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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: **Maneb**. Revised Health Effects Division (HED) Human Health Risk Assessment to Support Reregistration. Chemical ID No. 014505. List A Reregistration Case No. 0642. DP Barcode No. D295409

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The attached human health risk assessment for the active ingredient maneb summarizes risks associated with its use as a fungicide on agricultural crops, ornamentals and turf. The document has been revised in response to comments provided during the public comment period.

Changes include:

- Reduction of the database uncertainty factor from 10 to 1 for chronic dietary exposures, incidental oral exposures, and dermal exposures.
- Modification of residue values for tomatoes and leaf lettuce.
- Assessment of toddler turf exposure at the existing label rate and the proposed reduced rate.

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1.0 Executive Summary

Overall Summary
In general, risks from maneb *per se* and its metabolite ethylene thiourea (ETU) are below HED's level of concern. Risks from food are below HED's level of concern for acute and chronic (cancer and non-cancer) exposures. Residential postapplication exposure to maneb and ETU residues on treated turf from sod farms results in risk concerns using the existing label rate, requiring a pre-harvest interval (PHI) of 5 to 9 days for mitigation. Shorter PHIs are required when using the lower, proposed application rate. Acute and chronic (cancer and non-cancer) aggregate risk from exposure through food and water are not of concern.

Occupational handler risks for maneb and ETU are highest for mixer/loaders using wettable powders, and engineering controls are required in some cases to mitigate these risks. Potato seed piece handler risks can be mitigated with a dust mask or engineering controls. Seed treatment risks can be mitigated with additional PPE or engineering controls. Postapplication risks are of concern based on re-entry in accordance with registered labels (i.e., after 24 hours). Short-term postapplication risks for maneb *per se* are of concern for high exposure activities for fruit trees and grapes, requiring up to 26 days following application to achieve the target margin of exposure (MOE). Postapplication ETU cancer risks are in the range of $1x10^{-4}$ to 1×10^{-6} on the day of application.

Use and Usage Overview Provided the risks noted above for occupational workers and toddlers exposed to residues on turf can be mitigated, HED has no objection to reregistration of the active ingredient maneb. Recommendations for reassessed tolerances will be provided when modifications to all relevant sections of 40 CFR have been determined, and upon submission of field trial residue data to support tolerance assessment and reassessment.

Maneb [manganese ethylenebisdithiocarbamate] is a member of the ethylene bisdithiocarbamate (EBDC) group of fungicides, which includes the related active ingredients metiram and mancozeb. Maneb is a broad spectrum fungicide registered for foliar applications to a variety of fruit, vegetable, nut, and field crops. Maneb is also registered for seed and seed piece treatment. Horticultural uses include ornamental plants in nurseries and greenhouses and on sod farms. Maneb end-use products are available as wettable powder (WP), dry flowable (DF), liquid flowable and dust (D) formulations. Approximately 2 ½ million pounds of maneb are used in agricultural settings on an annual basis Agricultural uses are concentrated in (but not limited to) the following states: FL, ME, MN, ND NJ, RI, TX, and WI.

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 t 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 maneb and other EBDC products registered on the above-listed food/feed crops.

In the 1992 Special Review, and in the current risk assessment for maneb, exposure to both the parent EBDC, maneb, and its metabolite/degradate ETU have been considered, for dietary (food and water), residential (dermal), and occupational (dermal and inhalation) risk assessments. Crops treated with maneb may contain both maneb and ETU residues; in addition, cooking and/or processing may result in conversion of maneb residues to ETU, or in concentration or reduction of existing ETU residues. Therefore, both parent maneb and ETU residues may be consumed in the diet. During application of products containing maneb, 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 indicate these potential exposures. Additional exposure to both maneb and ETU may occur during activities conducted in and around growing crops following treatment with maneb, 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 maneb 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 maneb risk assessment (see Appendix I), in order to appropriately address potential exposure to ETU resulting from maneb 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.

<u>Maneb Hazard Assessment</u> The hazard database for maneb is incomplete; the missing studies include a subchronic inhalation study in the rat and a rat developmental neurotoxicity study. Other studies are reserved pending the outcome of a rat comparative thyroid assessment with the maneb metabolite ETU. However, the available toxicity data have been used to select endpoints for risk assessment for dietary and non-dietary routes of exposure, and for a variety of durations of exposure. Refinements to the current risk estimates may be possible with the submission of

missing toxicity data.

Maneb is not acutely toxic to rats *via* the oral and inhalation routes of exposure or to rabbits *via* the dermal route of exposure. Maneb is not a skin or eye irritant, but it is a strong dermal sensitizer.

Multiple studies demonstrate that the thyroid is a target organ for maneb after single and multiple doses *via* oral, dermal, and inhalation routes of exposure and across species [rat, dog, mouse, monkey]. Thyroid effects observed include changes in clinical chemistry parameters indicative of thyroid toxicity, increased thyroid weights, follicular (thyroid) cell hyperplasia, decreased T_4 (serum thyroxin), and increased incidence of diffuse follicular epithelial hypertrophy/hyperplasia.

Neurotoxicity is also a toxic effect observed following both acute and subchronic exposures to maneb. These effects include impaired forelimb grip strength in rats following acute oral exposure, and impaired mobility, decreased fore- and hind-limb grip strength, and high carriage, as well as a dose-related decrease in neurotoxin esterase [NTE] activity following subchronic oral dosing. There was an increase in digestion chambers in the peripheral nerves of rats of both sexes. Clinical signs of neurotoxicity included unsteady gait, dragging of the rear limbs, diminished sensitivity to pain in affected limbs, and paresis of rear limbs. In a mouse carcinogenicity study, there was a dose-related decrease in absolute brain weight Tremors were observed in rats in a subchronic oral study. There was an increased incidence of microscopic lesions of the skeletal muscle of rats following long-term exposure.

Maneb degrades and/or is metabolized to ETU. In oral rat metabolism studies with radiolabeled maneb 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 maneb 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 exposure bypasses the liver. Metabolism data indicate maneb does not bio-accumulate.

Maneb has been tested in a series of *in vitro* and *in vivo* genotoxicity assays, which have shown that maneb exhibits weak genotoxic potential. There is an acceptable mouse carcinogenicity study for maneb, but the study in the rat was considered unacceptable. Historically, maneb'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 maneb 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 maneb uses.

There is no evidence of prenatal developmental toxicity in the rat, but there is increased qualitative fetal susceptibility in rats. There is no evidence of increased susceptibility in the rat

two-generation reproduction study. The Hazard Identification Assessment Review Committee (HIARC) concluded that there is qualitative evidence of susceptibility based on the results of the rat developmental toxicity study in which fetal effects (decreased fetal viability) were observed at a dose level that produced less severe maternal toxicity (decreased body-weight gain/food consumption). However, there is low concern for the qualitative susceptibility observed in the rat developmental study because the dose-response was well-characterized, there was a clear NOAEL/LOAEL for maternal and developmental toxicity, the developmental effects were seen in the presence of maternal toxicity, and because the doses selected for overall risk assessment address concerns seen in the prenatal developmental toxicity study.

Since there are no residual uncertainties for pre- and/or post-natal toxicity, the special FQPA Safety Factor was removed (reduced to 1X) for maneb. A database uncertainty factor ($10X_{DB}$) is required for acute dietary exposures due to the lack of a developmental neurotoxicity study. Database uncertainty factors are not needed for other exposures and durations.

ETU Hazard Assessment 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 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.

Maneb Dose Response Assessment For the acute dietary assessment for females 13-50, HED has selected an endpoint from the rat developmental study. Effects observed were post-implantation loss, increased resorptions, and decreased fetal viability. The No Observed Adverse Effects Level (NOAEL) for these effects was 20 mg/kg bw/day. For the general US population HED selected an endpoint of slight impairment of the forelimb grip strength at 2000 mg/kg/day (rat acute neurotoxicity study) where a NOAEL of 1000 mg kg day was observed. Thyroid effects observed in the subchronic rat study were selected for the chronic dietary assessment, the incidental oral assessment (any duration), and the inhalation assessment (any duration). The

inhalation absorption is assumed to be 100%. The NOAEL observed was 5 mg/kg/day. Finally thyroid effects observed in the 21-day dermal rabbit study were selected as the endpoint for dermal exposures, any duration. The NOAEL from this study was 300 mg/kg/bw/day. The combined Uncertainty Factors (UFs) for all assessments, with the exception of the acute dietary assessment, are 100x. The combined UFs for the acute dietary assessment is 1000x.

ETU Dose Response 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 13-50)	NOAEL of 5 (Developmental rat/developmental brain defects)
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)

[The UF for ETU occupational assessments are 100x; and the Uf 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.]

Residential Assessment The use pattern for maneb is expected to result in exposure to maneb and ETU for the general population through food and drinking water. The use on sod farms may result in residential postapplication exposure due to contact with treated transplanted turf.

Maneb and ETU Dietary (Food) Exposure and Risk The residue chemistry database for maneb is generally adequate for risk assessment purposes, but additional field trial data are needed to reassess tolerances. The nature of maneb 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 maneb [and metabolites converted to carbon disulfide (CS_2)] and the metabolite ETU; residues of concern for tolerance enforcement include maneb and metabolites converted to CS_2.

HED has recommended a change to the existing tolerance expression (40 CFR §180.110) for maneb, and for similar changes in other EBDC tolerances Reassessed tolerances for all 3 EBDCs will be calculated in terms of CS_2, rather than in terms of zineb, an EBDC that is no longer registered. Adequate analytical methods are available for tolerance enforcement.

Highly refined dietary exposure and risk assessments were conducted for maneb and maneb-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 maneb during processing, and (3) ETU formed based on 7.5% metabolic conversion of maneb to ETU residues.

Acute dietary exposure and risk from maneb and ETU are below HED's level of concern for the general population and of the population subgroups. For females 13-49 years old estimated dietary exposure to maneb *per se* was 0.018 mg/kg/day, or 89% of the acute population adjusted dose (aPAD) of 0.02 mg/kg/day. Risk for the general US population and population subgroups including infants and children were all much lower, at less than 2% of the aPAD of 1.0 mg/kg/day. For ETU, an estimated exposure of 0.0026 mg/kg/day for females 13-49 corresponds to 52% of the ETU aPAD (0.005 mg/kg/day).

Chronic dietary exposure and risk from maneb and ETU are below HED's level of concern for the general US population and various population subgroups. All of the population subgroups are exposed at levels that correspond to <1% of the chronic population adjusted dose (cPAD) of 0.05 mg/kg/day. For ETU, children 1-2 years old had an estimated exposure of 0.000029 mg/kg/day, or 14% cPAD (0.0002 mg kg/day).

The cancer risk estimate for ETU was based on the same anticipated residues derived for the chronic dietary exposure assessment. The estimated dietary exposure of 0.000016 mg/kg/day for the general US population corresponds to a cancer risk of 9.6×10^{-7}.

<u>Maneb and ETU Residential Exposure</u> The registrants have agreed to cancel the two maneb labels that are intended for home gardens as these products are no longer being sold. The registrants have also agreed to modify the agricultural labels to eliminate the possibility that maneb would be applied to turf in areas such as lawns, parks and golf courses. The only remaining exposure scenario is one that can occur after treated turf is transplanted from the sod farms to areas such as residential lawns. Because toddlers are the most sensitive sub-population that is potentially exposed to maneb treated sod farm turf installed on residential lawns, risk management decisions that are based upon the toddler risks will also provide adequate risk mitigation for the adult sub-population.

Short term non-cancer MOEs were calculated for all of exposure pathways that can arise when children (i.e. toddlers) are exposed to sod farm turf treated with maneb and subsequently transplanted to residential lawns. It was assumed that the turf would be harvested one day after application (PHI = 1 day) and that it would take two days to harvest and transplant the turf. The MOEs were calculated at the label application rate of 17.4 lb ai/acre and the proposed rate of 8.7 lb ai/acre. If the label application rate of 17.4 lb ai/acre is used, the Total MOEs for maneb and ETU rise to the target MOEs with a PHI of 5 days. If the proposed application rate of 8.7 lb ai/acre is used, the Total MOEs for maneb and ETU rise to the target MOEs with a PHI of 3 days.

Drinking Water Assessment The OPP Environmental Fate and Effects Division (EFED) prepared the drinking water assessment for maneb 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 maneb (and for mancozeb 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. Information from the surface water monitoring study was used to refine outputs from the linked PRZM-EXAMS models, which determined ETU drinking water concentrations based on application of maneb to peppers in Florida. A ground water EDWC was selected from a targeted ground water monitoring study conducted in FL in a known EBDC use area. Surface water estimates were 25.2 ppb (acute/peak), 0.1 ppb (chronic/non-cancer), and 0.08 ppb (cancer). The ground water estimate was 0.21 ppb, to be used in acute/chronic and cancer assessments for risk from ground water sources of drinking water.

Maneb Aggregate Exposure Assessments Residues of maneb *per se* are not expected in drinking water, so the aggregate risks consist of exposures from food and residential sources. However, the only residential exposures are expected to be rare events (transplanted turf), so it is not appropriate to include the residential exposures in an aggregate assessment.

ETU Aggregate Exposure Assessment It is also not appropriate to aggregate residential ETU exposures, so the aggregate assessments include only food and drinking water. For the ETU acute, chronic, and cancer aggregate assessments, the ETU surface and ground water EDWCs provided by EFED were incorporated into a dietary food and water only exposure assessment using the DEEM-FCID™ model. Acute analysis was only required for Females 13-49 population. The total dietary food and water exposures correspond to 86% of the aPAD. Aggregate chronic non-cancer exposure was below 100 %cPAD for the general US population and all population subgroups. The most highly exposed population subgroup was children 1-2 years old (0.000036 mg/kg/day), or 18 %cPAD. The general US population estimated exposure of 0.000020 mg/kg/day which corresponds to a cancer risk of 1.2×10^{-6}, which is not of concern; most of the estimated exposure was from food.

Occupational Handler Exposure and Risk Occupational populations (handlers) are potentially exposed to maneb and ETU while making applications to a variety of tree fruits, nuts, fruits, vegetables, row crops, sod, ornamentals , potatoes (foliar and seed piece), and during seed treatments. In addition, post application exposure to maneb and ETU occurs after application when workers contact foliage during crop maintenance. In both handler and postapplication exposure assessments, risks for both maneb *per se* and ETU were calculated. For both handler and postapplication assessments, the maneb dose was multiplied by 0.075 to take into account

the 7.5 % in vivo metabolic conversion of maneb to ETU. This "metabolic" ETU was added the ETU exposure from handler and postapplication activities to obtain the total ETU exposur Handler assessments addressed combined dermal and inhalation exposures. but postapplicatio risks were derived solely from dermal exposure.

Current maneb labels typically require that occupational handlers wear an apron, coveralls and gloves over baseline clothing which includes long pants and long-sleeved shirts. For some of the mixer loader scenarios involving wettable powder formulations, the non-cancer maneb risks for this PPE ensemble are of concern and additional PPE over and above the label, such as respirators, are required to achieve Agency risk targets. In a few cases, such as those involving sod farm application rates, engineering controls such as water soluble bags are needed. The risks for mixing and loading dry flowable (DF) and liquid flowable formulations are much lower and can be mitigated in most cases with single layer PPE in place of the double layer PPE required by the label (respirators are required for some turf and almond scenarios). The risks for applying sprays using mechanized equipment such as aircraft, groundboom and airblast sprayers are not of concern with baseline clothing without gloves regardless of the formulation type. The risks of mixing/loading/applying sprays using handheld equipment such as handwands and backpack sprayers are not of concern if single layer clothing with gloves is worn.

The label for the dust formulation used for potato seed treatment requires double layer PPE with PF10 respiratory protection. The non-cancer maneb risks for loading dusts during commercial potato seed piece treatment are of concern with the label required PPE and may require engineering controls. The risks during the application of the dust during potato seed treatment could not be evaluated because unit exposure data are not available.
The risks for commercial and on-farm seed treatment are generally not of concern. The scenarios of concern include commercial seed treatment of oats and sorghum and planter box treatment of peanuts, rice and oats. It is understood that most peanut and rice seed are treated commercially, and the planter box scenarios were assessed only because they were included on the labels.

Risk calculations were also performed to assess the risk of ETU that is contaminant in the spray mix and is metabolized from absorbed maneb. The non-cancer short/intermediate term risks for ETU are in all cases less than the corresponding maneb risk across all scenarios and are not risk drivers. The non-cancer long term risks for ETU are of concern for a few scenarios, however, these risks can be mitigated with single layer PPE (the labels require double layer PPE). The cancer risks were also calculated for ETU using 30 exposure days per year. Most of the risks are below $1.0x10^{-4}$ without mitigation and almost all of the cancer risks are below $1.0x10^{-4}$ with the mitigation recommended to address the non-cancer maneb risks. Many of the risks are also below $1.0x10^{-5}$ with mitigation and some are below $1.0x10^{-6}$. Some of the high volume commercial mixer/loader scenarios, however, remain above $1.0x10^{-6}$ with engineering controls and might be of concern if $1.0x10^{-6}$ is chosen as a risk mitigation goal.

<u>Maneb and ETU Occupational Postapplication Assessments</u> Current label requirements specify 24 hour Restricted Entry Intervals (REIs) while Pre-Harvest Intervals (PHIs) range from zero

days for ornamentals to 145 days for almonds. 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. Low exposure activities include irrigation and scouting of immature plants; medium exposure activities include irrigation and scouting of mature plants and high exposure activities include pruning apple trees and harvesting cut flowers or greens.

Six chemical-specific dislodgeable foliar residue (DFR) studies were submitted for maneb, two each on apples, grapes and tomatoes. These data show that maneb 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 typical HED transfer coefficients and typical HED assumptions to estimate postapplication exposure and risk. For turf, the mancozeb TTR study was used to estimate postapplication residues of maneb.

