and doses were used to assess exposures up to 6 months, and because there was no difference in the estimated daily exposure for these durations, *via* inhalation route of exposure. Only inhalation MOEs were calculated for short/intermediate term mancozeb handler exposures because no effects were observed at the limit dose in the 28 day mancozeb dermal toxicity study. The long-term (chronic) exposure scenarios were assessed using a different dose, and were limited to exposures occurring in greenhouses. Postapplication exposures for mancozeb were not calculated because inhalation postapplication exposure is believed to be negligible. For ETU handler and postapplication assessments, non-cancer short- and intermediate-term risks were the same, but chronic risks were assessed using a different toxicological dose and endpoint.

ETU non-cancer dermal and inhalation exposures were combined because the endpoints (thyroid effects) selected as the basis for risk assessment were the same. Postapplication risk assessments included only dermal exposures. For mancozeb non-cancer dermal risk assessments, the endpoint for risk assessment was selected from an oral study, so a 1% dermal absorption factor was used. For mancozeb inhalation assessments, the endpoint and dose for risk assessment were selected from an inhalation study, so no inhalation absorption factor was used. For ETU dermal and inhalation assessments (non-cancer and cancer), endpoints for risk assessment were selected from oral studies, so 26% dermal and 100% inhalation absorption factors were applied.

For both occupational handler and postapplication risks, the dose selected for risk assessment, the NOAEL, was divided by the estimated exposure to determine the Margin of Exposure (MOE). The target MOE for mancozeb and ETU occupational exposure is 100, based on the combined uncertainty factors (UFS) associated with endpoint selection; MOEs less than 100 are of concern, and may require mitigation to reduce exposure.

7.1 Occupational Handler Risk Assessment

7.1.1 Handler Data and Assumptions

No chemical-specific handler exposure studies were submitted in support of the reregistration of mancozeb, so Pesticide Handler Exposure Database (PHED, Version 1.1, 1998) data were used to calculate unit exposure values to estimate occupational handler exposures to mancozeb and ETU during application to crops and ornamentals. In addition, data from the ORETF (Occupational and Residential Exposure Task Force) studies were used to evaluate handlers' exposures for treating turf. There are no recent or adequate data (either chemical-specific or in PHED) that reflect the specifics of the potato seed piece treatment scenario. Therefore, PHED data for other scenarios were extrapolated to seed piece treatment by assuming that the mixing and loading of mixing tanks or hoppers on seed

piece treatment equipment would produce similar exposures as mixing and loading tanks or hoppers on pesticide application equipment. In addition, HED contacted experts in the potato industry for information regarding reasonable assumptions with respect to the amount treated per day. There were no data to assess risks for planting treated potato seed pieces.

Mancozeb labels include seed treatment for cotton, tomato, flax, safflower, peanuts, wheat, barley, rice, rye, field corn, sorghum, triticale, field corn and oats. No chemical-specific data were submitted to evaluate exposures from seed treatment, so data from a recently-developed HED seed treatment SOP were used.

Current mancozeb labels require mixer loaders to wear an apron, coveralls, and gloves over long pants and a long-sleeved shirt. Applicators must wear similar clothing, but are not required to wear the apron. Mancozeb and ETU handler exposures and risks were estimated for workers wearing typical work clothing, or baseline, which includes a long-sleeved shirt, long pants, shoes, socks, and no gloves or respiratory protection. Exposures and risks were also estimated using additional personal protective equipment (PPE) such as gloves. These include Single Layer, or Baseline clothing with gloves, and Double Layer, or Single Layer with coveralls.

For determining inhalation risks, both single layer and double layer scenarios were also assessed with the addition of 2 different respirators, one with 80% inhalation protection (PF5) and one with 90% protection (PF10). Both dermal and inhalation exposures were estimated with the addition of engineering controls, such as an enclosed cockpit or cab, and water soluble packaging; engineering controls are not applicable to handheld application methods used in a greenhouse setting.

The PHED data for deriving unit exposures have been "graded" based on the quality and quantity of the available studies, and these grades result in low, medium or high confidence in the unit exposure values. In each handler assessment completed for mancozeb and ETU, the best available data were used to estimate unit exposures. PHED unit exposure data were not available for assessing exposure during mixing/loading/applying DF and WP formulations with a backpack sprayer.

For mancozeb handler risks, most PHED unit exposures were generated using data from studies with medium to high confidence. Some low confidence data (generally due to a low number of replicates) were used for dermal exposures for mixer/loaders (DF and WP formulations), inhalation exposures for airblast applicators with engineering controls, and dermal exposures for low and high pressure handwand and backpack sprayer applicators. Since there were no chemical-specific data to assess potato seed piece treatment, surrogate data from PHED were used to assess exposures, along with use information provided by potato industry experts.

The assumptions summarized below were combined with the PHED unit exposures and used in agricultural handler risk assessments; these assumptions are typically used in HED risk assessments, with the exception of potato seed piece assumptions, which were based on conversations with experts in the potato industry, and seed treatment acres planted, which were based on conversations with an

in-house expert, Dr. Bernard Schneider. Risks associated with seed treatment were calculated using unit exposures from the seed treatment SOP. Exposure scenarios evaluated in studies included in the SOP are mixing/loading, application, bagging, sewing and multiple tasks (one or more of the above).

Assumptions used to Calculate Handler Risks

- Adult body weight = 70 kg;
- Generic protection factors for clothing layers, gloves, engineering controls;
- Maximum application rates for short- and intermediate-term risks;
- Typical application rates (where available) for cancer risk;
- Average occupational workday = 8 hours;
- Acres treated per day:
  - Aerial: 350 acres (most crops); 1200 acres (high acreage crops, e.g. wheat/corn).
  - Chemigation: 350 acres (most crops); 40 and 10 acres (ornamentals).
  - Groundboom: 80 acres (most crops); 200 acres (high acreage); 40 and 10 acres (ornamentals).
  - Airblast: 40 acres.
  - High pressure handwand: 10 acres (ornamentals), assuming 100 gal/acre and 1000 gal/day.
  - Backpack sprayer/low pressure handwand: 0.4 acres/day, assuming 100 gallons/acre, and 40 gallons/day.
- Seed piece and Seed Treatment
  - Potato seed piece: 500/30 tons treated per day for commercial/on-farm;
  - Potato seed piece: 1 ton of seed planted/day, 40 acres;
  - Seed: amount of seed treated per day was based on capacity of Gustafson commercial equipment.
  - Seed: the amount of seed planted per day was based on the amount of seed planted per acre, multiplied by 80 acres/day.
- For ETU cancer risk, 30 days exposure/year for professional workers;

Because mancozeb (as well as the other EBDCs) is known to be unstable in tank mixes, the Agency required data to quantify formation of ETU in spray solutions during mixing/loading and application of mancozeb/EBDC formulations. These data were submitted to the Agency in conjunction with the 1992 Special Review, and were used to estimate occupational exposures to ETU. The tank mix data have also been used in the current risk assessment, with the underlying assumption that the manufacturing processes for mancozeb (and EBDC) products have not changed substantially. In estimating mixer/loader risks, a 0.1% conversion of mancozeb to ETU was assumed, and for applicators a 0.2% factor was used. These factors are not considered conservative; at the time the tank mix studies were submitted, the Agency stated that the full range of field conditions was not adequately represented in the studies, and that certain conditions (higher temperature and humidity) could result in a higher percent conversion to ETU.

7.1.2 Occupational Agricultural and Greenhouse Handler Risks

Mancozeb labels require double layer PPE and a chemical resistant apron for mixing/loading and double layer PPE without the apron for application. The labels do not require respiratory protection.

Mancozeb Combined Dermal and Inhalation Risks: Mancozeb long-term combined dermal and inhalation risks were all below HED's level of concern (i.e., the MOEs were greater than 100) provided Single Layer PPE is worn.

Mancozeb *per se* short- and intermediate-term inhalation risks are shown in Table 23. Only inhalation MOEs were calculated for short/intermediate term mancozeb exposures because no effects were observed at the limit dose in the 28 day mancozeb dermal toxicity study. For some of the mixer loader scenarios involving wettable powder, the risks are of concern and respiratory protection is required to achieve Agency risk targets. The risks for mixing and loading dry flowable and liquid flowable formulations are much lower and respiratory protection is not needed. The risks for the remaining scenarios are not of concern.

Calculations were also performed to assess the risk for ETU that was contaminant in the spray mix and that was metabolized from absorbed mancozeb.

ETU Non-Cancer Risks: Like mancozeb, ETU MOEs are of concern for high-volume mixer/loader wettable powder scenarios with label required PPE. Additional PPE, such as respirators, or engineering controls are needed to achieve MOEs of 100. The Chronic ETU MOEs of 25 are of concern with label required PPE for the scenarios that involving the mixing/loading of wettable powder for application to pachysandra. Additional PPE, such as respirators, are needed to achieve MOEs of 100. The risks for mixing/loading dry flowable and liquid formulations are much lower than for the wettable powder formulations, and are not of concern for the single layer clothing scenario.