Occupational Postapplication Risks

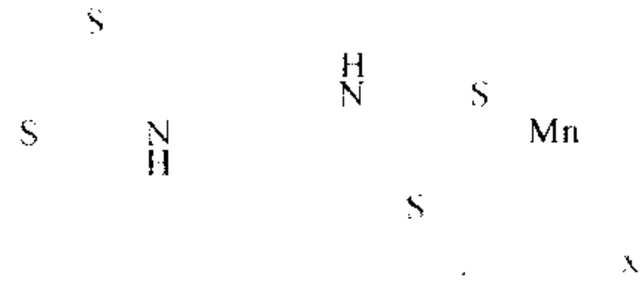
Post-application risk calculations for workers entering treated fields or greenhouses indicated that maneb non-cancer risks are of concern at the current REI for sweet and seed corn, apples and grapes. The time for these risks to decline to Agency targets is 5 to 11 days for corn, 5 to 6 days for apples and 14 to 26 days for grapes with the exact number of days dependent upon the regional dissipation rate and the specific worker task evaluated. The short/intermediate term ETU exposures are of a similar concern as the maneb exposures; however, the long term ETU exposures are of greater concern for the scenarios involving greenhouse grown cut flowers. Except for apples and grapes, the cancer risks are less than $1x10^{-4}$ on the day of application for all scenarios, however, the risks for some of the scenarios do not decline to less than $1x10^{-6}$ until more than 80 days after application. The registrant has proposed removing the grape, apple, and sweet corn uses for maneb.

2.0 Physical/Chemical Properties

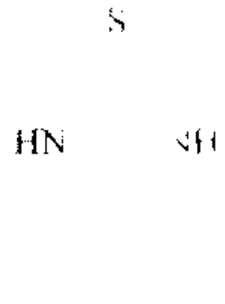
Technical maneb is a yellow powder which decomposes at 135 C, and has a density of 0.4-0.5 kg/L; it has a negligible vapor pressure of $<10^{-7}$ mbar at 20 C. Maneb is moderately soluble in water (0.417 g/L at 22-24 C), and is practically insoluble in organic solvents (<0.0010g/L in toluene, 0.0033 g/L in hexane, 0.0137 g/L in dichloromethane, and 0.133 g/L in methanol at 22-24 C). Maneb decomposes with heat and under acidic conditions. Other identifying codes and characteristics are as follows:

Empirical Formula:	$(C_4H_6MnN_2S_4)_x$
Molecular Weight:	$(265.3)_x$
CAS Registry No.:	12427-38-2
PC Code:	014505

The structures of maneb and its metabolite, ethylene thiourea (ETU), are shown below:



maneb



ethylenethiourea

3.0 Hazard Characterization

The maneb toxicology database is incomplete; however, the available data have been used to select dietary, incidental oral, dermal and inhalation endpoints for risk assessment. Data gaps include a developmental neurotoxicity study in the rat and a subchronic inhalation study in the rat (with special emphasis on thyroid and neurotoxic effects). A comparative thyroid assessment in rats (young and adult animals) is required for the metabolite ETU. A toxicity profile of maneb is presented in Tables 3.2 and 3.3.

3.1 Hazard Profile

Maneb is a fungicide in the class of ethylenebis dithiocarbamates, which also includes mancozeb 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 maneb after single and multiple doses *via* the oral, dermal, and inhalation routes of exposure and across species [rat, dog, mouse, monkey]. Neurotoxicity is also a major toxic effect observed following both acute and subchronic exposures to maneb.

Acute toxicity data show that maneb is not acutely toxic to rats *via* the oral and inhalation routes of exposure or to rabbits *via* the dermal route of exposure. Maneb is not a skin or eye irritant, but it is a strong dermal sensitizer.

Thyroid effects in dogs dosed with maneb included changes in clinical chemistry parameters indicative of thyroid toxicity, increased thyroid weight and follicular (thyroid) hyperplasia; increased thyroid weights were also observed in monkeys. In rats, increased thyroid weights, follicular cell hyperplasia and decreased T_4 (serum thyroxin) were observed after 90-day and 2-year exposures; in a 2-generation reproduction study in rats, there was increased incidence of diffuse follicular epithelial hypertrophy/hyperplasia. Following 21days of dermal exposure, increased thyroid weight and thyroid follicular cell hypertrophy were observed in rats; in mice dosed with maneb, thyroid effects included decreased T_4 and increased thyroid weights.

Neurotoxicity has been observed following exposure to maneb. Following acute oral exposure, a slight impairment of forelimb grip strength was observed in female rats. Following oral exposure

in a 90-day neurotoxicity study in rats, impaired mobility, decreased fore- and hindlimb grip strength, and high carriage were observed in female rats, and a dose-related decrease in neurotoxin esterase [NTE] activity was observed in male rats. There was also a higher incidence of microscopic lesions (digestion chambers) in the peripheral nerves of both sexes. Treatment-related clinical signs, including unsteady gait, dragging of the rear limbs, diminished sensitivity to pain in affected limbs, and paresis of rear limbs, were observed in a rat range-finding developmental toxicity study; these findings were similar to those seen in the definitive study, in which impaired mobility, dragging of hindlimbs, hunched posture, and prostration were observed. In the mouse carcinogenicity study, there was a dose-related decrease in absolute brain weight. Tremors were observed in several rats in a subchronic oral toxicity study. There was an increased incidence of microscopic lesions of the skeletal muscle of rats following long-term (2 years) exposure.

There is increased qualitative fetal susceptibility in rats; in the rat developmental toxicity study, fetal effects (decreased fetal viability) were observed at a dose level that produced less severe maternal toxicity (decreased body-weight gain/food consumption) There is no evidence of increased susceptibility in the rat two-generation reproduction study. There is no acceptable rabbit developmental toxicity study; this study is reserved pending outcome of a similar study with the metabolite ETU.

Following oral administration, maneb was rapidly and extensively absorbed from the gastrointestinal tract, and the metabolites were rapidly eliminated in the urine and feces. The major metabolites were ethylene thiourea (ETU), ethylenebisisothiocyanate sulfide (EBIS) and ethylene urea (EU). A major portion of the radiolabeled metabolites were polar water-soluble compounds that could not be adequately isolated for positive identification. There is no evidence of bioaccumulation.

Maneb has been tested in a series of *in vitro* and *in vivo* genotoxicity assays. Maneb is negative for gene mutation in both the bacterial/Ames assay with and without S9 and in the CHO/HGPRT assay with and without metabolic activation. Maneb did not cause structural chromosomal aberrations, and was negative in the host-mediated assay and the unscheduled DNA synthesis assay. In the assay for sister chromatid exchange [SCE] in Chinese hamster ovary cells [CHO], maneb was negative with and without metabolic activation.

There is an acceptable mouse carcinogenicity study for maneb, but the study in the rat was considered unacceptable. In mice, there was a treatment-related increase in hepatocellular adenomas in both sexes at the high dose level (350-440 mg/kg/day) at the terminal sacrifice, and there was an apparent increase in the incidence of alveogenic adenomas in the high dose males. Table 3.1 below provides a comparison of tumor data for ETU, mancozeb, maneb, and metiram.

Table 3.1 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 increases in tumor of any type at 1000 ppm (HDT) [75 ppm ETU]	No increases 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 increase in tumor of any type at 1000 ppm (HDT) [75 ppm ETU]	Increased incidence of hepatocellular adenomas and alveogenic adenomas in the lungs at 2400 ppm [180 ppm ETU]	No increase in tumors 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 maneb's potential for carcinogenicity (as well as that of the other EBDCs, mancozeb 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, maneb cancer risk has been calculated by estimating exposure to maneb-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 maneb and the other EBDCs should continue to be evaluated in this way.

The acute toxicity profile for maneb is shown in Table 3.2, while the hazard profile, based on submitted data, is presented in Table 3.3.

Table 3.2. Acute Toxicity of Maneb

Guideline No.	Study Type	MRID #	Results	Toxicity Category
870.1100	Acute Oral - rat	41975601	LD_{50} = >5000 mg/kg	IV
870.1200	Acute Dermal - rabbit	41975602	LD_{50} = 2000 mg/kg	III
870.1300	Acute Inhalation - rat	41975603	LC = 1.3 mg/L	III
870.2400	Primary Eye Irritation	41975604	not an eye irritant	III
870.2500	Primary Skin Irritation	41975605	not a skin irritant	III
870.2600	Dermal Sensitization	41975606	a dermal sensitizer	N/A
870.6200	Acute Neurotoxicity	43947601	NOAEL = 1000 mg/kg; LOAEL = 2000 mg/kg based on a slight impairment in forelimb grip strength	N/A

Table 3.3. Toxicity Profile of Maneb Technical.

Study Type [Guideline No.]	MRID No.	Doses Results
Acute Neurotoxicity - Rat [870.6200]	43947601	[500, 1000, 2000 mg/kg] NOAEL=1000 mg/kg, LOAEL=2000 mg/kg, based on slight impairment in forelimb grip strength in females.
Subchronic feeding - rat [870.3100]	40982601	80 ppm [males 5/females 6 mg/kg/day], 400 ppm [males 24/ females 30 mg/kg/day] 1300 ppm [males 77/females 103 mg/kg/day] NOAEL not determined, based on the increased incidence of renal tubular pigment observed at all dose levels. NOAEL for thyroid effects is 80 ppm [males 5/females 6 mg/kg/day]; LOAEL for thyroid effects [increased thyroid weights and follicular cell hyperplasia in males and decreased T_4 in both sexes] is 400 ppm [males 24/females 30 mg/kg/day]. Tremors were observed in 2 mid-dose and 2 high-dose females during weeks 5, 8, 9, and 12.
Subchronic feeding - monkey [870.3150] 6-month	00129980 00130306 00161552 Acc. No. 263810 Acc. No. 263821	[100, 300, 3000 ppm] NOAEL=100 ppm [5.2-5.7 mg/kg/day; 7.3 mg/kg/day from JMPR, 1993]; LOAEL=300 ppm [15.5-16.8 mg/kg/day], based on increased thyroid weight in males. At the 3000 ppm [144.8-171.0 mg/kg/day] dose level, there was a decrease in body-weight gain and food consumption, reduced ^{131}I absorption and a lower mean percentage of protein-bound ^{131}I, enlarged thyroids, increased thyroid weight, and histopathological lesions in the thyroids.
Subchronic feeding - dog [870.3150]		see chronic dog
21-Day dermal toxicity - rabbit [870.3200]	40876101	100, 300, or 1000 mg/kg/day Systemic NOAEL=100 mg/kg/day; Systemic LOAEL=300 mg/kg/day, based on microscopic thyroid changes [both sexes]. Slight dermal irritation was observed at all dose levels at the site of application. T3/T4/TSH not monitored.

Table 3.3 continued on following page

Table 3.3. Toxicity Profile of Maneb Technical.

Study Type [Guideline No.]	MRID No.	Doses Results
Subchronic inhalation - rodent [870.3465]	00162084 40982701 40982401 40982601	10, 30, and 100 mg m³ NOAEL=30 mg/m³ [0.03 mg/L]. LOAEL=100 mg/m³ [0.10 mg/L], based on slightly lower mean T_4 concentrations in both sexes, an apparent treatment-related increase in lung + trachea weight in both sexes, decreased T_3 concentrations in the females, and decreased thyroid + parathyroid weight in females.
	41975901	100 mg/m³ (4 weeks dosing) Maneb, Mn, and ETU were detected in lung tissue in both sexes following the 4-week exposure but not following the 2-week recovery period.
Subchronic neurotoxicity - rat [870.6100]	43947602	[75, 300, 1200 ppm] NOAEL=300 ppm [21/23 mg/kg/day]; LOAEL=1200 ppm [80/100 mg/kg/day], based on decreased NTE in males and decreased forelimb grip strength in females.
Chronic toxicity - rat [870.4100]	00129979/00130305 40125101/40559201	30 ppm [males 2.18/females 2.24 mg/kg/day] 100 ppm [males 6.60 females 7.32 mg/kg/day] 300 ppm [males 20.4 females 21.8 mg/kg/day] 1000 ppm [males 68.4/females 74.5 mg/kg/day] NOAEL = 300 ppm [males 20.4/females 21.8 mg/kg/day]; LOAEL = 1000 ppm [males 68.4/females 74.5 mg/kg/day], based on thyroid effects [↑ half-life for ^{131}I-retention ↓ mean T_4 content at 6 and 12 months, and ↑ thyroid weight in both sexes] and ↑ incidence of urinary bladder lesions [epithelial dysplasia in males].
Chronic toxicity - dog [870.4100]	42251601	50 ppm [males 1.53/females 1.71 mg/kg/day] 200 ppm [males 6.36/females 7.18 mg/kg/day] 1000 ppm [males 33.84/females 35.25 mg/kg/day] 2200 ppm [males 66.47/females 72.93 mg/kg/day] NOAEL=200 ppm [males 6.36/females 7.18 mg/kg day] LOAEL=1000 ppm [males 33.84/females 35.25 mg kg day], based on clinical chemistry parameters indicative of thyroid toxicity, increased thyroid weight, and follicular (thyroid) hyperplasia.

Table 3.3 continued on following page

Table 3.3. Toxicity Profile of Maneb Technical.

Study Type [Guideline No.]	MRID No.	Doses Results
Carcinogenicity - mouse [870.4200]	42642401	60 ppm [males 8.6/females 10.8 mg/kg/day] 240 ppm [males 34.8/females 45.0 mg/kg/day] 2400 ppm [males 354.7/females 439.3 mg/kg/day] NOAEL=Not determined There was a dose-related decrease in the mean thyroxine [T_4] values in females at study termination, and no NOAEL for this effect in females was attained. At the high-dose level, both sexes displayed an increased incidence of hepatocellular adenomas, and the high-dose males displayed an apparent increase in alveologenic adenomas in the lungs.
Developmental toxicity - rat [870.3700]	42520001	[20, 100, 500 mg/kg/day] Maternal NOAEL=20 mg/kg/day Maternal LOAEL=100 mg/kg/day based on increased clinical signs [soft stool], decreased body-weight gain and food consumption. Developmental NOAEL=20 mg/kg/day Developmental LOAEL=100 mg/kg/day, based on increased post-implantation loss, increased resorption and decreased fetal viability. At 500mg/kg, dams had loss of body weight, and neurobehavioral signs were observed by day 11 of gestation, which increased in incidence with time during dosing, and persisted throughout the study. Developmental effects observed at the high-dose level included decreased fetal body weight and an increased incidence of malformations [bent limb bones] and developmental variations [retarded skeletal ossification and bent ribs].
Developmental toxicity - rabbit [870.3700]	40982401	[5, 20, 80 mg/kg/day] No NOAEL or LOAEL was established for maternal or developmental toxicity in the rabbit due to deficiencies in the study.

Table 3.3 continued on following page

Table 3.3. Toxicity Profile of Maneb Technical

Study Type [Guideline No.]	MRID No.	Doses Results
2-Generation reproduction - rat [870.3800]	42049401	75 ppm [F0 males 5.3 /F0 females 6.0 mg/kg/day; F1 males 5.8/F1 females 6.4 mg/kg/day] 300 ppm [F0 males 21.2/F0 females 24.1 mg/kg/day; F1 males 23.1 females 25.1 mg/kg/day] 1200 ppm ppm [F0 males 83/F0 females 100 mg/kg day; F1 males 92/F1 females 106 mg/kg/day]. Maternal NOAEL=75 ppm (F0 6.0/F1 6.4 mg/kg/day); Maternal LOAEL=300 ppm (F0 24.1/F1 25.1 mg/kg/day), based on decreased body weight/body-weight gain and food consumption. Paternal NOAEL=75 ppm (F0 5.3/F1 5.8 mg/kg/day); Paternal LOAEL=300 ppm (F0 21.2/F1 23.1 mg/kg/day), based on a significant ↑ in lung [both generations] and liver [F1] weight and an *incidence of diffuse follicular epithelial hypertrophy/hyperplasia [F1].* Reproductive NOAEL=300 ppm [males F0 21.2/F1 23.2 mg/kg/day; females F0 24.1/F1 25.1 mg/kg/day]; Reproductive LOAEL=1200 ppm [males F0 83/F1 92 mg/kg/day; females F0 100 F1 106 mg/kg/day], based on delayed vaginal opening in the F1 female offspring.
Chronic tox./carcinogenicity - rat [870.4100]	00129979/ 00130305 40125101/ 40559201	30 ppm [males 2.18 females 2.24 mg/kg/day] 100 ppm [males 6.60/females 7.32 mg/kg/day] 300 ppm [males 20.4/females 21.8 mg/kg/day] 1000 ppm [males 68.4/females 74.5 mg/kg/day] [See under chronic toxicity.] The data on tumor incidence have not been submitted for statistical review to date. Due to the lack of any significant effect on survival or body-weight gain during the first 90-day interval, it appears that the rats could have tolerated higher dose levels. It is concluded that the dose levels were not adequate for the *assessment of carcinogenic potential.*
Developmental neurotoxicity - rat [870.6300]		DATA GAP

Table 3.3 continued on following page

Table 3.3. Toxicity Profile of Maneb Technical.

Study Type [Guideline No.]	MRID No.	Doses Results
Gene Mutation [870.5100] [870.5300]	40091302 Mutagenicity *Salmonella* [Ames]	Dose range 3-300; negative for base pair substitution and frameshift mutations with and without metabolic activation.
		Negative with rat S9, without rat S9, and with mouse S9.
	00149569 40091303 40788901 *in vitro* mammalian CHO/HGPRT	Negative. B6C3F1 mouse, TA1530; dose levels, 0.5, 2, 5 g/kg
	00153177 00153178 [mouse host-mediated]	
Cytogenetics/Structural Chromosomal Aberrations [870.5900] [870.5385]	00149568 40091301 *in vitro* sister chromatid exchange assay (SCE/CHO)	Negative w/metabolic activation; positive without metabolic activation up to 30 µg/mL
		Single 4.9 g/kg and 5x 1.64 g/kg; no significant increase in chromosomal aberration in bone marrow samples over the complete mitotic cycle with activation; positive without activation.
	00149570 *in vivo* bone marrow cytogenetics	
Other Genotoxic Effects [870.5550]	00149571 40163901 Unscheduled DNA Synthesis	Negative - rat hepatocytes, did not appear to induce unscheduled DNA synthesis; dose range 0.5-100 µg/mL
	Dominant Lethal	negative for induction of neoplastic transformation in absence of metabolic activation; 0.05-0.2 µg/mL
	00149572 00164348 in vitro transformation [C3H-10T½ cells]	

Table 3.3 continued on following page

Table 3.3. Toxicity Profile of Maneb Technical.

Study Type [Guideline No.]	MRID No.	Doses Results
Metabolism - rat [870.7485]	Acc. Nos.: 259890, 263913	Following both single & repeated low-dose exposures, majority of the radiolabel was excreted in both the urine & feces within the first 24 hours (low dose) or 24-120 hours (high dose). Less than 1% of the dose was eliminated as CO_2 following all exposures. In single-dose study, elimination and tissue distribution were similar to those observed in the 3-dose study. There were no sex differences, and more radiolabel was found in the urine than in the feces. Thyroid, liver, and kidney displayed the highest levels of radiolabel. The amount of maneb *per se* in urine as a % of the radiolabel was 0.3% in males and 0.15% in females. ETU was the major metabolite in the urine and feces of both sexes.
Dermal absorption 870.7600	MRID 41669301	Dermal absorption = 2%. Dermal absorption of maneb is relatively small. Dermal absorption [as a % of dose] was below the limit of detection for the first 10 hours. In order to produce measurable absorption, a total exposure period of 72 hours, which included 24 hours of maneb exposure and a wash, was required. Four to five times as much maneb [applied as an aqueous solution] remains on/in skin after washing as found following exposure to the formulation-vehicle suspension. Time-related dermal absorption was greater with the aqueous maneb solution than with the formulation vehicle suspension. The amount absorbed increased with time of exposure, ranging from 0.1% following a half-hour exposure to 5.1% following a 24-hour exposure period, a wash and sacrifice 48 hours later. Measurable quantities of the dose remain on the skin following a wash and, when applied as an aqueous solution maneb appears to remain on the skin for continued absorption. In general whole blood/plasma concentrations were below the limit of detection

3.2 FQPA Considerations

The potential for increased susceptibility of infants and children from exposure to maneb was reevaluated by the Health Effects Division Hazard Identification Assessment Review Committee (HIARC) on February 20, 2003. The purpose of that HIARC meeting was to reevaluate maneb and the other EBDCs in accordance with the February, 2002 OPP FQPA 10X Safety Factor guidance document. The potential for susceptibility was reevaluated subsequently by the EBDC team on July 30, 2004 to follow 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).

Studies available for FQPA consideration include an acceptable developmental toxicity study in rats and an acceptable reproduction study in rats. Data gaps for maneb with respect to FQPA

include a developmental neurotoxicity study in rats [DNT] on maneb, a comparative thyroid toxicity study in adult and young animals on ETU, and a rabbit developmental toxicity study with ETU.

The data indicate a qualitative susceptibility in the rat developmental toxicity study on maneb in that decreased fetal viability is observed at a dose level that produces decreased body-weight gain/food consumption in the maternal rat. The decreased fetal viability is considered more adverse than decreased body weight/food consumption. There is no evidence of increased susceptibility in the 2-generation reproduction study in the rat.

There is no adequate rabbit developmental toxicity study with which to assess susceptibility. However, there is low concern for the qualitative susceptibility seen in the rat developmental toxicity study since the dose-response is well characterized; there are clear NOAELs/LOAELs for maternal and developmental toxicities, and the developmental effects are seen in the presence of maternal toxicity. There are no residual uncertainties for pre and/or postnatal toxicities in the rat since the doses selected for overall risk assessments will address the concerns seen in the prenatal developmental toxicity study. With respect to the issue of thyroid effects in the young, available data show that the thyroid effects occur only at high-dose levels in the adult animal; and the required comparative thyroid study on ETU will address thyroid effects. Since there is a clear NOAEL for the thyroid effects observed in the adult animals, and the effects were observed only at dose levels above the doses selected for overall risk assessment, there are no residual uncertainties with regard to thyroid toxicity. Therefore, there are no residual uncertainties, and the hazard-based Special FQPA Safety Factor (10X) is removed (1X).

There is concern for developmental neurotoxicity resulting from exposure to maneb, due to the developmental effects observed in the rat and evidence of neurotoxicity observed in several studies on maneb. A developmental neurotoxicity study [DNT] is required.

A comparative thyroid study in young and adult animals had previously been required for maneb and the other EBDC fungicides, as well as their common metabolite/degradate ETU. Cerexagri, Inc. suggested that the comparative thyroid study be conducted with ETU and evaluated prior to any similar testing with maneb, because ETU is believed responsible for thyroid toxicity occurring in the EBDC toxicity studies.

The EBDC risk assessment team agrees that it is appropriate for the comparative thyroid study to be conducted with ETU. ETU is a direct-acting thyroid toxicant which inhibits thyroid peroxidase enzyme and is believed to be responsible for the thyroid toxicity with the EBDCs. The comparative thyroid study should be conducted using ETU and requirement for a comparative thyroid study with maneb, as well as the other EBDC fungicides, is reserved.

A dose analysis was conducted on maneb in order to determine the need for and size of a database uncertainty factor [UF_{DB}] in the absence of a submitted developmental neurotoxicity study (DNT) for maneb. Assuming the doses tested in the required DNT will be similar to those in the available

2-generation reproduction study [the NOAEL in the subchronic neurotoxicity study on males 21 (males)/23 (females) mg/kg/day], the doses [from reproduction study] will be 5/6, 21/24 and 83/100 mg/kg/day. In the following table the assumed NOAEL for offspring effects in the DNT [in this case we will assume 5/6 mg/kg/day is the clear NOAEL] is compared this NOAEL to the doses selected for risk assessment. Only the doses selected for the acute dietary endpoints exceed the assumed DNT NOAEL, so a database uncertainty factor is only required for these risk assessments.

Endpoint [1]	Dose Selected mg/kg/day	Assumed NOAEL of DNT mg/kg/day	Conclusion
Acute Dietary - Females 13+	20	5/6	The DNT NOAEL is lower than the dose selected for risk assessment and a UF_{DB} of 3X is required.
Acute Dietary - General Population	1000	5/6	The DNT NOAEL is lower than the dose selected for risk assessment and a UF_{DB} of 10X is required.
Chronic Dietary	5	5/6	The DNT NOAEL is in the same range as the dose selected for risk assessment and no UF_{DB} is required.
Short-Term Incidental Oral	5	5/6	The DNT NOAEL is the same as the dose selected for risk assessment and no UF_{DB} is required.
Intermediate-Term Incidental Oral	5	5/6	The DNT NOAEL is the same as the dose selected for risk assessment and no UF_{DB} is required.
Short-Term Dermal	6	5/6	The DNT NOAEL is the same as the dose selected for risk assessment and no UF_{DB} is required.
Intermediate-Term Dermal	6 (2% Dermal Absorption Factor)	5/6	The DNT NOAEL is the same as the dose selected for risk assessment and no UF_{DB} is required.
Long-Term Dermal	6 (2% Dermal Absorption Factor)	5/6	The DNT NOAEL is the same as the dose selected for risk assessment and no UF_{DB} is required.
Short-Term Inhalation	5	5/6	The DNT NOAEL is the same as the dose selected for risk assessment and no UF_{DB} is required.
Intermediate-, and Long-Term Inhalation	5	5/6	The DNT NOAEL is the same as the dose selected for risk assessment and no UF_{DB} is required.

[1] The shaded rows indicate endpoints where a database uncertainty factor should be applied.

3.3 Dose Response Assessment

The HIARC evaluated the toxicology database of maneb on February 20, 2003 and selected the doses and endpoints for risk assessment based on a variety of exposure pathways. Since exposure to the metabolite and degradate ETU occurs in conjunction with the use of maneb, endpoints and doses for ETU selected at the February 18, 2003 HIARC meeting are included in Appendix 1.

Maneb Acute Dietary Endpoint (Females 13-50 years old) The rat developmental toxicity study was used to establish an acute reference dose for females 13-50 years old, based on increased post-implantation loss and resorptions and decreased fetal viability at the LOAEL of 100 mg/kg/day. Application of the standard 100X combined uncertainty factors (UFs) for interspecies extrapolation and intraspecies variability, as well as a 10X database UF (UF_{DB}) to the NOAEL of 20 mg/kg/day results in an acute reference dose (aRfD) of 0.02 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, 0.02 mg/kg/day. The endpoint is relevant for acute dietary risk assessment as defined in OPP, since the toxic effects are assumed to occur following a single exposure, and would be protective of this population subgroup.

Maneb Acute Dietary Endpoint (General US Population) An acute neurotoxicity study in the rat was used to establish an acute reference dose for the general population, based on slight impairment of forelimb grip strength at the LOAEL of 2000 mg/kg/day. Application of the standard 100X combined uncertainty factors (UFs) for interspecies extrapolation and intraspecies variability, and the 10X UF_{DB} results in an acute reference dose (aRfD) of 1.0 mg/kg/day. With a Special FQPA SF of 1X, the aPAD is the same as the aRfD, 1.0 mg/kg/day. The study is considered appropriate because the effect was seen after a single dose.

Maneb Chronic Dietary Endpoint The chronic reference dose (cRfD) for the general population was selected from a subchronic oral toxicity study in rats. The endpoint selected was thyroid effects, i.e. increased thyroid weights and follicular cell hyperplasia in males and decreased T_4 (serum thyroxin) in females, observed at the LOAEL of 24 mg/kg/day. After application of the standard 100X combined uncertainty factors (UFs) to the study NOAEL of 5 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. This study was considered the most appropriate for selecting the chronic endpoint and dose, since it had a clear NOAEL for target organ (thyroid) effects.

When HIARC selects an endpoint for chronic risk assessment from a subchronic study, an additional UF of either 3X or 10X is typically applied to account for the shorter dosing duration. However, in this case the HIARC concluded there was no cumulative toxicity for the target organ following long-term exposures, and no additional uncertainty factor is needed for risk assessment. Additionally, a database uncertainty factor [UF_{DB}] is not required for this exposure scenario because it is not expected that the required DNT will identify a lower effect/no-effect dose.

However, it is noted that this results in an apparent "discrepancy" between the acute PAD for the population sub-group [females 13+] for which a UF_{DB} is needed, resulting in an aPAD of 0.00 mg/kg/day, and the chronic PAD, resulting in a cPAD of 0.05 mg/kg/day. The chronic RfD is greater than the acute RfD for females 13+. This anomaly is likely a result of the differences in application of database uncertainty factors, dose spacing (the acute study had greater spacing between dosing, possibly resulting in an artificially low NOAEL), or the differences in exposure method (gavage in the acute study while the dose in the sub-chronic study was administered in the diet.

Maneb 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. increased thyroid weights, follicular cell hyperplasia and decreased T_4 (serum thyroxin), observed at the LOAEL of 24 mg/kg/day. The thyroid is the target organ in several species following oral exposures over various durations. Although this 13-week study was selected for exposures from 1 to 30 days, HIARC concluded that the effects observed in the study could have occurred earlier; for example, thyroid lesions were seen in the 21-day dermal toxicity study. The standard 100X UFs, are considered applicable to the selected dose for risk assessment. Therefore, the target MOE for residential incidental oral exposures is 100.

Dermal Absorption Factor The HIARC selected a value of 2% from an acceptable rat dermal absorption study. However, since a route specific study was selected for all durations of dermal exposure, this is not applicable.

Maneb Dermal Endpoints (Any Duration) The results of a 21-day dermal toxicity study in rabbits were used to select dermal endpoints following short-, intermediate- and long-term dermal exposures, i.e, exposures lasting from 1 day up to more than 6 months of exposure. The endpoint for risk assessment was microscopic thyroid changes (follicular cell hypertrophy) in both sexes and increased thyroid weights in males at the LOAEL of 1000 mg/kg/day (oral equivalent, 20 mg/kg/day). The study NOAEL is 300 mg/kg/day (oral equivalent, 6 mg/kg/day) and is the dose for dermal risk assessment. The dermal toxicity study was chosen for dermal risk assessments because effects were observed in the target organ *via* the exposure route of concern. The study was chosen for both intermediate- and long-term exposures because oral studies have indicated that effects on the thyroid do not intensify with time; this also obviates the need for additional uncertainty factors to extrapolate from shorter to longer durations of exposure.

The Margin of Exposure (MOE) is the ratio of the dose selected for risk assessment to estimated exposure on a mg/kg basis. OPP risk assessments typically use the MOE as a measure of risk from dermal and inhalation exposures. In order to be protective, the desired, or target MOE is the combined UFs associated with the dose and endpoint. For maneb dermal risk assessments, the combined UF (target MOE) for occupational assessments is 100, which includes the standard 10X factors to account for interspecies extrapolation and intraspecies variability. The combined UF is also 100 for residential dermal exposures because the FQPA database uncertainty factor is not

required.

Maneb Inhalation Endpoints (Any Duration) A subchronic oral 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 5 mg/kg/day, based on thyroid effects [increased thyroid weights and follicular cell hyperplasia in males and decreased T_4 (serum thyroxin) in females] at the LOAEL of 24 mg/kg/day. The oral study was preferred over the subchronic inhalation study, which was considered unacceptable because the doses were too low. In the absence of relevant information, toxicity by the inhalation route is considered to be equivalent to toxicity by the oral route of exposure, and a 100% oral absorption factor is used in risk assessment. The study endpoint of thyroid effects is considered appropriate for all durations of exposure, since the thyroid is a target organ in several species and over subchronic and chronic durations, and because available data indicate thyroid effects do not intensify over time.

For maneb inhalation risk assessments, the combined UF (target MOE) for occupational and residential assessments is 100, which includes the standard 10X factors to account for interspecies extrapolation and intraspecies variability. For residential inhalation exposures, no FQPA database uncertainty factor is required because it is not expected that the DNT will identify a lower effect/no-effect dose.

Table 3.4 Maneb Toxicological Doses/Endpoints for Use in Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment, Uncertainty Factors (UFs)	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Maneb Dietary Exposures			
Acute Dietary **Females 13+**	**NOAEL = 20 mg/kg/day** UF=100X (inter and intraspecies) UF=$10X_{database}$ Total UF=1000X **Acute RfD = 0.02 mg/kg/day**	**FQPA Special Safety Factor = 1X** aPAD= Acute RfD / FQPA SF **aPAD= 0.02 mg/kg/day**	Developmental Toxicity, Rat LOAEL=100 mg/kg/day, based on increased post-implantation loss and resorptions, decreased fetal viability
Acute Dietary **General Population**	**NOAEL=1000 mg/kg/day** UF=100X (inter and intraspecies) UF=$10X_{database}$ Total UF=1000X **Acute RfD=1.0 mg/kg/day**	**FQPA Special Safety Factor = 1X** aPAD= Acute RfD / FQPA SF **aPAD=1.0 mg/kg/day**	Acute Neurotoxicity, Rat LOAEL=2000 mg/kg/day, based on slight impairment of forelimb grip strength
Chronic Dietary **General Population**	**NOAEL=5 mg/kg/day** UF=100X (inter and intraspecies) Total UF=100X **Chronic RfD = 0.05 mg/kg/day**	**FQPA Special Safety Factor = 1X** cPAD = Chronic RfD / FQPA SF **cPAD = 0.05 mg/kg/day**	Subchronic toxicity, Rat LOAEL=24 mg/kg/day based on thyroid effects [increased thyroid weight and follicular cell hypertrophy in males and decreased T_4 in females]

Table 3.4 Maneb Toxicological Doses/Endpoints for Use in Risk Assessment.

Exposure Scenario	Dose Used in Risk Assessment, Uncertainty Factors (UFs)	FQPA SF and Endpoint for Risk Assessment	Study and Toxicological Effects
Carcinogenic Risk [oral/dermal/inhalation]	**$Q_1^* = 6.01 \times 10^{-2}$ (mg/kg/day)$^{-1}$**	Maneb is classified as a **Group B2** carcinogen; use low-dose extrapolation for human risk assessment, based on ETU	
Maneb Incidental Oral Exposures (Residential, Postapplication)			
Any duration [1-30 days] [>30 days to 6 mos.]	**NOAEL=5 mg/kg/day** UF=100X (inter and intraspecies)	**FQPA Special Safety Factor = 1X** **Residential MOE=100**	Subchronic toxicity, Rat LOAEL = 24 mg/kg/day based on thyroid effects [increased thyroid weight and follicular cell hypertrophy in males and decreased T_4 in females]
Maneb Dermal Exposures			
Any Duration [1-30 days] [>30 days to 6 mos.] [>6 mos.]	**Dermal NOAEL=300 mg/kg/day** UF = 100X (inter and intraspecies)	**FQPA Special Safety Factor = 1X** **Residential MOE=100** **Occupational MOE=100**	21-day Dermal Toxicity, Rabbit LOAEL = 1000 mg/kg/day, based on microscopic thyroid changes [follicular cell hypertrophy] in both sexes and increased thyroid weights in males.
Maneb Inhalation Exposures			
Any Duration [1-30 days] [>30 days to 6 mos.] [>6 mos.]	**NOAEL=5 mg/kg/day** UF=100X (inter and intraspecies) **Inhalation Absorption=100%**	**FQPA Special Safety Factor = 1X** **Residential MOE=100** **Occupational MOE=100**	Subchronic toxicity, Rat LOAEL = 24 mg/kg/day based on thyroid effects [increased thyroid weight and follicular cell hypertrophy in males and decreased T_4 in 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 were 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, maneb and ETU may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption. Maneb and ETU have demonstrated effects on thyroid hormones.