ETU Cancer Risks: ETU cancer risks were calculated assuming 30 exposure days per year. Most of the risks are less than $1x10^{-4}$ with single layer PPE (which includes gloves but not respirators) and all of the risks are less than $1x10^{-4}$ with additional mitigation (such as respirators or water soluble bags). Some of the high volume commercial mixer/loader scenarios (i.e., wettable powders, turf application rates), however, remain as high as $6x10^{-6}$ with engineering controls and might be of concern if $1x10^{-6}$ is chosen as a risk mitigation goal. The risks for mixing/loading dry flowable and liquid formulations are much lower than for the wettable powder formulations, and are all less than $2.5x10^{-5}$ with single layer PPE.

Table 23: Mancozeb Short/Intermediate Term Inhalation MOEs for Occupational Applicators/Handlers (MOE in Bold are less than 100 and are of concern)

Exposure Scenario	Typical Crop (s)	lb ai per acre	acres per day	Baseline (No Resp)	PF5 Respirator	PF10 Respirator	Engineering Control
Mixer/Loaders (M/L)							
M/L Wettable Powder (WP) for Aerial Application or Chemigation	turf: sod farms	17.4	350	**5.6**	**28**	**56**	>1000
	small grains, cotton	1.6	1200	**18**	**89**	180	>1000
	vegetables (Note 1)	2.4	350	**41**	200	410	>1000
	potatoes, sugar beets	1.6	350	**61**	300	610	>1000
	sweet corn	1.2	350	**81**	410	810	>1000
M/L WP for Groundboom	turf: sod farms	17.4	80	**25**	120	250	>1000
	turf: golf courses	17.4	40	**49**	250	490	>1000
	cranberries	4.8	80	**89**	440	890	>1000
	small grains, cotton	1.6	200	110	530	>1000	>1000
	grapes (East)	3.2	80	130	670	>1000	>1000
	vegetables (Note 1)	2.4	80	180	890	>1000	>1000
	grapes (West)	2.0	80	210	>1000	>1000	>1000
	potatoes, sugar beets	1.6	80	270	>1000	>1000	>1000
	ornamentals	1.6	40	530	>1000	>1000	>1000
M/L WP for Airblast	apples - Prebloom	4.8	40	180	890	>1000	>1000
	grapes (East)	3.2	40	270	>1000	>1000	>1000
	apples- Extended	2.4	40	360	>1000	>1000	>1000
	grapes (West); papaya	2	40	430	>1000	>1000	>1000
M/L WP for Turfgun	turf: golf course	17.4	5	390	>1000	>1000	>1000
M/L WP for HP Handwand	pachysandra	14	10	240	930	>1000	>1000
M/L Dry Flowable (DF) for Aerial or Chemigation	Same as above	1.2 - 17.4	350 to 1200	Baseline MOEs are 310 or greater.			
M/L DF for Groundboom, Aiblast, Turfgun or HP Handwand	Same as above	1.2 - 17.4	5 - 200	Baseline MOEs are 1400 or greater.			
M/L Liquids for Aerial Application or Chemigation	Same as above	1.2 - 17.4	350-1200	Baseline MOEs are 200 or greater.			
M/L Liquids for Groundboom, Airblast, Turfgun or HP Handwand	Same as above	1.2 - 17.4	5 -200	Baseline MOEs are 880 or greater.			
Applicators (APP)							
Aerial Application	Same crops as above for mixing and loading.	1.2 - 17.4	350-1200	MOEs are 3500 or above			
Groundboom Application		1.2 - 17.4	40-200	Baseline MOEs are 1400 or above.			
Airblast Application		2.0 - 4.8	40	Baseline MOEs are 1700 or above.			
Turfgun Application	turf	17.4	5	>1000	>1000	>1000	NA
HP Handwand Application	pachysandra	14	10	>1000	>1000	>1000	NA
Mixer/Loader/Applicators (M/L/A)							
M/L/A WP with a Low Pressure (LP) Handwand	pachysandra	14	0.4	240	>1000	>1000	NA
	conifers	3.2	0.4	>1000	>1000	>1000	
	ornamentals	1.6	0.4	>1000	>1000	>1000	
M/L/A WP with Backpack Sprayer	same as above		0.4	No data available			
M/L/A WP with Turfgun	Turf	17.4	5	270	>1000	>1000	NA

Table 23: Mancozeb Short/Intermediate Term Inhalation MOEs for Occupational Applicators/Handlers (MOE in Bold are less than 100 and are of concern)