4.0 Exposure Assessment and Characterization

4.1 Summary of Registered Uses

Maneb is a contact fungicide widely used in agriculture and horticulture to prevent downy mildews, anthracnose, rusts, leaf spots and blight. Maneb formulations include wettable powders, dry flowables, liquid flowables and dusts. Agricultural uses include pome fruit crops (e.g., apples), field grown fruits and vegetables (e.g., cucumbers, onions, tomatoes, and grapes), some row crops (e.g., corn and potatoes), potato seed piece treatment and seed treatment (e.g. rice, wheat and cotton). Horticultural uses include ornamental plants in nurseries and greenhouses and on sod farms.

There are currently 29 active maneb labels and 1 section 24C (State) registration. The application rates in agriculture range from 1.2 lb ai/acre for corn to 6.4 lb ai/acre for almonds. Multiple applications are permitted per season, ranging from 3 for cranberries to 15 for sweet corn, with application intervals of 7 to 14 days. Some uses (e.g., grapes) have separate rates for eastern and western regions. The application rates in horticulture are 1.2 lb ai/acre for most ornamentals up to 17.4 lb ai/acre for turf. Horticulture and turf applications are allowed as much as once weekly with no annual limit.

Application methods include aerial, airblast, groundboom, chemigation, and hand application methods such as handwand and backpack sprayers. The application methods for seed and seed piece treatment include commercial stationary equipment, on farm stationary equipment and tractor drawn planter boxes.

The maximum application rates were derived from the labels and/or the Use Closure Memo of April 21, 1999. The typical rates were primarily taken from the EPA Quantitative Usage Analysis (QUA) for Maneb of December 2, 2002. In some cases, application rates were taken from the National Agriculture Statistics Service (NASS) use data, California Department of Pesticide Regulation (CA DPR) use data and from use data provided by Elf Atochem following the SMART meeting. A summary of use sites and application rates for agricultural crops is shown in Appendix 2. Application rates for seed treatment, also found in Appendix 2, were derived from labels.

In response to comments in the Phase 3 Public Participation Process for the EBDC REDs, BEAD has provided updated usage information in as Screening Level Usage Analysis (SLUA) (J Carter, 3/31/05). Percent crop treated (PCT) values from both the QUA and SLUA were used in this assessment. In general the PCT values are similar from both analyses. The newer PCT values were used in most cases; however, if a commodity was not listed in the SLUA, but was included in the QUA, then the value in the QUA was used. Commodities that are not included in either assessment are assumed to be 100% crop treated.

Maneb uses in horticulture are primarily on cut cultivated greens (i.e., ferns) according to the NASS Floriculture Survey. Only small amounts (<1000 lbs) were used on cut flowers or other horticulture sites.

4.2 Dietary Exposure/Risk Pathway

Maneb 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 maneb residues, calculated as zineb, are established in/on numerous crops under 40 CFR §180.110. Currently established tolerances range from 0.1 ppm (almond and potato) to 45 ppm in sugarbeet tops.

Mancozeb and metiram, the only other ethylenebisdithiocarbamate pesticides with current registrations, have tolerances for residues in apples and potatoes as does maneb. 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 maneb, mancozeb 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 maneb (40 CFR §180.110) is as follows:

Tolerances are established for residues of the fungicide maneb (manganous ethylenebisdithiocarbamate), *calculated as carbon disulfide*, CS_2, in or on raw agricultural

commodities.

The qualitative nature of maneb residues in plants and livestock is adequately understood based on acceptable metabolism studies conducted on lettuce, potato, and tomato and in goats and hens. In plants and livestock, the terminal residues of concern for risk assessment are maneb (and metabolites converted to CS_2) and ETU; however, for tolerance reassessment, only the parent maneb (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 maneb *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 maneb (and mancozeb 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.

Maneb 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 maneb reregistration data requirements for magnitude of the residue data are only partially fulfilled. Adequate field trial data depicting maneb 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. In many cases, however, the registrants have not

responded to deficiencies detailed in the 1992 Residue Chemistry Chapter of the Update to the Registration Standard. Thus reassessment of only some tolerances is possible. 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 maneb (and for metiram and mancozeb) 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 does occur through the skin of certain vegetables and fruits, generally those with thinner skins.

The processing studies indicate EBDC (and maneb *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 maneb (and metiram and mancozeb) dietary exposure and risk assessments by using empirical EBDC-to-ETU conversion factors from processing/cooking studies.

In oral rat metabolism studies conducted with radiolabeled 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 maneb 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 maneb 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 maneb, mancozeb 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); 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., maneb, mancozeb, 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.

4.3 Water Exposure/Risk Pathway

The OPP Environmental Fate and Effects Division (EFED) prepared a drinking water exposure assessment for ETU, which is applicable for maneb, 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 FIFRA 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 Dietary Exposure and Risk

Maneb and ETU 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., $>1x10^{-6}$).

4.4.1 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,

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; (3) acute risks do not reflect the most sensitive endpoint for EBDCs; 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 (nonmonitored) 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.

Maneb per se Data Sources and Assumptions To estimate maneb 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 and relevant processing factors were included in the assessment.

ETU (from Maneb) Data Sources and Assumptions To estimate maneb-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. For all included commodities, 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.

The results of the acute dietary exposure assessments for maneb *per se* and ETU are shown in Table 4.1. For maneb, acute dietary exposures were compared to the aPAD of 1 mg/kg/day for the general US population (and population subgroups including infants and children) or the aPAD of 0.02 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, the only population with an endpoint for acute dietary exposure.

For maneb *per se*, estimated acute dietary risk at the 99.9th percentile of exposure is below the Agency's level of concern For the general U.S. population, the estimated maneb dietary (food) exposure was 0.014 mg/kg/day which corresponds to 1.4% of the aPAD. For females 13-49 years old, the most exposed population subgroup, an estimated maneb exposure of 0.018 mg/kg/day corresponds to 89% of the aPAD

The maneb-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 0.0026 mg/kg/day corresponds to 52% aPAD.

The registrant has proposed removing the uses on sweet corn, grapes, and apples. The dietary

exposure and risk analyses were conducted eliminating these uses. The %aPAD did not change for any population group, indicating that these uses are not significant contributors to maneb and ETU exposure in the diet.

Table 4.1. Maneb and ETU Acute Dietary Exposure and Risk.

Population Subgroup	aPAD (mg/kg/day)	99.9th Percentile Exposure (mg/kg/day)	% aPAD
Maneb Acute Risk			
General U.S. Population	1.0	0.014	1.4
All Infants (< 1 year)	1.0	0.002	0.2
Children 1-2 years	1.0	0.012	1.2
Children 3-5 years	1.0	0.013	1.3
Children 6-12 years	1.0	0.008	0.8
Youth 13-19 years	1.0	0.015	1.5
Adults 20-49 years	1.0	0.016	1.6
Adults 50+ years	1.0	0.013	1.3
Females 13-49 years	**0.02**	**0.018**	**89**
ETU Acute Risk			
Females 13-49 years (all foods)	**0.005**	**0.003**	**52**

4.4.2 Chronic Dietary Exposure and Risk

To estimate maneb *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 and relevant processing factors were included.

The maneb-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 maneb *per se* to ETU.

Data that would be the most useful to further refine HED's exposure and risk estimates are representative residue data on leaf lettuce, preferably market basket survey data. Less critical, but also useful for refinement, would be similar MBS-type data on endive, mustard greens, and turnip greens.

The results of the chronic (non-cancer) dietary exposure assessments for maneb *per se* and ETU are shown in Table 4.2. For maneb, 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.

Maneb *per se* chronic (non-cancer) dietary exposure and risk are below HED's level of concern (i.e. <100% cPAD). For maneb *per se*, the highest exposed population subgroup is females 13-49 years old, with an exposure of 0.0001 mg/kg/day, which is less than 1% of the cPAD. Results for this population and other population subgroups are shown in Table 4.2.

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 0.000016 mg/kg/day corresponds to 7.9 %cPAD. The highest exposed population subgroup is children 1-2 years old; with an exposure of 0.000029 mg/kg/day, or 14% cPAD.

Apples, leaf lettuce, and sweet corn are minor contributors to the chronic dietary exposure for both ETU and maneb, and do not affect the %cPAD substantially when removed from the dietary analysis.

Table 4.2. Maneb and ETU Chronic Dietary Exposure and Risk.

Population Subgroup	**Maneb** Chronic Exposure and Risk			**ETU** Chronic Exposure and 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	0.000081	<1	0.0002	0.000016	7.9
All Infants (< 1 year)	0.05	0.000020	<1	0.0002	0.000009	4.3
Children 1-2 years old	0.05	0.000076	<1	**0.0002**	**0.000029**	**14**
Children 3-5 years	0.05	0.000072	<1	0.0002	0.000022	11
Children 6-12 years	0.05	0.000043	<1	0.0002	0.000013	6.3
Youth 13-19 years	0.05	0.000067	<1	0.0002	0.000011	5.7
Adults 20-49 years	0.05	0.00009	<1	0.0002	0.000014	7.1
Adults 50+ years	0.05	0.000092	<1	0.0002	0.000020	10
Females 13-49 years	**0.05**	**0.000103**	**<1**	0.0002	0.000015	7.5

4.4.3 Cancer Dietary Exposure and Risk

The estimated chronic dietary exposure to ETU (from sources attributable to maneb) of 0.000016 mg/kg/day for the general U.S. population corresponds to a cancer risk estimate of 9.6×10^{-7}, which is below the level of concern. When grapes, sweet corn, and apples are removed, the risk is slightly reduced, 9.5×10^{-7}.

4.5 Residential Exposure/Risk Pathway

Maneb is used on sod farms and the labels currently state "Do not use on residential, pasture or range grasses." The registrants have agreed to modify the label to include a statement such as "For Use on Sod farms Only" which will eliminate the possibility that maneb would be applied to turf in such areas as parks and golf courses where residential exposures might occur. The only

remaining exposure scenario occurs after the treated turf is transplanted from the sod farms to areas such as residential lawns.

4.5.1 Home Uses

Maneb registrants are not supporting home garden uses for maneb, and there are no active labels with residential uses for handlers (i.e., those involving a homeowner applying products in the home or garden).

4.5.2 Postapplication/Recreational Uses

Provided the registrants modify the labels to prohibit uses on residential lawns, exposures are limited to postapplication, following contact with transplanted sod that had been treated on a sod farm. Based on this use pattern, only the most sensitive sub-population (toddlers) was evaluated for postapplication exposure and risk. Preharvest intervals for sod farm turf established based on children's exposure and risk will provide adequate protection to the less sensitive adult populations. Toddlers' postapplication exposure to residues on transplanted sod farm turf consists 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 exposure (occurs when children touch treated turf and then put their hands in their mouths); (2) object-to-mouth exposure (results from children mouthing a handful of treated turf); and (3) soil ingestion exposure (occurs when children ingest soil that has been treated with a pesticide).

In assessing post-application exposure for toddlers, HED typically combines exposures from dermal and nondietary ingestion, since these activities are assumed to co-occur; this approach was also used to estimate exposures to maneb and ETU based on application to turf. In accordance with HED policy, a cancer assessment for children (toddlers) was not conducted. The target Margin of Exposure (MOE) for residential risk is 100 for dermal and 1000 for incidental oral, based on the combined uncertainty factors (UFs) associated with endpoint selection for dermal and incidental oral risk assessments.

In the absence of turf transferrable residue (TTR) data for maneb, a TTR study conducted with mancozeb was used as a surrogate source of data. The study was conducted at 3 separate sites and turf varieties, in CA, PA and NC, in which mancozeb was applied with a groundboom sprayer to turf. 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 resulting mancozeb dissipation rates on turf were translated to maneb. However, because ETU was not detected in the mancozeb TTR study, exposure to ETU from turf was estimated from the amount of maneb assumed to be present on turf, and on a 2.2% conversion of maneb to ETU, derived from maneb dislodgeable foliar residue (DFR) studies on grapes, apples and tomatoes.

<u>Assumptions Used to Calculate Residential Postapplication Risks (Toddlers)</u>

Short-term postapplication exposures to toddlers were estimated in accordance with the *SOPs for Residential Exposure*. The following assumptions were used:

- Application is assumed one day before harvest; sod was assumed to be transplanted 2 days after harvest.
- The maximum application rate of 17.4 lb ai/A was used.
- For hand-to-mouth risks, 0-day residue levels were assumed to be 5% of the application rate.
- For hand-to-mouth risks, 20 hand-to-mouth events occur per hour (assuming 20cm^2 surface area and 50% saliva extraction efficiency).
- For object-to-mouth risks, 0-day residue levels were assumed to be 20% of the application rate.
- The mancozeb dissipation rates from the TTR study were used to estimate maneb residues. To partially account for the fact that transplanted turf requires substantial irrigation to become established, the TTR data from the California site, which received 2.5 inches of irrigation during the study period, was used to determine the dissipation rate.
- ETU residues on turf were calculated based on 2.2% conversion from maneb.
- Soil residues are in the top centimeter of soil, and soil density is 0.67 mL/g.
- Toddlers weigh 15kg.
- Dermal transfer coefficients were based on the *SOPs for Residential Exposure*.

Residential Post Application Risk Summary

The maneb MOEs were calculated at the label application rate of 17.4 lb ai/acre and the proposed rate of 8.7 lb ai/acre. These MOEs are shown in Table 4.3. If the label application rate of 17.4 lb ai/acre is used the Total MOE rises to the target MOE with a PHI of 5 days. If the proposed application rate of 8.7 lb ai/acre is used, the Total MOE rises to the target MOE with a PHI of 3 days.

Table 4.3: Summary of Maneb Postapplication Residential Risks for Toddlers Exposed to Turf

Application Rate (lb ai/acre)	Exposure Pathway	MOE on Day 3 (PHI = 1 day*)	Target MOE	PHI Needed to Achieve the Target MOE
17.4	Dermal	48	100	3
	Hand-to-Mouth (HTM)	62	100	3
	Object-to-Mouth (OTM)	250	100	0
	Soil Ingestion	62000	100	0
	Total MOE	24	100	5

Table 4.3: Summary of Maneb Postapplication Residential Risks for Toddlers Exposed to Turf				
Application Rate (lb ai/acre)	**Exposure Pathway**	**MOE on Day 3 (PHI = 1 day*)**	**Target MOE**	**PHI Needed to Achieve the Target MOE**
8.7	Dermal	96	100	
	Hand-to-Mouth (HTM)	124	100	
	Object-to-Mouth (OTM)	500	100	
	Soil Ingestion	124000	100	
	Total MOE+	49	100	
* The current PHI is essentially 1 day because the REI is 24 hours.				
+ Total MOE = 1/((1/Dermal MOE)+(1/HTM MOE) + (1/OTM MOE) +(1/Soil MOE))				

The ETU MOEs are shown in Table 4.4. If the label application rate of 17.4 lb ai/acre is used the Total MOE rises to the target MOE with a PHI of 5 days. If the proposed application rate of 8.7 lb ai/acre is used, the Total MOE rises to the target MOE with a PHI of 3 days.

Table 4.4: Summary of ETU from Maneb Postapplication Residential Risks for Toddlers Exposed to Turf				
Application Rate (lb ai/acre)	**Exposure Pathway**	**MOE on Day 3 (PHI = 1 day*)**	**Target MOE**	**PHI Needed to Achieve the Target MOE**
17.4	Dermal	460	1000	3
	Hand-to-Mouth	1100	1000	1
	Object-to-Mouth	3600	1000	0
	Soil Ingestion	24000	1000	0
	Total+	300	1000	5
8.7	Dermal	920	1000	3
	Hand-to-Mouth	2200	1000	1
	Object-to-Mouth	7200	1000	0
	Soil Ingestion	48000	1000	0
	Total+	600	1000	3
* The current PHI is essentially 1day because the REI is 24 hours.				
+ Total MOE = 1/((1/Dermal MOE)+(1/HTM MOE) + (1/OTM MOE) +(1/Soil MOE))				

Short term non-cancer MOEs for both maneb and ETU were calculated for all of exposure pathways that can arise when children (i.e. toddlers) are exposed to sod farm turf treated with maneb and subsequently transplanted to residential lawns. It was assumed that the turf would be harvested one day after application (PHI = 1 day) and that it would take two days to harvest and transplant the turf. The MOEs were calculated at the label application rate of 17.4 lb ai/acre and the proposed rate of 8.7 lb ai/acre. If the label application rate of 17.4 lb ai/acre is used the Total

MOEs for maneb and ETU rise to the target MOEs with a PHI of 5 days. If the proposed application rate of 8.7 lb ai/acre is used, the Total MOEs for maneb and ETU rise to the target MOEs with a PHI of 3 days.

The risks for toddlers exposed to treated sod farm turf was calculated because it was thought that some exposure could occur after this turf was installed in a residential setting. To partially account for the fact that transplanted turf requires substantial irrigation to become established, the TTR data from the California site, which received 2.5 inches of irrigation during the study period, was used to determine the dissipation rate. Given that transplanted turf would typically be irrigated at a higher rate, the toddler risks can be considered to be upper bound estimates.