Exposure Scenario	Typical Crop (s)	lb ai per acre	acres per day	Baseline (No Resp)	PF5 Respirator	PF10 Respirator	Engineering Control
M/L/A DF with LP Handwand or Backpack Sprayer	ornamentals	1.6 to 14	0.4	No data available			
M/L/A DF with Turfgun	Turf	17.4	5	>1000	>1000	>1000	NA
M/L/A Liquids with LP Handwand	ornamentals	1.2 - 14	0.4	Baseline MOEs are 8700 or above.			
M/L/A Liquids with Backpack Sprayer	ornamentals	1.2 - 14	0.4	Baseline MOEs are 8700 or above.			
M/L/A Liquids with Turfgun	Turf	17.4	5	>1000	>1000	>1000	NA
MOEs for Flagger							
Flag Aerial Spray Applications	all crops above	1.2 - 17.4	350	Baseline MOEs are 690 or above.			

Note 1 - Vegetables include cucurbits, bulb vegetables and tomatoes

HP - High Pressure
LP - Low Pressure
ND - No unit exposure data is available
NA - Not applicable

Respirator Types: PF5 = Filtering Facepiece Respirator, PF10 = Half Face Cartridge Respirator

7.1.3 Occupational Handler Risk for Potato Seed Piece Treatment

Only short- and intermediate-term risks were calculated for seed piece treatment. Long term exposures are not anticipated, since the scenarios only occur for a few weeks or months at a time, and do not occur on a year-round basis. Asparagus and caprifig seed piece treatment risks could not be calculated, because there was no information on the amount that could be used in a day. However, only calimyrna figs are treated with mancozeb, and the entire crop is grown on 7300 acres in CA. The amount used per day is much lower than in other scenarios, such as grapes or apples, and therefore these exposures are considered protective of those incurred while treating asparagus or figs.

Mancozeb Short- and Intermediate-Term Risks: Mancozeb non-cancer risk from mixing/loading dusts for commercial potato seed piece treatment is of concern using label required PPE, with an MOE of 33; and respiratory protection is required to achieve an MOE > 100. It was not possible to calculate the risks for applying liquid dips and dusts because there were no unit exposure data for these scenarios. It was also not possible to calculate the risk for hand planting the treated seed pieces, but MOEs were >100 for loading and planting seed pieces with a tractor planting. Additional data must be submitted for HED to estimate exposures associated with applying dusts to seed pieces.

ETU Short- and Intermediate-Term Risks: ETU Combined dermal and inhalation MOEs for potato

seed piece treatment were above 100 for scenarios that could be assessed provided double layer clothing and a PF5 respirator are worn.

ETU Cancer Risks: The cancer risks from ETU based on application of mancozeb to potato seed pieces were calculated assuming 30 days per year. Cancer risk was $1x10^{-4}$ for loading dusts for commercial seed piece treatment, and was $3x10^{-5}$ with the PF5 respirator required to mitigate mancozeb and ETU non-cancer risks. For on-farm seed piece treatment, cancer risk was $3x10^{-6}$ with single layer PPE, and $<1x10^{-6}$ with the addition of a PF5 respirator.

7.1.4 Occupational Handler Risk for Seed Treatment

Mancozeb Short- and Intermediate-Term Risks: Most of the scenarios that involve the mixing and loading of wettable powders for commercial seed treatment have risks of concern with single layer PPE, with MOEs ranging from 14 to 89, and require respiratory protection to achieve the target MOE of 100. One of the these scenarios (Mix/Load Wettable Powder for Oats) requires engineering controls to achieve the target MOE. It is important to note, however, that dry flowable or liquids are the preferred formulations for seed treatment and wettable powders are not used. The commercial seed treatment scenarios that use these formulations are not of concern. A planter box seed treatment scenario involving peanut seed is potentially of concern, with an MOE of 55 for single layer with PF5 protection; however, most peanut seed is treated at the seed plant, and this scenario is not likely to occur.

ETU Non-Cancer Risks: Most of the scenarios involving the mixing/loading of wettable powders for commercial seed treatment are of concern with MOEs of 19 to 89 at label required PPE and respiratory protection is needed to achieve the target MOE of 100. The remaining scenarios are not of concern.

ETU Cancer Risks: The cancer risks based on exposure to ETU following application of mancozeb to seeds were calculated using 30 days per year for commercial seed treatment and ten days per year for on-farm seed treatment. Most of the commercial seed treatment risks are below $1x10^{-4}$ with single layer PPE (which includes gloves but not respirators) and all of the risks are below $1x10^{-4}$ with the additional mitigation (such as respirators or water soluble bags) recommended to address non-cancer risk. If the wettable powders scenarios are excluded, the remaining scenarios have risks that are below 1.0×10^{-5} with single layer PPE.

7.2 Postapplication

7.2.1 Postapplication Data and Assumptions.

The chemical-specific dislodgeable foliar residue (DFR) data submitted for mancozeb, as well as the mancozeb turf transferable residue (TTR) study were discussed under the residential postapplication exposure and risk assessment. These data were also used to generate exposure estimates for

occupational postapplication activities. Additional assumptions specific to the occupational postapplication exposure and risk assessment are summarized below.

Assumptions Used to Calculate Postapplication Risks:

- Adult body weight = 70 kg;
- Maximum (label) application rates were used for non-cancer assessments
- Maximum (label) application rates were used for cancer assessments except for apples, grapes and pears, which relied on average rates from NASS or CA DPR data.
- Single day exposures (rather than a rolling average) were used due to (1) low dissipation rate for mancozeb; and (2) multiple applications permitted.
- A pseudo-first order kinetics analysis was used for mancozeb dissipation, as per Agency guidelines.
- The risk for hand-harvesting asparagus was assumed to be negligible because mancozeb has a 120-day PHI for asparagus.
- DFR data were extrapolated to other crops using a simple proportional approach to account for application rate, which is typical in HED assessments.
- Cancer risks - 30 days per year
- Generic transfer coefficients were used per HED policy (ExpoSAC SOP 003.1, Agricultural Transfer Coefficients. These coefficients range from 100 cm^2/hr for low exposure scenarios, such as scouting immature row crops, to 17,000 cm^2/hr for very high exposure scenarios such as hand harvesting sweet corn. Other high exposure scenarios include hand harvesting cut flowers (transfer coefficient = 7,000 cm^2/hr).

7.2.2 Postapplication Risks

ETU Non-Cancer Postapplication Risks: All of the ETU short- and intermediate-term MOEs, meet or exceed the required uncertainty factor of 100 at the currently labeled REI of 24 hours.

Of the fifteen crop groups evaluated for short- and intermediate-term risk, only 3 groups were thought to have chronic exposures. These include greenhouse cut flowers, greenhouse ornamental plants and greenhouse tomatoes. The mancozeb MOEs for all of the scenarios associated with these three crops are greater than 100 on day 0 and are not of concern. With the exception of the high exposure cut flower scenario (which includes hand harvesting, pruning, thinning and pinching), most of the ETU MOEs are greater than 100 on day 0. The ETU MOE of 67 for the cut flower scenario rises to above100 by day 6.

ETU Cancer Postapplication Risks: Cancer risks were calculated assuming thirty days of exposure per year. The cancer risks are $<1x10^{-4}$ on the day of application for all of the scenarios and some are $<1x10^{-5}$. The risks for many of the scenarios, however, do not decline to $<1x10^{-6}$ until 2 to >35 days (for deciduous tree fruit) after application. It was not possible to accurately calculate residue dissipation for periods longer than the length of the respective DFR studies (i.e. 35 days for apples and grapes) because the measured DFR values towards the end of the study were close to the LOQ

and/or the negative controls.

7.3 Incident Reporting

A total of 11 incidents were reported in the OPP Incident Data System (IDS) from 1992 to 2001. Most of these incidents involved skin rashes or contact dermatitis while a few involved dizziness and nausea. There were 44 cases reported in the California Pesticide Illness Surveillance Program (1982-1999) in which mancozeb was used alone or was judged to be responsible for the health effects. Most of these cases (33) occurred over 2 years (1985 and 1986) prior to the most recent Special Review, after which the application rate for grapes was reduced; workers who developed rashes were tending grapes, which is one of the scenarios with high post-application exposure estimates.

8.0 Data Needs/Label Requirements

The following data gaps have been noted in the supporting disciplinary chapters (i.e., toxicology, residue and product chemistry) for mancozeb reregistration.

Toxicology

870.6200 Acute neurotoxicity [870.6200]
Comparative thyroid assay between young and adult animals [Special Study].

Residue Chemistry

860.1200 Directions for Use (potato, Sugar beet, apple, field corn, wheat, barley, oats).
860.1340 Enforcement Analytical Method - Livestock Commodities.
860.1380 Storage Stability Data [carrot, onion (dry bulb.)]
860.1500 Crop Field Trials [celery, wheat hay (will be translated to barley and oat hay), tobacco, cottonseed, cotton gin by-products, seed or propagation stock treatments (safflower)]
860.1520 Processing Studies [wheat (middlings and germ), cottonseed, potato, barley (pearled), and oats (rolled)]
860.1480 Ruminant Feeding Study
860.1850 Confined Rotational Crop

Occupational/Residential Exposure

Information regarding preferred formulation types, if any. This information is critical because the wettable powder formulations create the highest exposures particularly when used at high rates. These exposures can be greatly reduced by using the other formulations or by using the wettable powder in water soluble bags.