The percentage of applied maneb that converts to ETU on the leaf surface (2.2 percent) is possibly an overestimate because it was based on an average of seven maneb DFR studies, two of which had very long storage times which may have caused excessive ETU formation. If these two studies are excluded, the ETU formation rate drops by a factor of ten to 0.20 percent. The measured ETU formation rate in the twelve mancozeb DFR studies was 0.61 percent and the sample storage times were not excessive.

4.5.3 Other

Spray drift is a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

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: 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 exposures and risks from various sources, HED considers both the route and duration of exposure.

There is a potential for exposure to maneb (and ETU from maneb uses) in residential settings. The maneb use on sod farms may result in postapplication exposure to treated turf that has been transplanted to residential lawns. HED has assessed short-term postapplication exposure and risk to toddlers from maneb *per se* and ETU; these risks had MOEs well below the target MOEs and therefore cannot be added to exposure through food or drinking water.

For most pesticide active ingredients, water monitoring data are considered inadequate to generate quantitative surface and ground water drinking water exposure estimates, so model estimates have been used to estimate residues in drinking water (EDWCs). In order to determine if aggregate risks are of concern, HED then calculates 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.

In order to fully implement the requirements of FQPA, HED and EFED have been working toward refining the screening-level DWLOC approach to conducting aggregate risk assessments that combine exposures across all pathways. As part of this process EFED and HED have agreed that chronic and cancer EDWCs can be used directly in chronic/cancer dietary exposure assessments to calculate aggregate dietary (food + water) risk. This is done by using the relevant PRZM-EXAMS value as a residue for water (all sources) in the dietary exposure assessment conducted using the DEEM-FCID™ model. The principal advantage of this approach is that the actual individual body weight and water consumption data from the CSFII are used, rather than assumed weights and consumption estimates for broad age groups.

Since exposure to maneb *per se* is not expected from the water pathway, aggregate exposure and risk for maneb *per se* are limited to combined food and residential exposures. However, the residential exposures are limited to transplanted turf that had been treated at a sod farm. HED does not consider aggregating the turf exposures as these are expected to be rare events. Therefore, maneb aggregate risk assessments are not required.

For ETU, aggregate risks include dietary food + water + residential pathways of exposure. As stated in the previous paragraph, HED does not consider it appropriate to aggregate the residential exposures. Accordingly the following aggregate risk assessments are required:

(1) ETU acute aggregate (food + water)
(2) ETU chronic (food + water)
(3) ETU cancer (food + water)

The only aggregate risk assessments that have been completed for maneb include acute and chronic exposure to ETU through food and drinking water. The aggregate dietary exposure (food plus water) was compared to the ETU acute and chronic PADs, and to the cancer potency factor

(Q_1^*), to determine the aggregate risk associated with the estimated exposures. It should be noted that since the ETU EDWCs were derived from all sources of ETU (i.e., from multiple EBDC active ingredients), they are overestimates for maneb-derived ETU.

5.1 Aggregate Acute Risk Assessment

An acute dietary exposure and risk from ETU in food and drinking water was conducted using the DEEM-FCID™ model. Results are presented int Table 5.1 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.

Table 5.1. Results of Acute Dietary Exposure Analysis -Food and Water*

Population Subgroup	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
Females 13-49 years old	0.005	0.001290	26	0.002132	43	0.004321	86

*Estimated Drinking Water Concentration = 25.2 ppb

5.2 Aggregate Chronic Risk Assessment

The chronic dietary exposure and risk from maneb-derived ETU in food is below HED's level of concern for the General US Population and various population subgroups. The ETU surface and ground water EDWCs provided by EFED were incorporated into a dietary (water only) exposure assessment using the DEEM-FCID™ model. Results are presented in Table 5.2 below. For the chronic non-cancer assessment, the surface water EDWC of 0.1 ppb was used as the water residue value in the exposure assessment. For the cancer assessment, the surface water EDWC of 0.08 ppb was used as the water residue value. For ground water exposure, the ground water value of 0.21 ppb was used. The most highly exposed subgroup was Children, 1-2 years old, with a food and drinking water exposure (using the ground water EDWC) at 18% of the cPAD. This is below the level of concern.

Table 5.2. ETU Chronic (Non-Cancer) Aggregate Risks - Surface/Ground Water

Population Subgroup	cPAD (mg/kg/day)	Surface Water EDWC (0.1 ppb)		Groundwater EDWC (0.21 ppb)	
		Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD
General U S Population	0.0002	0.0000018	9.1	0.0000020	
All Infants (< 1 year old)	0.0002	0.000016	7.8	0.000023	
Children 1-2 years old	**0.0002**	**0.000032**	**16**	**0.000035**	**18**
Children 3-5 years old	0.0002	0.000026	13	0.000029	
Children 6-12 years old	0.0002	0.000015	7.3	0.000017	8.4
Youth 13-19 years old	0.0002	0.000013	6.4	0.000015	
Adults 20-49 years old	0.0002	0.000016	8.1	0.000018	9.2
Females 13-49 years old	0.0002	0.000022	11	0.000024	12
Adults 50+ years old	0.0002	0.000017	8.4	0.000019	9.5

** The values for the highest exposed population for each type of risk assessment are bolded.

5.3 Aggregate Cancer Risk Assessment

Aggregate ETU cancer risks for the general US population are below HED's level of concern: estimated exposure was at most 0.000020 mg/kg/day, which corresponds to a cancer risk of 1.2×10^{-6}. Most of the estimated exposure was from food.

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 (maneb, metiram 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 maneb risk assessments (from food and water, and in occupational settings) are based on combined ETU exposure associated with maneb. 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 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 and Risk Assessment

Occupational populations (handlers) are potentially exposed to maneb and ETU while making applications to crops, ornamentals, seed pieces and seeds. Some of these exposures are expected to occur in greenhouses, such as in the production of tomatoes or cut flowers. In addition, potential exposure to maneb 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 maneb and ETU handler risk assessments, mixer/loader scenarios were identified for each formulation - dust, wettable powder, liquid and dry flowable - including mixing/loading sprays for aerial, chemigation, groundboom, airblast and high pressure handwand applications. For applicators, the scenarios include airblast, groundboom, aerial and high-pressure handwand applications. Two mixer/loader/applicator scenarios were identified - low pressure handwand and high pressure handwand and a flagger scenario was identified for aerial application. Potato seed piece scenarios include loading or applying dusts, and secondary handler scenarios which involve loading treated seed pieces for tractor planting, and planting seed pieces with a tractor. For seed treatments, the following handler scenarios were identified - loader/applicator, bagger, sewer, multiple activities, on-farm planter box treatment, and loading and planting treated seed.

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.

Both handler and postapplication exposure and risk were estimated for maneb *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 maneb dermal exposure (including a 2% dermal absorption factor) was multiplied by 0.075 to take into account the 7.5 % *in vivo* metabolic conversion of maneb to ETU. This "metabolic" ETU was added to the ETU exposure from handler and postapplication activities to obtain the total ETU exposure.

For maneb non-cancer handler and postapplication assessments the short- and intermediate-term risks were the same, because the same endpoints and doses were used to assess all durations of exposure, and because there was no difference in the estimated daily exposure for these durations (*via* both dermal and inhalation routes of exposure). The long-term exposure scenarios were all based on uses in greenhouses. For ETU handler and postapplication assessments, non-cancer short-term and intermediate-term risks were the same, but chronic risks were assessed using a different toxicological dose and endpoint.

For the handler assessments, maneb dermal and inhalation risks were combined, since the endpoints (toxic effects) selected for risk assessment, thyroid effects, were the same. Similarly, 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 maneb non-cancer dermal risk assessments, the endpoint for risk assessment was selected from a dermal study, so the 2% dermal absorption factor was not necessary; it was used, however, to determine exposure to ETU following absorption and metabolism (7.5%) of maneb *in vivo*. For maneb inhalation assessments, the endpoint and dose for risk assessment were selected from an oral study, so a 100% 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 maneb 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 through the use of personal protective equipment (PPE) or through changes in the use pattern, such as application rate or re-entry interval (REI).

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 maneb, so Pesticide Handler Exposure Database (PHED, Version 1.1, 1998) data were used to calculate unit exposure values to estimate occupational handler exposures to maneb and ETU during application to crops and ornamentals. 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. There were no data to assess risks for planting treated potato seed pieces. 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 maneb 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. Maneb 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). It should be noted that for the dust formulation for potato seed piece treatment, labels require workers to wear long pants, long-sleeve shirts, gloves and coveralls, as well as a PF10 respirator. Both dermal and inhalation exposures were estimated with the addition of engineering controls, such as an enclosed cockpit or cab, and water soluble packaging.

The PHED data for deriving unit exposures at the baseline, PPE and engineering control mitigation levels (for exposure to the hand, dermal exposure and inhalation exposure) 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 maneb 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 of dry flowables with engineering controls (e.g., lock and load systems) or for mixing/loading/applying DF and WP formulations with a backpack sprayer.

For maneb 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 for maneb, 60 kg for ETU short/intermediate term exposures; 70 kg for ETU chronic and lifetime exposure
- 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)
  - Groundboom: 80 acres (most crops); 200 acres (high acreage); 40 acres (ornamentals)
  - Airblast: 40 acres.
  - High pressure handwand: 10 acres, 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

Because maneb (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 maneb/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 maneb (and EBDC) products have not changed substantially. In estimating mixer/loader risks, a 0.2% conversion of maneb to ETU was assumed, and for applicators a 0.6% 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

Maneb 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 (with the exception of the dust formulation for seed piece treatment, which requires a PF10 respirator).

Maneb Combined Dermal and Inhalation Risks Maneb long-term combined dermal and inhalation risks were all below HED's level of concern (i.e., the MOEs were greater than 100 at all levels of PPE, and for all handler scenarios). Maneb *per se* short- and intermediate-term combined dermal and inhalation risks are shown in Table 7.1. Only the mixer/loader scenarios have risks of concern. For some mixer/loader scenarios involving wettable powder formulations, the non-cancer risks are of concern based on label-required PPE, and respiratory protection is required to achieve an MOE greater than 100. The addition of respiratory protection achieves a much greater risk reduction than the addition of a second layer of clothing. In a few cases, such as those involving sod farm application rates, engineering controls such as water soluble bags are needed to attain the target MOE. The risks for mixing/loading dry flowable and liquid flowable formulations are much lower than risks for the wettable powder formulations, and can be mitigated in most cases (except for turf and almonds) with baseline PPE and gloves (coveralls and respirators are not needed).

Risks for applicators and mixer/loader/applicators were all below HED's level of concern, with MOEs >100. The risk for applying sprays using mechanized equipment such as aircraft, groundboom and airblast sprayers is not of concern with baseline PPE without gloves (i.e. less PPE than required by the label) regardless of the formulation type. Estimated risks for mixing/loading/applying wettable powders using handheld equipment (e.g. handwand) are not of concern due to the high spray volume (100 gallons per acre) which reduces the amount of area that can be treated in a day.

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

ETU Non-Cancer Risks Short- and intermediate-term MOEs for ETU are approximately 10 times higher than corresponding MOEs for maneb. Like maneb, ETU MOEs are of concern for high-volume mixer/loader wettable powder scenarios with baseline PPE. Additional PPE, such as respirators, or engineering controls are needed to achieve MOEs of 100. A summary of short- and intermediate-term ETU non-cancer risks is provided in Table 7.2. Long-term ETU non-cancer

MOEs are of concern with baseline clothing for mixing/loading wettable powder or liquid formulations for application to ornamentals or tomatoes. These MOEs are above 100 once gloves are added.

ETU Cancer Risks ETU cancer risks were calculated assuming 30 exposure days per year and are summarized in Table 7.3. 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) recommended to address the non-cancer maneb risks. Many of the risks are also below $1x10^{-5}$ with maximum mitigation (engineering controls) and some are below $1x10^{-6}$.

Table 7.1. Maneb Short/Intermediate Term MOEs for Agricultural Handlers.[1]

Exposure Scenario	Typical Crops[2]	lbs ai/acre	Acres per Day	Clothing/PPE[3]					
				Base-line	SL No Resp	DL No Resp	DL PF5	DL PF10	EC
Mixer/Loader (M/L)									
M/L (WP) for Aerial and Chemigation	turf: sod farms fruits and nuts field crops, vegetables	17.4 2.0 to 6.4 1.2 to 2.4	350	**0.55** **≥1.5** **≥4.0**	**1.3** **≥3.4** **≥9.1**	**1.3** **≥3.5** **≥9.2**	**5.3** **≥15** **≥39**	**8.9** **≥24** **≥64**	140 [illegible] 1000
M/L WP for Ground-boom	turf: sod farms cranberries, grapes field crops, vegetables	17.4 2.0 to 4.8 1.2 to 2.4	80	**2.4** **≥8.7** **≥17**	**5.5** **≥20** **≥40**	**5.6** **≥20** **≥40**	**23** **≥85** ≥170	**39** ≥140 ≥280	620 1000 1000
M/L WP for Airblast	fruits and nuts	2.0 to 6.4	40	**≥13**	**≥30**	**≥30**	≥130	≥210	[illegible]
M/L WP for HP Handwand	ornamentals, tomatoes	1.2 to 2.4	10	≥140	>300	>300	>1000	>1000	[illegible]
M/L Dry Flowable (DF) for Aerial and Chemigation	turf: sod farms fruits and nuts field crops, vegetables	17.4 2.0 to 6.4 1.2 to 2.4	350	**31** **≥84** ≥220	**31** **≥84** ≥220	3[illegible] [illegible] [illegible]	62 [illegible] [illegible]	6[illegible] [illegible] [illegible]	[illegible] N ND
M/L DF for Groundboom	turf: sod farms all other crops	17.4 1.2 to 4.8	80	130 >400	130 >400	160 >500	270 >900	290 >1000	ND ND
M/L DF for Airblast	fruits and nuts	2.0 to 6.4	40	>700	>700	>800	>1000	>1000	ND
M/L DF for HP Handwand	ornamentals, tomatoes	1.2 to 2.4	10	>1000	>1000	>1000	>1000	>1000	ND
M/L Liquids for Aerial or Chemigation	turf: sod farm fruits and nut field crop vegetables	17.4 2.0 to 6.4 1.2 to 2.4	350	**1.2** **≥3.2** **≥8.4**	**36** **≥99** ≥260	39 [illegible] [illegible]	[illegible] [illegible] [illegible]	110 >300 >1000	[illegible] [illegible] [illegible]
M/L Liquids for Groundboom	turf: sod farms all other crops	17.4 1.2 to 4.8	40 to 80	**5.1** **≥18**	160 >500	179 >600	480 >1000	620 >1000	>1000 >1000
M/L Liquids for Airblast	fruits and nuts	2.0 to 6.4	40	**≥28**	>800	900	1000	>1000	>1000
M/L Liquids for HP Handwand	ornamentals, tomatoes	1.2 to 2.4	10	≥290	>1000	1000	1000	>1000	>1000
Applicator - All MOEs >100 at Baseline clothing									
Mixer/Loader/Applicator (M/L/A) - All MOEs >100 at Baseline clothing									

Table 7.1. Maneb Short/Intermediate Term MOEs for Agricultural Handlers.[1]

Exposure Scenario	Typical Crops[2]	lbs ai/acre	Acres per Day	Clothing/PPE[3]					
				Base-line	SL No Resp	DL No Resp	DL PF5	DL PF10	EC
Flagger - All MOEs >100 at Baseline clothing									

***MOEs in bold are less than 100 and are of concern.**

ND= No Data

[1] Margins of Exposure (MOEs) include both dermal and inhalation risks.

[2] Crop Groups

Fruits and nuts- includes almonds, cranberries, grapes and pome fruits.
Field crops - includes corn, dry beans, potatoes and sugar beets.
Vegetables - includes brassica, cucurbits, garlic, greens, lettuce, onions, peppers and tomatoes.

[3] PPE Levels

Baseline - includes long pants and long sleeve shirts without gloves.
Single Layer (SL) - includes baseline PPE with chemical resistant gloves.
Double Layer (DL) - includes coveralls over baseline PPE and chemical resistant gloves - typically required by maneb labels.
PF5 - Filtering facepiece respirator (i.e. a dustmask) with a protection factor of 5.
PF10 - Half face cartridge respirator with a protection factor of 10.
EC - Engineering control - includes water soluble bags, closed loading systems and enclosed cabs.