There are no data to evaluate the mix/load/apply scenarios for high pressure handwand application of

WP and DF formulations. The PHED data for both high and low pressure handwand application of liquids (mix/load/apply and apply only) is of low quality. These data gaps make it difficult to accurately assess the risks of the handwand method of application which is commonly used in horticulture. There are data gaps for loading and applying dust formulations for seed piece treatments; the degree of dustiness is also not known.

Information on application rates, timing, and cultural practices for home garden crops such as sweet corn could be used to refine mancozeb post application risks for home gardeners. Additional TTR data using different dislodging techniques such as the wet hand press could be used to refine the hand-to-mouth and object-to-mouth turf exposures.

Appendix I. ETU Hazard Profile, and Doses and Endpoints for Risk Assessment.

ETU Hazard Profile

The toxicity database for ETU is limited. Of nine submitted studies evaluated by HIARC, three studies were unacceptable because ETU concentrations in feed varied widely and two other studies had only one dose group. The HIARC (05/28/03 memo, TXR 0051924) named the following studies as data gaps: developmental toxicity study (rabbit); 2-generation reproduction (rat); comparative study for thyroid toxicity in adults and offspring (rat); and developmental neurotoxicity (rat).

The thyroid is a target organ for ETU as it is for the EBDC fungicides. Thyroid toxicity in subchronic and chronic rat, mouse, and dog studies included decreased levels of the thyroid hormone, T4, increases or decreases in the thyroid hormone, T3, compensatory increases in levels of thyroid stimulating hormone, increased thyroid weight, and microscopic thyroid changes, chiefly hyperplasia.

Anemia occurred in the subchronic and chronic dog studies. Increased liver weight and hepatocellular hypertrophy occurred in several studies, however, overt liver toxicity was limited to the chronic dog study in which hepatocellular necrosis was seen.

Developmental defects in the rat developmental study indicated increased qualitative susceptibility since numerous, severe developmental defects occurred at a dose which only caused decreased maternal food consumption and body weight gain. These developmental defects were similar to defects seen in an accompanying developmental toxicity study with mancozeb, however, ETU was considered a more severe developmental toxicant than mancozeb because: (a) it took a smaller dose of ETU (50 mg/kg/day) to cause developmental defects than did mancozeb (512 mg/kg/day), (b) many of the same developmental defects occurred with greater frequency with ETU than with mancozeb, (c) more types of developmental defects occurred with ETU than with mancozeb, and (d) developmental defects which occurred with ETU were accompanied by minimal maternal toxicity whereas developmental defects which occurred with mancozeb were accompanied by more severe maternal toxicity.

The developmental defects seen in the rat developmental study with ETU included hydrocephaly and related lesions, skeletal system defects, and other gross defects. These defects showed increased susceptibility to fetuses because they occurred at a dose which only caused decreased maternal food consumption and body weight gain. A developmental study in rabbits was not submitted. No reproductive toxicity was attributed to treatment in the 2-generation reproduction study in rats. Neurotoxicity studies with ETU were not available.

Treatment with ETU produced increases in tumor incidence in rodents. Thyroid follicular cell adenomas and carcinomas were increased in a study with F344 rats. Thyroid follicular cell adenomas and pituitary adenomas were increased in a study with SD rats. Thyroid follicular cell adenomas and carcinomas, hepatocellular adenomas and carcinomas, and pituitary adenomas were increased in a study with B6C3F1 mice.

The HED Cancer Assessment Review Committee evaluated the carcinogenicity potential of ETU and classified ETU as a group B2 probable human carcinogen (Bill Sette, Ph.D., 4/16/90). The Q1* for ETU, using a 3/4 scaling factor, was determined to be 6.01 x 10-2 mg/kg/day-1 based upon female mouse liver tumors in an NTP study (memo, Bernice Fisher and Hugh Pettigrew, 2/24/95). The Q_1^* for ETU is also used for the EBDC compounds, mancozeb, metiram, and maneb which are metabolized to ETU (memo, HED Document No. 013554, 7/7/99).

ETU Endpoint and Dose Selection

The HIARC evaluated the toxicology database of ETU on May 28, 2003 and selected the doses and endpoints for risk assessment based on a variety of exposure pathways resulting from use of the EBDC fungicides.

ETU Acute Dietary Endpoint: The ETU acute dietary endpoint for females 13 - 50 years old was selected from a non-guideline developmental toxicity study in rats (Khera, K.S.; Teratology 7:243-252, 1973, MRID No. 4593760). The LOAEL was 10 mg/kg/day based on developmental effects of the brain, including exencephaly, dilated ventricles, and hypoplastic cerebellum. The NOAEL for the study was 5 mg/kg/day. Application of the combined standard 10X UFs to account for intraspecies variability and interspecies extrapolation, and the 10X UF_{DB}, (database uncertainty factor) results in an acute reference dose (aRfD) of 0.005 mg/kg/day. The acute population adjusted dose (aPAD) reflects incorporation of the Special FQPA SF into the RfD. Since the Special FQPA SF was removed (reduced to 1X) for ETU, the aPAD is equivalent to the aRfD, 0.005 mg/kg/day.

The ETU acute dietary endpoint applies only to females 13-50 years old, but is protective of the general population including infants and children. No endpoint attributed to a single dose was identified for the general population in the other available toxicity studies.

ETU Chronic Dietary Endpoint: HIARC selected the ETU chronic dietary endpoint from a chronic toxicity study in dogs. The study NOAEL was 0.18 mg/kg/day based on decreased body weight gain, increased thyroid weight, and microscopic changes in the thyroid observed at the LOAEL of 1.99 mg/kg/day. The combined 1000X UF (standard 100X and an additional 10X UF_{DB}) results in a chronic reference dose, RfD, of 0.0002 mg/kg/day. The cPAD of 0.0002 mg/kg/day is the same as the RfD, since the Special FQPA SF was reduced to 1X.

ETU Incidental Oral Exposure (Short- and Intermediate-Term) Endpoints:
ETU Aggregate Children (Short- and Intermediate-Term) Endpoints:

A non-guideline 4-week range-finding toxicity study conducted in dogs was used to select incidental oral endpoints and doses for risk assessment. In addition, the HIARC concluded that short- and intermediate-term aggregate exposures, combining dietary, incidental oral, dermal and inhalation pathways, should be compared to this endpoint and NOAEL for risk assessment. The study NOAEL was 7 mg/kg/day based on gross thyroid lesions and decreased thyroid hormone levels at the LOAEL of 34 mg/kg/day. The endpoint is appropriate for the population (infants/children) and duration of exposure (up to 30 days); in addition, the study can be used for intermediate-term incidental oral risk assessment, since it is supported by a subchronic toxicity study in dogs in which the NOAEL for thyroid effects was similar, at 6 mg/kg/day. The combined UF applied to both short- and intermediate-term incidental oral risk assessments is 1000X, based on the standard 100X UF, as well as a 10X UF_{DB}. An additional UF to extrapolate from a shorter- to a longer-term study was not needed, since the NOAEL for thyroid effects in the subchronic dog study was similar to that observed in the 4-week dog study.

ETU Dermal Absorption

ETU Dermal Absorption Factor: 26%, from a dermal absorption study in rats. The value of 26% dermal absorption was determined after 10 hours of exposure followed by washing of the skin.

ETU Dermal Exposure (Short- and Intermediate-Term) Endpoints:
ETU Inhalation Exposure (Short- and Intermediate-Term) Endpoints
ETU Aggregate Females 13-50 (Short and Intermediate-Term) Endpoints:

In the absence of adequate dermal and inhalation toxicity studies for ETU, the non-guideline oral study in rats (Khera) was used to select endpoints for short- and intermediate-term dermal and inhalation risk assessments. The study NOAEL was 5 mg/kg/day based on developmental effects of the brain, including exencephaly, dilated ventricles, and hypoplastic cerebellum, observed at the LOAEL of 10 mg/kg/day; the endpoint is considered applicable for females 13 - 50 years old.

Because an oral toxicity study was chosen, the 26% dermal absorption factor for ETU should be used in the dermal exposure assessment, and 100% absorption for inhalation exposure should be assumed for calculating inhalation exposure and risk. The target MOE for residential exposures is 1000, which includes the standard 100X combined UF, as well as the 10X UF_{DB} for an incomplete database. The target MOE for occupational assessments is 100.

The HIARC recommended that short- and intermediate-term aggregate risk assessments for the population females 13-50 be calculated by comparing aggregate exposure (dietary, dermal, and inhalation) to the NOAEL from the developmental toxicity study in rats. The endpoint is considered relevant for the population (females 13 - 50) and duration of exposure.