Table 7.2. ETU Short/Intermediate Term MOEs for Agricultural Handlers.[1]

Exposure Scenario	Typical Crops[2]	lbs ai/acre	Acres per Day	Clothing/PPE[3]					
				Base-line	SL No Resp	DL No Resp	DL PF5	DL PF10	EC
Mixer/Loader (M/L)									
M/L (WP) for Aerial or Chemigation	turf: sod farms fruits and nuts field crops. vegetables	17.4 2.0 to 6.4 1.2 to 2.4	350	**5.3** **≥14** **≥39**	**16** **≥43** ≥120	**16** **≥44** ≥120	**62** >170 ≥450	**97** ≥260 ≥700	>1000 >1000 >1000
M/L WP for Ground-boom	turf: sod farms cranberries. grapes field crops. vegetables	17.4 2.0 to 4.8 1.2 to 2.4	80	**23** **≥85** ≥170	**69** ≥250 ≥500	**70** ≥260 ≥510	270 ≥990 >1000	420 >1000 >1000	>1000 >1000 >1000
M/L WP for Airblast	fruits and nuts	2.0 to 6.4	40	≥130	≥370	≥380	>1000	>1000	>1000
M/L WP for HP Handwand	ornamentals. tomatoes	1.2 to 2.4	10	>1000	>1000	>1000	>1000	>1000	>1000
M/L Dry Flowable (DF) for Aerial or Chemigation	turf: sod farms fruits and nuts field crops. vegetables	17.4 2.0 to 6.4 1.2 to 2.4	350	300 ≥810 >1000	300 ≥810 >1000	370 1000 >1000	540 >1000 >1000	570 >1000 >1000	ND ND ND
M/L DF for Groundboom	turf: sod farms All other crops	17.4 1.2 to 4.8	40 to 80	>1000 >1000	>1000 >1000	>1000 >1000	>1000 >1000	>1000 >1000	ND ND
M/L DF for Airblast	fruits and nuts	2.0 to 6.4	40	>1000	>1000	>1000	>1000	>1000	ND
M/L DF for HP Handwand	ornamentals. tomatoes	1.2 to 2.4	10	>1000	>1000	>1000	>1000	>1000	ND

Table 7.2. ETU Short/Intermediate Term MOEs for Agricultural Handlers.[1]

Exposure Scenario	Typical Crops[2]	lbs ai/acre	Acres per Day	Clothing/PPE[3]					
				Base-line	SL No Resp	DL No Resp	DL PF5	DL PF10	EC
M/L Liquids for Aerial or Chemigation	turf: sod farms All other crops	17.4 1.2 to 6.4	350	9.7 **≥26**	410 >1000	450 1000	1000 1000	>1000 1000	>1000 1000
M/L Liquids for Groundboom	turf: sod farm All other crop	17.4 1.2 to 4.8	40 to 80	**42** ≥150	1000 1000	1000 1000	1000 1000	1000 1000	1000 1000
M/L Liquids for Airblast	fruits and nuts	2.0 to 6.4	40	≥230	1000	1000	1000	>1000	1000
M/L Liquids for HP Handwand	ornamentals, tomatoes	1.2 to 2.4	10	>1000	1000	>1000		>1000	
Applicator - All MOEs >100 at Baseline clothing									
Mixer/Loader/Applicator - All MOEs >100 at Baseline clothing									
Flagger All MOEs >100 at Baseline clothing									

***MOEs in bold are less than 100 and are of concern.**

[1] Margins of Exposure (MOEs) include both dermal and inhalation risks.

[2] Crop Groups (see Table 13)

[3] PPE Levels (see Table 13).

Table 7.3. ETU (from Maneb) Cancer Risks for Agricultural Handlers (30 Days per Year).

Exposure Scenario	Typical Crops[1]	Typical Rate (lb) ai/acre	Acres per Day	Clothing/PPE[2]					
				Base line	SL No Resp	DL No Resp	DL PF5	DL PF10	EC
Mixer/Loader (M/L)									
M/L WP for Aerial Application or Chemigation	turf: sod farms fruits and nuts field crops, vegetables	17.4 1.8 to 3.6 1.2 to 2.4	350	**2e-03** **<5e-04** **<3e-04**	**8e-04** **<2e-04** **<1e-04**	**8e-04** **<2e-04** **<1e-04**	**2.e-04** <4e-05 <3e-05	**1e-04** <3e-05 <2e-05	8e-06 <2e-06 <1e-06
M/L WP for Ground-boom	turf: sod farms All other crops	17.4 1.2 to 3.0	80	**5e-04** <9e-05	**2e-04** <3e-05	**2e-04** 3e-05	5e-05 <8e-06	3e-05 <5e-06	2e-06 <3e-07
M/L WP for Airblast	fruits and nuts	1.9 to 3.6	40	<6e-05	<2e-05	2e-05	<5e-06	3e-06	<1e-06
M/L WP for HP Handwand	ornamentals, tomatoes	1.2 to 1.4	10	<6e-06	<2e-06	<2e-06	<5e-07	2e-07	<1e-06
M/L DF for Aerial Application or Chemigation	turf: sod farms All other crops	17.4 1.2 to 3.6	350	4e-05 <9e-06	4e-05 <9e-06	3e-05 <7e-06	2e-05 <5e-06	2e-06 <5e-06	ND ND
M/L DF for Groundboom	turf: sod farms *All other crops*	17.4 1.2 to 3.0	40 to 80	1e-05 <2e-06	1e-05 <2e-06	8e-06 <1e-06	2e-06 <5e-07	9e-06 <2e-06	ND ND
M/L DF for Airblast	fruits and nuts	1.8 to 3.6	40	<1e-06	<1e-06	<8e-07	<2e-07	<9e-07	ND
M/L DF for HP Handwand	ornamentals, tomatoes	1.2 to 1.4	10	<1e-07	<1e-07	<8e-08	<6e-08	<9e-08	ND

Table 7.3. ETU (from Maneb) Cancer Risks for Agricultural Handlers (30 Days per Year).

Exposure Scenario	Typical Crops[1]	Typical Rate (lb) ai/acre	Acres per Day	Clothing/PPE[2]					
				Base-line	SL No Resp	DL No Resp	DL PF5	DL PF10	EC
M/L Liquids for Aerial Application or Chemigation	turf: sod farms fruits and nuts field crops, vegetables	17.4 1.8 to 3.6 1.2 to 2.4	350	**1e-03** **<3e-04** **<2e-04**	3e-05 <6e-06 <4e-06	3e-05 <6e-06 <4e-06	1e-05 <2e-06 <2e-06	9e-06 <2e-06 <1e-06	5e-06 <1e-06 <7e-07
M/L Liquids for Groundboom	turf: sod farms All other crops	17.4 1.2 to 3.0	40 to 80	**3e-04** <5e-05	7e-06 <1e-06	6e-06 <1e-06	3e-06 <5e-07	2e-06 <4e-07	1e-06 <2e-07
M/L Liquids for Airblast	fruits and nuts	1.8 to 3.6	40	<3e-05	<7e-07	<6e-07	<3e-07	<2e-07	<1e-07
M/L Liquids for HP Handwand	ornamentals, tomatoes	1.2 to 1.4	10	<3e-06	<7e-06	<7e-08	<3e-08	<2e-08	<1e-08
Applicator (App)									
Aerial Applicator	turf: sod farms All other crops	17.4 1.2 to 3.6	350	ND					5e-06 <9e-07
Groundboom Applicator	turf: sod farms All other crops	17.4 1.2 to 3.0	80	5e-06 <9e-07	5e-06 <9e-06	5e-06 <8e-07	2e-06 <4e-07	2e-06 <3e-07	9e-07 <2e-07
Airblast Applicator	fruits and nuts	1.8 to 3.6	40	<7e-06	<6e-06	<5e-06	<4e-06	<4e-06	<4e-07
HP Handwand Application	ornamentals .tomatoes	1.2 to 1.4	10	<2e-06	<8e-07	<6e-07	<5e-07	<5e-07	N/A
Mixer/Loader/Applicator (M/L/A)									
M/L/A WP with LP Handwand	tomatoes, ornamentals	1.2 to 1.4	0.4	ND	<2e-06	<2e-06	<8e-07	<6e-07	N/A
M/L/A WP with Backpack. M/L/A DF with LP Handwand. M/L/A DF with Backpack				No unit exposure data are available for these scenarios					
M/L/A Liquids with LP Handwand	tomatoes, ornamentals	1.2 to 1.4	0.4	<7e-06	<8e-08	<8e-08	<3e-08	<3e-08	N/A
M/L/A Liquids with Backpack	tomatoes, ornamentals	1.2 to 1.4	0.4	ND	<2e-07	<2e-07	1e-07	<1e-07	N/A
Flagger									
(14) Flag Aerial Applications	turf: sod farms All other crops	17.4 1.2 to 3.6	350	1e-05 <3e-06	1e-05 <3e-06	1e-05 <3e-06	8e-06 <2e-06	7e-06 <1e-06	2e-07 <4e-08

***Cancer Risks in Bold Equal or Exceed 1e-04 which is equivalent to 1 x 10^{-4}**

ND = No Data
N/A = Not applicable

[1] Crop Groups (See Table 12)

[2] PPE Levels (See Table 12)

7.1.3 Occupational Handler Risk for Potato Seed Piece Treatment

Only short/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.

Maneb Short/Intermediate-Term Risks Maneb non-cancer risks from mixing/loading dusts for commercial seed piece treatment are of concern (i.e., combined dermal and inhalation MOEs are <100) with maximum PPE (double layer clothing and PF10 respirators), and engineering controls are needed to achieve an MOE > 100. The risk for applying dusts to potato seed pieces could not be calculated due to a lack of data for that scenario. However, risks for secondary handlers, or those who load and plant the treated seed pieces, were not of concern. Maneb risks for potato seed piece treatment are shown in Table 7.4.

ETU Short Intermediate-Term Risks Combined dermal and inhalation MOEs for potato seed piece treatment are all above 100 for all scenarios provided gloves are worn.

ETU Cancer Risks The cancer risks from ETU based on application of maneb to potato seed pieces were calculated assuming 30 days per year. For loading dusts, most of the risks are below $1.0x10^{-4}$ with single layer PPE (which includes gloves but not respirators) and all of the risks are below $1.0x10^{-4}$ with the additional mitigation (such as respirators or water soluble bags) recommended to address the non-cancer maneb risks. There were no data to assess cancer risk for those applying dusts to seed pieces. Cancer risks for secondary handlers were all below $3x10^{-7}$ at the baseline clothing scenario, and were lower with the application of additional PPE.

Table 7.4. Maneb Combined Short/Intermediate Term MOEs for Potato Seed Piece Treatment.

Exposure Scenario	Treatment Rate	Amount Treated per Day	Clothing/PPE					
			Base-line	SL	SL PF5	SL PF10	DL PF10	Eng Controls
Mix/Load Dusts								
(1a) Commercial Seed Piece Treatment	0.08 lb ai/cwt	10,000 cwt	4.2	9.5	38	61	68	>1000
(1b) On-Farm Seed Piece Treatment	0.08 lb ai/cwt	800 cwt	52	120	480	770	850	>1000
Applicator No unit exposure data available for this scenario								
Secondary Handler Exposure - All MOEs >1000								

[1] PPE Levels
Baseline - includes long pants and long sleeve shirts without gloves
Single Layer (SL) - includes baseline PPE with chemical resistant gloves
Double Layer (DL) - includes coveralls over baseline PPE and chemical resistant gloves.
PF5 - Filtering face piece respirator (i.e. a dust mask) with a protection factor of 5.
PF10 - Half face air purifying respirator with a protection factor of 10
EC - Engineering controls

7.1.4 Occupational Handler Risk for Seed Treatment

Seed treatment labels required a range of PPE, including single layer without respirator up to double layer with a PF10 respirator.

Maneb Short/Intermediate-Term Risks With the exception of 2 multiple activity scenarios at baseline clothing (treating sorghum and oats) and 3 planter box scenarios with single layer clothing and PF10 respirator (treating oats, rice and peanuts), MOEs for all scenarios were greater than 100. Risks for multiple activity scenarios are not of concern when single layer clothing and a PF5 respirator are used. Planter box MOEs for crops other than peanuts, rice and oats were greater than 100, and not of concern for single layer clothing (no data were available to assess MOEs for the baseline clothing scenario). The MOE for peanuts was 18 and the MOE for rice was 64 (based on Single Layer and PF10 respirator); however, most peanut and rice seed is treated commercially, and the planter box scenarios were assessed only because they were included on the labels. The MOE for planter box treatment of oats was 72; there were no data to determine exposure and risk at additional levels of PPE (Double Layer with PF10 respirator) or with engineering controls.

ETU Non-Cancer Risks Short/intermediate-term MOEs for seed treatment are greater than the corresponding MOEs for maneb and are above 100 for all of the scenarios.

ETU Cancer Risks The cancer risks based on exposure to ETU following application of maneb to seeds were calculated using 30 days per year for commercial seed treatment and 10 days per year for on-farm seed treatment. Risks for all levels of personal protection (other than the baseline clothing scenario, for which there were no data) were at most $3x10^{-5}$ (planter box treatment for peanuts), but in general were in the 10^{-6} and 10^{-7} range.

7.2 Occupational Postapplication Risk Assessment

7.2.1 Postapplication Data and Assumptions

Chemical-specific dislodgeable foliar residue (DFR) data have been submitted for maneb, and were used to estimate potential exposures to maneb and ETU upon re-entry to treated areas, either for harvest, scouting, irrigation or crop maintenance (e.g., pruning or thinning). One recent study (1999) and 5 older studies (1988 - 1991) were used in the current assessment. These consisted of 2 DFR studies on apples, a DFR and worker re-entry study on grapes, and 3 DFR studies on tomatoes. In addition, a mancozeb turf transferable residue (TTR) study was used as a surrogate source of data to estimate postapplication risks for maneb uses on turf. Although TTR data are not typically translated from one active ingredient to another, it was considered appropriate in this case due to similarities between maneb and mancozeb, and based on a comparison of available DFR data for the 2 active ingredients.

The maneb DFR studies consisted of airblast and ground boom application methods, both East and West regions, and 3 crops (apples, grapes and tomatoes); one each of the apple and tomato studies were considered inadequate for use in postapplication exposure calculations. The remaining DFR studies were extrapolated to other crop types based first on the region, followed by application method and crop type. Maneb dislodgeable residues were considerably higher than ETU residues on the day of application; ETU residues were typically at or just above the LOQ, while maneb residues ranged from 4 to 85 times the LOQ. Maneb half-lives ranged from 7.2 (NY apples) to 32.8 (CA grapes) days. The ETU half-life could only be calculated in one NY and one WA apple study, and these were 8.4 and 17.7 days, respectively.

The mancozeb half-life on turf ranged from 1.8 to 6.6 days; samples were not collected beyond 14 days after application. The ETU dissipation rate could not be directly calculated for turf, since ETU residues were very low even on the day of application.

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 almonds, apples and grapes, which relied on average rates from NASS data.
- Single day exposures (rather than a rolling average) were used due to (1) low dissipation rate for maneb; and (2) multiple applications permitted.
- A pseudo-first order kinetics analysis was used for maneb dissipation, as per Agency guidelines.
- 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 days per year.
- Risks for pruning and harvesting almonds were considered negligible due to application timing.
- Only the extended application rates are used for assessing the deciduous tree fruit scenarios, because the pre-bloom application rates can only be used early in the season when there is a lesser amount of foliage.
- The very high exposures scenarios for grapes, which included cane turning and girdling with a transfer coefficient of 10000 cm^2/hr, were not assessed for the following reasons:
  - A. The PHI for eastern wine grapes is 66 days which allows the last application to be made approximately 3 to 4 weeks prior to cane turning which occurs mid July to early August
  - B. In California maneb can only be used through bloom which occurs well before can turning which, according to CALIPA, occurs 3 to 4 weeks before harvest to improve the color of red table grapes.
  - C. Girdling is done only on table grapes in California, and it is done in June and July which is outside the maneb window of application.

D. According to the USDA Crop Profile for California Table Grapes, 97 percent of the nation's table grapes are grown in California.

- Generic transfer coefficients were used as shown in Table 7.5. Although a grape re-entry study was submitted, the results support the use of the generic transfer coefficients. The transfer coefficients for ornamentals plants were taken from ARTF studies #ARF039, #ARF043 and #ARF044. These studies were recently submitted by the Agricultural Re-entry Task Force (ARTF) and have been reviewed by HED. These studies were found to be acceptable and mean values were selected for risk assessment in accordance with Policy 003.1.

Table 7.5. Post-application Exposure Scenarios and Transfer Coefficients.

Crop Type (Specific Crops)	Post-application Exposure Scenarios	Transfer coefficient (cm²/hr)
Berry, Low (Cranberry)	Low - Irrigation, scouting, pruning thinning	
Bunch/Bundle (Banana)	Low - Irrigation, hand weeding, scouting immature/low foliage plants Medium - Irrigation and scouting mature/high foliage plants High - Hand harvesting, stripping, training, thinning, topping	
Cut Flowers	Low - Irrigation, scouting, thinning weeding immature low foliage plants Medium - Irrigation, scouting mature/high foliage plants High - Hand harvesting, pruning, thinning, pinching	
Field/Row Crops, Low/Medium (Dry beans and sugar beets)	Low - Irrigation, scouting, thinning, weeding immature plants Medium - Same as above on mature plants	
Field/Row Crop, Tall (Corn)	Medium - Scouting, weeding more mature plants High - Scouting, weeding, irrigation mature plants Very High - Sweet corn hand harvesting or seed corn detasseling	
Ornamentals (Excluding Cut Flowers)	Low - pruning citrus Medium - Hand pinching mums High - Moving Potted Plants	
Tree, Fruit, Deciduous (apples)	[illegible]	
Tree, Fruit, Evergreen (Papaya)	Low - Irrigation, scouting, hand weeding Medium - Pruning, thinning, harvesting	
Tree, Nut (almond)	Low - Irrigation, scouting, thinning, weeding High - Pruning, thinning	
Turf	Low - Mowing High - Transplanting, hand weeding	
Vegetable, Brassica	Low - Irrigation, scouting, thinning, weeding immature plants Medium - Scouting mature plants High - Hand harvesting, irrigation, pruning, topping tying mature plants	
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	
Vegetable, Fruiting (Tomato, peppers)	Low - Irrigation, scouting, thinning, weeding immature plants Medium - Irrigation and scouting mature plants High - Hand harvesting, pruning, staking, tying	
Vegetable, Leafy	Low - Irrigation, scouting, thinning, weeding immature plants Medium - Irrigation and scouting mature plants High - Hand harvesting, pruning and thinning mature plants	
Vegetable, Root (Onions, Potatoes)	Low - Irrigation, scouting, thinning weeding immature plants Medium - Irrigation and scouting mature plants High - Hand harvesting	
Vine/Trellis (Grape)	Low - Hedging, irrigation, scouting, hand weeding Medium - Scouting, training, tying High - Leaf pulling, thinning, pruning, training/tying Very High - Girdling and Cane Turning	

7.2.2 Postapplication Risks

Maneb Non-Cancer Postapplication Risks Maneb postapplication risks were calculated for different crop groups as described above. Within each crop group, transfer coefficients were used to represent different types of cultural practices which are applicable to each crop group. For grapes and deciduous tree fruit, MOEs for maneb are of concern (i.e. are less than 100) at the currently labeled REI of 24 hours for certain high and very high exposure activities. The time needed to achieve the target MOE of 100 ranges from 5 to 26 days, with the longest time needed for some of the high exposure tasks involving western grapes. A summary of maneb postapplication risks is shown in Table 7.6.