ETU Dermal Exposure (Long-Term) Endpoint:
ETU Inhalation Exposure (Long-Term) Endpoint:

The HIARC selected long-term dermal and inhalation endpoints from the chronic toxicity study in dogs. The NOAEL is 0.18 mg/kg/day based on decreased body weight gain, increased thyroid weight, and microscopic changes in the thyroid at the LOAEL of 1.99 mg/kg/day. Since an oral study was selected, estimated dermal exposure should be adjusted by 26%, the ETU dermal absorption factor. For calculating inhalation risks, a 100% absorption factor should be used. For residential exposures, the target MOE for ETU is 1000, based on the combined UFs of 100X for intra-species variability and interspecies extrapolation, and an additional 10X UF_{DB} for an incomplete database. For occupational exposures, the target MOE for dermal and inhalation exposures is 100.

ETU Toxicological Doses and Endpoints for Use in Human Health Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment and UFs	Special FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
ETU Dietary Exposures			
Acute Dietary **Females 13 - 50**	NOAEL = 5 mg/kg/day UF = 100X (inter and intraspecies) UF = $10X_{database}$ Total UF = 1000X Acute RfD = 0.005 mg/kg/day	Special FQPA SF = 1X aPAD = Acute RfD / FQPA SF aPAD = 0.005 mg/kg/day	Developmental Rat Toxicity (Khera Study, MRID No. 45937601) LOAEL = 10 mg/kg/day, based on developmental defects of brain.
Acute Dietary **General Population**	N/A	No appropriate endpoint attributable to a single exposure (dose) was identified.	
Chronic Dietary	NOAEL = 0.18 mg/kg/day UF=100X (inter and intraspecies) UF = $10X_{database}$ Chronic RfD=0.0002 mg/kg/day	FQPA SF = 1X cPAD = Chronic RfD / FQPA SF cPAD = 0.0002 mg/kg/day	Dog Chronic Oral Toxicity LOAEL= 1.99 mg/kg/day based on thyroid toxicity
Cancer [oral/dermal/inhalation]	$Q_1^* = 6.01x10^{-2}$ $(mg/kg/day)^{-1}$	ETU is classified as a **Group B2** carcinogen with a low-dose extrapolation approach for human risk assessment, based on liver tumors in female mice	
ETU Incidental Oral Exposures [Residential/Postapplication]			
Short-Term [1-30 days] Intermediate-Term [>30 days to 6 months]	NOAEL = 7 mg/kg/day UF = 100X (inter and intraspecies) UF = $10X_{database}$ Total UF = 1000X	FQPA = 1X Residential MOE = 1000 Occupational MOE = N/A	4-week range-finding dog study LOAEL= 34 mg/kg/day based thyroid toxicity
ETU Dermal Exposures			
Short-Term [1-30 days] Intermediate-Term [30 days - 6 months]	NOAEL = 5 mg/kg/day UF = 100X (inter and intraspecies) UF = $10X_{database}$ Total UF = 1000X DA = 26%	FQPA = 1X Residential MOE = 1000 Occupational MOE = 100	Developmental Rat Toxicity (Khera Study, MRID No. 45937601) LOAEL = 10 mg/kg/day, based on developmental defects of brain.
Long-Term [> 6 months]	NOAEL = 0.18 mg/kg/day UF = 100X (inter and intraspecies) UF = $10X_{database}$ Total UF = 1000X DA = 26%	FQPA = 1X Residential MOE = 1000 Occupational MOE = 100	Dog Chronic Oral Toxicity LOAEL= 1.99 mg/kg/day based on thyroid toxicity

ETU Toxicological Doses and Endpoints for Use in Human Health Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment and UFs	Special FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
ETU Inhalation Exposures			
Short-Term [1-30 days] Intermediate-Term [30 days - 6 months]	NOAEL = 5 mg/kg/day UF = 100X (inter and intraspecies) UF = $10X_{database}$ Total UF = 1000X IA = 100%	FQPA = 1X Residential MOE = 1000 Occupational MOE = 100	Developmental Rat Toxicity (Khera Study, MRID No. 45937601) LOAEL = 10 mg/kg/day, based on developmental defects of brain.
Long-Term [>6 months]	NOAEL = 0.18 mg/kg/day UF = 100X (inter and intraspecies) UF = $10X_{database}$ Total UF = 1000X IA = 100%	FQPA = 1X Residential MOE = 1000 Occupational MOE = 100	Dog Chronic Oral Toxicity LOAEL= 1.99 mg/kg/day based on thyroid toxicity