Table 7.6. Maneb Postapplication (Non-Cancer) Risks.

Crop Group	Application Rate (lb a.i/acre)	MOE on Day 0 (Days when MOE > 100)			
		Low*	Medium*	High*	Very High*
Berry, low (Cranberry)	4.8	220	NA	NA	NA
Bunch/bundle (Banana)	2.4	4000	300	200	NA
Field/row crops, Low/Medium - West Field/row crops, Low/Medium - East	1.6 1.6	8200 5900	550 400	NA NA	NA NA
Field/Row crop, tall (Corn) - West Field/Row crop, tall (Corn) - East	1.2 1.2	NA NA	2700 2000	1100 790	**.64 (5)** **46 (11)**
Flowers and Greens, cut	1.2	320	200	110	NA
Ornamentals Excluding Cut Flowers	1.2	7200	4500	2000	NA
Tree, fruit, deciduous - West	2.4	260	NA	**86 (5)**	NA
Tree, fruit, deciduous - East	2.4	180	NA	**58 (6)**	NA
Tree, fruit, evergreen (Papaya)	2	470	160	NA	NA
Tree, nut (Almond)	6.4	190	NA	NA	NA
Turf - California Turf - North Carolina Turf - Pennsylvania	17.4 17.4 17.4	18000 32000 41000	NA NA NA	550 960 1200	NA NA NA
Vegetable, Brassica - West Vegetable, Brassica - East	1.6 1.6	410 300	210 150	160 120	NA NA
Vegetable, Cucurbit - West Vegetable, Cucurbit - East	1.6 1.6	1600 1200	550 400	330 240	NA NA
Vegetable, fruiting - West Vegetable, fruiting - East	1.6 2.4	1600 790	1200 560	820 400	NA NA

Table 7.6. Maneb Postapplication (Non-Cancer) Risks.					
Crop Group	Application Rate (lb a.i./acre)	MOE on Day 0 (Days when MOE > 100)			
		Low*	Medium*	High*	Very High*
Vegetables, leafy - West	1.6	1600	550	330	NA
Vegetables, leafy - East	1.6	1200	400	240	NA
Vegetable, root - West	2.4	1800	370	220	NA
Vegetable, root - East	2.4	1300	260	160	NA
Vine/trellis (Grapes) West	2.0	590	290	**59 (26)**	NA
Vine/trellis (Grapes) East	3.2	260	130	**26 (14)**	NA

* Task Descriptions for each crop and exposure scenario are provided in Table 7.5

The short/intermediate term endpoint for ETU was used to evaluate non-cancer risks for all of the crop groups and the results are summarized in Table 7.7. Some of the short/intermediate term MOEs for ETU are below 100 at the REI and are of concern. The time needed to achieve an MOE of 100 ranges up to 19 days with the longest time required for western fruit trees.

Table 7.7 - ETU Postapplication Non-Cancer Risks (Short and Intermediate Term)					
Crop Group	Application Rate (lb a.i./acre)	MOE on Day 0 (Days when MOE > 100)			
		Low*	Medium*	High*	Very High*
Berry, low (Cranberry)	4.8	200	NA	NA	NA
Bunch/bundle (Banana)	2.4	32000	2500	1600	NA
Field/row crops, Low/Medium - West	1.6	52000	3500	NA	NA
Field/row crops, Low/Medium - East	1.6	49000	3200	NA	NA
Field/Row crop, tall (Corn) - West	1.2	NA	17000	6900	410
Field/Row crop, tall (Corn) - East	1.2	NA	16000	6500	380
Flowers, cut	1.2	2600	1600	900	NA
Ornamental Plants	1.2	59000	37000	16000	NA
Tree, fruit, deciduous - West	2.4	150	NA	**49 (19)**	NA
Tree, fruit, deciduous - East	2.4	160	NA	**54 (8)**	NA
Tree, fruit, evergreen (Papaya)	2	3900	1300	NA	NA
Tree, nut (Almond)	6.4	110	NA	NA	NA

Table 7.7 - ETU Postapplication Non-Cancer Risks (Short and Intermediate Term)					
Crop Group	**Application Rate (lb a.i./acre)**	**MOE on Day 0 (Days when MOE > 100)**			
		Low*	**Medium***	**High***	**Very High***
Turf - California	17.4	14000	NA	410	NA
Turf - North Carolina	17.4	81000	NA	2500	NA
Turf - Pennsylvania	17.4	110000	NA	3400	NA
Vegetable, Brassica - West	1.6	2600	1300	1000	NA
Vegetable, Brassica - East	1.6	2400	1200	970	NA
Vegetable, Cucurbit - West	1.6	10000	3500	2100	NA
Vegetable, Cucurbit - East	1.6	9700	3200	1900	NA
Vegetable, fruiting - West	1.6	10000	7400	5200	NA
Vegetable, fruiting - East	2.4	6500	4600	3200	NA
Vegetables, leafy - West	1.6	10000	3500	2100	NA
Vegetables, leafy - East	1.6	9700	3200	1900	NA
Vegetable, root - West	2.4	12000	2300	1400	NA
Vegetable, root - East	2.4	11000	2200	1300	NA
Vine/trellis (Grapes) - West	2.0	4500	2100	430	NA
Vine/trellis (Grapes) - East	3.2	240	120	**24 (17)**	NA

*Task descriptions for each crop and exposure scenario are included in Table 7.5

The long term endpoint for ETU was also used to evaluate non-cancer risks for the two crop groups that are thought to have long term exposures (greenhouse tomatoes and cut flowers). With the exception of the cut flower scenario (which includes hand harvesting, pruning and thinning), all of the ETU MOEs are greater than 100 on day 0. The MOE for the cut flower scenario rises to 100 on day 18. These results are presented in Table 7 8

Table 7.8 - ETU Postapplication Long term Non-Cancer Risks					
Crop Group	**Application Rate (lb ai/acre)**	**Long term MOE on Day 0 (Days when MOE >100)**			
		Low*	**Medium***	**High***	**Very High***
Greenhouse Cut Flowers	1.2	110	**68 (7)**	**39 (18)**	NA
Greenhouse Ornamental Plants	1.2	2500	1500	680	NA
Greenhouse Tomatoes	2.4	270	190	140	NA

*Task descriptions for each crop and exposure scenario are included in Table 7.5

The cancer risks derive solely from ethylene thiourea (ETU) which is an environmental degradate and metabolite of maneb. The ETU dose was calculated in the same manner as for non cancer risks included both directly absorbed ETU and ETU that was metabolically converted from maneb. Cancer risks were calculated from the average daily dose in the same manner as to handlers.

The cancer risk calculations for maneb postapplication workers are summarized in Table . Cancer risks for were calculated assuming thirty days of exposure per year. With the exception of deciduous fruit trees and grapes, 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 two to >84 days (for western fruit trees) after application. It was not possible to accurately calculate residue dissipation for periods longer than the length of the respective DFR studies (i.e. 84 days for western fruit trees) because the measured DFR values towards the end of the study were close to the LOQ and/or the negative controls.

Table 7.9 - Maneb Postapplication Cancer Risks (30 days per year)

Crop Group	Application Rate (lb a.i./acre)	Cancer Risk on Day 0 (Days when cancer risk <1e-06)			
		Low*	Medium*	High*	Very High*
Berry, low (Cranberry)	3	3e-05 (42)	NA	NA	NA
Bunch/bundle (Banana)	2.4	0	4e-06 (>22)	7e-06 (>22)	NA
Field/row crops, Low/Medium - West Field/row crops, Low/Medium - East	1.6 1.6	2e-07 2e-07	3e-06 (>28) 3e-06 (>22)	NA NA	NA NA
Field/Row crop, tall (Corn) - West Field/Row crop, tall (Corn) - East	1.2 1.2	NA NA	6e-07 7e-07	2e-06 (9) 2e-06 (9)	3e-05 (>30) 3e-05 (>22)
Flowers, cut	1.2	4e-06 (>22)	7e-06 (>22)	1e-05 (>22)	NA
Ornamental Plants	1.2	2e-07	3e-07	7e-07	NA
Tree, fruit, deciduous - West	3.6	1e-04 (>84)	NA	**2e-04 (>84)**	NA
Tree, fruit, deciduous - East	3.6	1e-04 (>42)	NA	**2e-04 (>42)**	NA
Tree, fruit, evergreen (Papaya)	2	3e-06 (20)	8e-06 (>22)	NA	NA
Tree, nut (Almond)	3.1	5e-05 (>84)	NA	NA	NA
Turf - California Turf - North Carolina Turf - Pennsylvania	17.4 17.4 17.4	3e-07 1e-07 9e-08	NA NA NA	3e-05 (>14) 4e-06 (>14) 3e-06 (>14)	NA NA NA

Table 7.9 - Maneb Postapplication Cancer Risks (30 days per year)					
Crop Group	**Application Rate (lb a.i./acre)**	**Cancer Risk on Day 0 (Days when cancer risk <1e-06)**			
		Low*	**Medium***	**High***	**Very High***
Vegetable, Brassica - West Vegetable, Brassica - East	1.6 1.6	4e-06 (>28) 4e-06 (>22)	8e-06 (>28) 9e-06 (>22)	1e-05 (>28) 1e-05 (>22)	NA NA
Vegetable, Cucurbit - West Vegetable, Cucurbit - East	1.6 1.6	1e-06 1e-06	3e-06 (>28) 3e-06 (>22)	5e-06 (>28) 6e-06 (>22)	NA
Vegetable, fruiting - West Vegetable, fruiting - East	1.4 1.4	1e-06 1e-06	1.2e-06 (4) 1.3e-06 (6)	2e-06 (12) 2e-06 (12)	NA NA
Vegetables, leafy - West Vegetables, leafy - East	1.6 1.6	1e-06 1e-06	3e-06 (>28) 3e-06 (>22)	5e-06 (>28) 6e-06 (>22)	NA NA
Vegetable, root - West Vegetable, root - East	2.4 2.4	9.2e-07 9.8e-07	5e-06 (>28) 5e-06 (>22)	8e-06 (>28) 8e-06 (>22)	NA NA
Vine/trellis (Grapes) - West Vine/trellis (Grapes) - East	1.8 2.1	2e-06 (34) 3e-05 (41)	5e-06(64) 6e-05(>42)	2e-05 (>80) **3e-04 (>42)**	NA NA

*Task descriptions for each crop and exposure scenario are included in Table 7.5
Bold = Cancer Risk Exceeds 1e-04 on Day Zero

A summary of all the occupational post-application risks for maneb is included in Table 7.10. Current label requirements specify 24 hour REIs. In some of the scenarios, the MOEs for maneb do not exceed the required uncertainty factor of 100 at the REI. To a lesser extent the MOEs for ETU also do not exceed 100 at the REI. A few of the scenarios also have cancer risks that exceed $1.0x10^{-4}$ on Day 1, however, the cancer risks are generally less severe than the maneb non-cancer risks, particularly if 1.0×10^{-4} is chosen as a risk target.

Table 7.10- Summary of Maneb Post-application Risks of Concern	
Crop Group	**Risks of Concern on Day 1 (which is the REI)**
Field/Row crop, tall (Corn)	Maneb non-cancer risk for sweet corn harvesting and seed corn detasseling.
Flowers, cut	ETU long term risk for medium exposure tasks (irrigation, scouting mature/high foliage plants) and high exposure tasks (hand harvesting, pruning, thinning and pinching).
Tree, fruit, deciduous	Maneb non-cancer risks for high exposure tasks (pruning and thinning). ETU non-cancer risks for high exposure tasks. Cancer risks for high exposure tasks.
Vine/trellis (Grapes) - West	Maneb non-cancer risk for high exposure tasks (leaf pulling, thinning, pruning and training/tying)

Table 7.10- Summary of Maneb Post-application Risks of Concern	
Crop Group	**Risks of Concern on Day 1 (which is the REI)**
Vine/trellis (Grapes) - East	Maneb and ETU non-cancer risks for high exposure task Cancer risks for high exposure tasks.

7.3 Incident Data Review

There were no incidents reported in the OPP Incident Data System from 1992 to 2001. There were 37 exposures reported to the Poison Control Centers (1993-1998) and 24 received follow-up to determine medical outcome. Ten experienced no symptoms and 14 experienced minor symptoms, primarily nausea and diarrhea. There were four reports of dermal effects and three were considered to be related to maneb exposure. There were 18 cases reported in the California Pesticide Illness Surveillance Program (1982-1999) in which maneb was used alone or was judged to be responsible for the health effects. Most of these cases (12) involved postapplication exposure to field residues, and the most common effect was skin rashes. The reports in the literature also indicated that maneb causes skin sensitization.

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 maneb reregistration. Although not specifically required, a turf transferable residue study (TTR) for maneb would be useful to refine estimated risks to toddlers playing on treated turf. In addition, an acceptable DFR study on apples is needed, because currently available data overestimate postapplication risks for apples.

<u>Toxicology</u>
Developmental toxicity, rabbit [870.3700].
Subchronic inhalation toxicity, rat [870.3465].
Developmental neurotoxicity, rat [870.6300].
Comparative thyroid assay between young and adult animals [Special Study].

<u>Residue Chemistry</u>

860.1200	Directions for use.
860.1380	Storage stability data, plants.
860.1500	Crop field trials [potato, turnip tops, green onions, endive, head and leaf lettuce, loose-head Chinese cabbage, collards, kale, mustard greens, nonbell pepper, apple, cranberry, almond hull, popcorn grain and stover, sweet corn (K + CWHR, forage and stover), banana, fig, papaya, and seed treatment (barley, field corn, cotton, flax, oats, peanuts, rice, rye, safflower, sorghum, wheat).

860.1520 Processing studies [apple, fig and potato].
860.1850 Confined Rotational Crop Study.

Product Chemistry
There are data gaps for the Cerexagri 86% FI; refer to the product chemistry chapter for details.

9.0 Supporting Documents

1) Third Report of the Hazard Identification Assessment Review Committee, 04/02/03, L. Taylor, TXR NO. 0051764.
2) Toxicology Chapter for the Maneb RED, 3/08/00, L. Taylor, DP Barcode D251397.
3) Outcome of the HED Metabolism Assessment Review Committee Meeting of 1/16/02, C. Swartz, 12/3/02, TXR # 0050408.
4) Maneb. Revised Product and Residue Chemistry Chapters of the HED RED. June 2005, F. Fort
5) Maneb. Revised Anticipated Residues for Dietary Exposure Assessment. F. Fort and W. Hazel, 10/12/04, DP Barcode No. D305870.
6) Maneb and Ethylenethiourea. Revised Acute/Probabilistic, Chronic and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision, F. Fort, June 2005, DP Barcode No. D295410.
7) Mancozeb, Maneb, and Metiram: Processing and Cooking Factors for Use in Dietary Exposure Assessments to Support Reregistration, C. Olinger, 11/05/03, DP Barcode D289569, D289570, and D289571.
8) 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.
9) Occupational and Residential Exposure Aspects of the Maneb RED, T. Dole, June 2005, DP Barcode No. D295411.
10) Revised Incident Report, 12/17/02, J. Blondell and M. Spann, D286185.
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 Maneb, F. Hernandez, 12/2/02.
13) Screening Level Usage Analysis, J. Carter, 3/31/05.

Appendix 1. 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, maneb, mancozeb and metiram, 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 February 20, 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 cerbellum 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.

Appendix 1. ETU Hazard Profile, and Doses and Endpoints for Risk Assessment

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 at the lowest dermal dose 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 cerbellum, 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.

Appendix 1. ETU Hazard Profile, and Doses and Endpoints for Risk Assessment.

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.

Appendix 1. ETU Hazard Profile, and Doses and Endpoints for Risk Assessment.

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]	$Q_1^* = 6.01 \times 10^{-2}$ (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

Appendix 2. Maneb Application Rates

Table A2-1. Maneb Agricultural Application Rates.

Crop Group	Crop or Target	Label Application Rates (lb ai/acre)			Average Application Rates (lb ai/acre)	
		Maximum Per Application	Minimum Per Application	Maximum Per Season	Per Application	Per Year
Berry, Low	Cranberries	4.8	2.4	14.4	[illegible]	[illegible]
Bunch, Bundle	Bananas	2.4	1.6	24	[illegible]	[illegible]
Field Crop, Low/Medium	Beans (dry) Sugarbeets	1.6 [illegible]	1.2 1.2	9.6 [illegible]	[illegible]	[illegible]
Field/Row Crop, Tall	Sweet Corn, Popcorn, Sweet Corn for seed	-	0.4	18 East of West	[illegible]	[illegible]
Ornamentals	Variety	[illegible]	0.43	NA	[illegible]	[illegible]
Tree, Fruit, Deciduous	Apples: Prebloom Apples: Extended	4.8 2.4	NA NA	19.2 16.8		[illegible]
	Kadota Figs	2.4	NA	2.4	[illegible]	[illegible]
Tree, Fruit, Evergreen	Papayas	2	1.6	28	ND	ND
Tree, Nut	Almonds	6.4	4.8	[illegible]	[illegible]	[illegible]
Turf	Sod Farms	17.4	3	NA	ND	NA
Vegetable, Brassica	Broccoli/Brussel Sprouts Cauliflower Cabbage Chinese Cabbage/Kohlrabi	[illegible] [illegible]	1.2 [illegible] 1.2 1.2	[illegible]	[illegible]	[illegible]
Vegetables, Cucurbit	Cucumbers Eggplant Melons: cantaloupes Melons: honeydew Melons: watermelon Pumpkin Squash	1.6 1.6 1.6 1.6 1.6 1.6 1.6	[illegible] [illegible] [illegible] 0.72 1.2 1.2	[illegible]	[illegible]	[illegible]
Vegetable, Fruiting	Peppers: West of Miss. Peppers: East of Miss. Tomatoes: West of Miss. Tomatoes: East of Miss	1.6 2.4 1.6 2.4	1.2 1.2 1.2 1.2	[illegible]	[illegible]	[illegible]
Vegetable, Leafy	Collards Kale Lettuce Mustard Greens Turnip Tops	1.2 1.6 1.6 1.2 1.2	NA 1.12 1.2 NA NA	[illegible]	ND [illegible]	NA
Vegetable, Root	Garlic Onions (dry bulb) Onions (green) Potatoes	2.4 2.4 2.4 1.6	1.6 1.6 1.6 1.2	[illegible] 11.2	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]
Vine/Trellis	Grapes: West Grapes: East	2.0 3.2	1.2 1.2	6 19.2	[illegible] [illegible]	[illegible] [illegible]

1 - National Cranberry Institute Data.
2 - Maneb Usage Comparisons, Elf Atochem memo of April 23, 1999.
3 - For leafy vegetables, rates are lb ai/cutting. EPA QUA report of December 2, 2002.
4 - CA DPR Data: 1993 to 2001.
5 - NASS data: Fruits (1993 to 2001), Vegetables (1992 to 2000), Field Crops (1993 to 2001), Floriculture and Nursery (2000).

6 - Rates for ornamentals are given in lbs ai/100 gallons and were converted to lb ai/acre by assuming that 100 gallons of spray would be applied per acre.
7 - Use is limited to cut cultivated greens per 2000 NASS Floriculture and Nursery Survey.
ND - No data available.

Table A2-2. Maneb Application Rates for Seed and Seed Piece Treatment.	
Seed or Seed Piece Type	**Max Appl. Rate (lb ai per cwt)**
barley	0.2
corn (field)	0.27
cotton (acid delinted)	0.15
cotton (reginned)	0.3
flax	0.35
oat	0.31
peanut (shelled)	0.8
potato seed pieces	0 08
rice	0 2
rye	0 18
safflower	0.1
sorghum	0.23
soybean	0.06
tomato	0.4
wheat	0.16
Note - 1 cut weight (cwt) equals 100 pounds	

Appendix 3. Tolerance Reassessment Summary

Maneb tolerances are established under 40 CFR §180.110(a) and §180.110(b). The permanent tolerances listed under 40 CFR §180.110(a) are expressed in terms of the residues of the fungicide maneb (manganese ethylenebisdithiocarbamate), calculated as zinc ethylenebisdithiocarbamate. The time-limited tolerance listed in 40 CFR §180.110(b) is currently expressed in terms of the residues of maneb and its metabolite ethylenethiourea (ETU

The only established maneb tolerances are for plant commodities. No maneb tolerances have yet been established in livestock or processed food/feed commodities. The Agency is now recommending that maneb tolerances also be established in livestock commodities. Based on a reevaluation of the available plant and livestock metabolism studies, the Agency has reaffirmed that the residues of toxicological concern, i.e. to be included in risk assessment, are the parent EBDC (including maneb) and ETU (MARC decision dated 2/28/03; D288607, -08, and -09, C. Swartz). For regulatory/enforcement purposes, the Agency recommends that tolerances in plant and livestock commodities at 40 CFR §180.110(a) be established for residues of maneb per se. HED has further proposed that EBDC (including maneb) tolerances be calculated as carbon disulfide rather than as zineb.

Since issuance of the Maneb Update, the Agency has updated the list of raw agricultural and processed commodities and feedstuffs derived from crops (Table 1, OPPTS GLN 860.1000). As a result of changes to Table 1 maneb tolerances for certain RACs that have been removed from the livestock feeds table need to be revoked. Also, some commodity definitions must be corrected. A summary of maneb tolerance reassessments is presented in Table V.

Tolerances Listed Under 40 CFR §180.110(a)

Sufficient data have been submitted (or were translated when appropriate) to reassess the established tolerances in/on the following commodities, pending label amendments for some crops: almonds; beans (dry form); broccoli; Brussels sprouts; cabbage; cauliflower; cucumbers; eggplant; grapes; kohlrabi; melons; onions (bulb); pumpkins; sugar beet tops; summer squash; winter squash; and tomatoes.

Insufficient data are available to reassess the established tolerances in/on the following commodities: apples; bananas; Chinese cabbage; collards; cranberries; endive (escarole); figs; kale; lettuce; mustard greens; onions (green); papayas; peppers; potatoes; sweet corn (kernels plus cob with husk removed); and turnip tops.

The established tolerances in/on the following commodities should be revoked since maneb uses on certain crops were disallowed for reregistration as per EBDC PD 4: apricots; beans (succulent form); carrots; celery; nectarines; and peaches.

A maneb tolerance for garlic has also not been established and need not be proposed. In accordance with 40 CFR §180.1, the reassessed tolerance for onions (dry bulb) may apply to

garlic; the registered use patterns of maneb on garlic and onions (dry bulb) are identical.

Tolerances To Be Proposed Under 40 CFR §180.110(a)

A tolerance is required and must be proposed in "beet, sugar, root" based on the available field trial data.

Tolerances are required and must be proposed in/on the following commodities after adequate field trial data have been submitted and evaluated: almond, hulls; corn, pop, grain; corn, pop, stover; corn, sweet, forage; and corn, sweet, stover.

A tolerance in "beet, sugar, pulp, dried" needs to be proposed based on the results of an acceptable sugar beet processing study. The processing studies submitted for grapes and tomatoes indicate that residues of maneb and ETU did not concentrate in the respective processed commodities of these crops. The requirements for processing studies on apples, figs, and tomatoes remain outstanding, and the Agency will assess the need for tolerances in the processed commodities of these crops when the requested studies have been submitted.

Field residue data and tolerances in/on cowpea forage and hay will not be required provided labels are amended such that maneb use on beans specifically exclude cowpeas.

Tolerances in eggs, milk, and the fat, meat byproducts, and meat of cattle, goats, hogs, horses, poultry, and sheep must be proposed based on the results of reviewed livestock metabolism studies.

Additional data are required to support use of maneb on crops with seed or propagation stock treatments. Tolerances must be proposed that reflect either the maximum expected residue levels or, if no measurable residues are detected, the limit of quantitation of the analytical method.

Tolerances Listed Under 40 CFR §180.110(b)

Sufficient data have been submitted to reassess the established time-limited tolerance in walnuts associated with a Section 18 registration. The available data support establishment of a permanent tolerance in walnuts currently proposed.

Table A3-1. Tolerance Reassessment Summary for Maneb.

Commodity	Established Tolerance (ppm)	Reassessed Tolerance [1] (ppm)	Comment (Correct commodity terminology)
Tolerances Listed Under 40 CFR §180.110 (a)			
Almonds	0.1	0.1	[*Almond, nutmeat*]
Apples	[illegible]	TBD [2]	Additional apple field trial data are required. [*Apple*]
Apricots	10	Revoke	Disallowed for reregistration.
Bananas (not more than 0.5 ppm) shall be in the pulp after peel is removed and discarded (preharvest application only)	4	TBD	Additional banana field trial data and submissions of foreign label are required. [*Bananas, whole (Pre-H)*]
Beans (dry form)	7	2.5	[*Bean, dry*]
Beans (succulent form)	10	Revoke	Disallowed for reregistration.
Broccoli	10	6	
Brussels sprouts	10	6	Translated from broccoli data.
Cabbage	10	21	
Chinese cabbage	10	TBD	Additional field trial data are required. [*Cabbage, Chinese*]
Carrots	7	Revoke	Disallowed for reregistration
Cauliflower	10	6	Translated from broccoli data
Celery	5	Revoke	Disallowed for reregistration
Collards	10	TBD	Additional field trial data on collards are required.
Cranberries		TBD	Additional cranberry field trial data are required. [*Cranberry*]
Cucumbers	4	2.0	[*Cucumber*]
Eggplants	7	2.5	Translated from tomato data. [*Eggplant*]
Endive (escarole)	10	TBD	To be translated from data requested for leaf lettuce.
Figs	7	TBD	[*Fig*]
Grapes	7	2.5	[*Grape*]
Kale	10	TBD	
Kohlrabi	10	6	Translated from broccoli data.
Lettuce	10	TBD	Additional field trial data on head lettuce are required. [*Lettuce, head*]
		TBD	Additional field trial data on leaf lettuce are required. [*Lettuce, leaf*]
Melons	4	3	
Mustard greens	10	TBD	Additional field trial data on mustard greens are required.
Nectarines	10	Revoke	Disallowed for reregistration.
Onions	7	6	[*Onion, bulb*]

(continued) Footnotes follow.

Table A3-1 *(continued)*.

Table A3-1. Tolerance Reassessment Summary for Maneb.			
Commodity	Established Tolerance (ppm)	Reassessed Tolerance [1] (ppm)	Comment *[Correct Commodity Definition]*
		TBD	[*Onion, green*]
Papayas	10	TBD	Additional papaya field trial data are required. [*Papaya*]
Peaches	10	Revoke	Disallowed for reregistration.
Peppers	7	TBD	Additional field trial data on non-bell peppers are required. [*Pepper, bell and non-bell*]
Potatoes	0.1	TBD	Additional potato field trial data are required. [*Potato*]
Pumpkins	7	3	Translated from melon data. [*Pumpkin*]
Sugar beet tops	45	120	[*Beet, sugar, tops*]
Summer squash	4	2.0	Translated from cucumber data. [*Squash, summer*]
Winter squash	4	3	Translated from melon data. [*Squash, winter*]
Sweet corn (kernels plus cob with husk removed)	5	TBD	[*Corn, sweet (K + CWHR)*]
Tomatoes	4	2.5	[*Tomato*]
Turnip roots	7	Revoke	Turnips grown for roots may not be treated.
Turnip, tops	10	TBD	Additional field trial data on turnip tops are required.
Tolerances To Be Proposed Under 40 CFR §180.110 (a) [2]			
Almond, hulls	None	TBD	Additional field trial data on almond hulls are required.
Beet, sugar, root	None	1.2	
Beet, sugar, pulp, dried	None	2.5	
Cattle, fat	None	0.02	
Cattle, mbyp	None	0.02	
Cattle, meat	None	0.02	
Corn, pop, grain	None	TBD	To be translated from data requested for sweet corn (K + CWHR).
Corn, pop, stover	None	TBD	To be translated from data requested for sweet corn stover.
Corn, sweet, forage	None	TBD	
Corn, sweet, stover	None	TBD	
Eggs	None	0.02	

(continued; footnotes follow)

Table A3-1 *(continued)*

Table A3-1. Tolerance Reassessment Summary for Maneb.			
Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comment *[Correct Commodity Definition]*
Cattle, fat	None	0.02	
Cattle, mbyp	None	0.02	
Cattle, meat	None	0.02	
Goats, fat	None	0.02	
Goats, mbyp	None	0.02	
Goats, meat	None	0.02	
Hogs, fat	None	0.02	
Hogs, mbyp	None	0.02	
Hogs, meat	None	0.02	
Horses, fat	None	0.02	
Horses, mbyp	None	0.02	
Horses, meat	None	0.02	
Milk	None	0.02	
Poultry, fat	None	0.02	
Poultry, mbyp	None	0.02	
Poultry, meat	None	0.02	
Sheep, fat	None	0.02	
Sheep, mbyp	None	0.02	
Sheep, meat	None	0.02	
Tolerance Listed Under 40 CFR §180.110 (b)			
Walnuts	0.05	0.03	Expiration/revocation date 12/31/03 associated with a Sec. 18*[Walnut]*

[1] The reassessed tolerances are for the residues of maneb expressed as carbon disulfide, per se, and are contingent upon the recommended label revisions outlined in Table B.

[2] TBD = To be determined. Reassessment of tolerance(s) cannot be made at this time because additional data are required.

[3] Does not include tolerances that may be required from use of maneb on crops with seed or propagation stock treatments.

CODEX HARMONIZATION

There are no established or proposed Codex MRLs for residues of maneb *per se*; however, Codex limits for dimethyldithiocarbamates fungicides are grouped under dithiocarbamates. The maximum residue limits (MRLs) for dithiocarbamates are established for several commodities resulting from the use of mancozeb, **maneb**, metiram, propineb, thiram, and ziram and are currently expressed as ppm carbon disulfide. When the tolerance reassessments are finalized U.S. tolerances will be harmonized with Codex MRLs with respect to residue definition. A numerical comparison of the Codex MRLs and the corresponding **reassessed** U.S. tolerances for maneb is presented in Table A3-2.

Table A3-2. Codex MRLs for dithiocarbamates[1] and applicable U.S. tolerances for maneb. Recommendations are based on conclusions following reassessment of U.S. tolerances (see Table A3-1).

Codex		Reassessed U.S. Maneb Tolerance, ppm	Comments
Commodity, As Defined	MRL (mg/kg)		
Almond hulls	20	To be determined (TBD)	*Source of Codex data:* *maneb, ziram*
Almonds	0.1 (*)	0.1	US tolerance and Codex MRL are now harmonized *Source of Codex data:* maneb, ziram
Asparagus	0.1	Not supported for reregistration	*Source of Codex data:* mancozeb
Banana	2	TBD	*Source of Codex data:* mancozeb
Barley	1	Not supported for reregistration	*Source of Codex data:* mancozeb
Barley straw and fodder, dry	25		*Source of Codex data:* mancozeb, maneb
Cabbages, head	5	21	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb, maneb
Carrot	1	Revoke	*Source of Codex data* mancozeb
Cherries	1	Not supported for reregistration	*Source of Codex data.* thiram
Cos lettuce	10	TBD	*Source of Codex data:* maneb
Cranberry	5	TBD	*Source of Codex data:* mancozeb
Cucumber	2	2.0	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb, maneb
Currants, black, red, white	10	Not supported for reregistration	*Source of Codex data:* mancozeb, metiram
Edible offal (mammalian)	0.1	0.02	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb, metiram

(*continued; footnotes follow*)

Table A3-2 (*continued*).

Codex		Reassessed U.S. Maneb Tolerance, ppm	Comments
Commodity, As Defined	MRL (mg/kg)		
Eggs	0.05 (*)	0.02	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb
Garlic	0.5	6 for bulb onions	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb
Grapes	5	2.5	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb, metiram, maneb, propineb
Hops, dry	30	Not supported for reregistration	*Source of Codex data:* metiram
Kale	15	TBD	*Source of Codex data:* mancozeb, maneb
Leek	0.5	TBD	*Source of Codex data:* mancozeb
Lettuce, head	10	TBD	*Source of Codex data:* mancozeb, maneb, metiram
Maize fodder	2	TBD	*Source of Codex data:* mancozeb
Mandarins	10	Not supported for reregistration	*Source of Codex data:* mancozeb
Mango	2		*Source of Codex data:* mancozeb
Meat (from mammals other than marine mammals)	0.05 (*)	0.02	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb, metiram
Melons, except watermelon	0.5	3.0	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb, propineb
Milks	0.05 (*)	0.02	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb, metiram
Onion, bulb	0.5	6	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb, propineb
Oranges, sweet, sour	2	Not supported for reregistration	*Source of Codex data:* mancozeb
Papaya	5	TBD	*Source of Codex data:* mancozeb
Peanut	0.1 (*)	Not supported for reregistration	*Source of Codex data:* mancozeb
Peanut fodder	5		*Source of Codex data:* mancozeb
Pepper, sweet	1	TBD	*Source of Codex data:* mancozeb, maneb

(continued; footnotes follow)

Table A3-2 *(continued)*.

Codex		Reassessed U.S. Maneb Tolerance, ppm	Comments
Commodity, As Defined	MRL [2] (mg/kg)		
Plums (including prunes)	1	Not supported for reregistration	*Source of Codex data:* thiram
Pome fruits	5	TBD for apples	*Source of Codex data:* mancozeb, metiram, propineb, thiram, ziram
Potato	0.2	TBD	*Source of Codex data:* mancozeb, maneb, metiram
Poultry meat	0.1	0.02	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb
Poultry, edible offal of	0.1	0.02	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb
Pumpkins	0.2	3.0	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb
Spring onion	10	TBD	*Source of Codex data:* maneb
Squash, summer	1	3.0	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb
Sugar beet	0.5	1.2	Use pattern in US supports the higher tolerance *Source of Codex data:* mancozeb maneb
Sugar beet leaves or tops	20	120	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb, maneb
Sweet corn (corn-on-the-cob)	0.1 (*)	TBD	*Source of Codex data:* mancozeb
Tomato	5	2.5	Use pattern in US supports the lower tolerance. *Source of Codex data:* mancozeb, maneb, metiram, propineb
Watermelon	1	5.0 for melons	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb, maneb
Wheat	1	Not supported for reregistration	*Source of Codex data:* mancozeb, maneb, metiram
Wheat straw and fodder, dry	25		*Source of Codex data:* mancozeb, maneb, metiram
Winter squash	0.1	3.0	Use pattern in US supports the higher tolerance. *Source of Codex data:* mancozeb

(continued; footnotes follow)

Table A3-2 (*continued*).

[1] Plant and animal commodities, maximum residue limits (MRLs), and source of data for residues of dithiocarbamates and ethylene thiourea (ETU) were obtained from a search conducted on 2/9/00 of the FAO STAT Database, Codex Alimentarius Pesticide Residues in Food (http://apps1.fao.org/servlet/org.fao.waicent.codex.PesticideServlet).

[2] All MRLs are at CXL step. An asterisk (*) signifies that the MRL was established at or about the limit of detection.

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