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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

June 14, 2007

MEMORANDUM

SUBJECT: Ethylenethiourea (ETU) from EBDCs: Health Effects Division (HED) Human Health Risk Assessment of the Common Metabolite/Degradate ETU
PC Code : 600016, DP Barcode: D337241.
Regulatory Action: *Registration Action*
Risk Assessment Type: *Aggregate*

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The attached human health risk assessment is for ethylene thiourea (ETU), which is the common metabolite/degradate of the ethylene bisdithiocarbamate (EBDC) fungicides mancozeb, maneb and metiram. Several new uses for mancozeb and metiram have been proposed, requiring an update of the most recent ETU aggregate assessment conducted by Christine Olinger (D317416, 6/8/05) in support of the reregistration of the EBDCs. This risk assessment summarizes human health risks from exposure to ETU resulting from all registered and proposed uses of the parent EBDCs and supersedes all previous assessments.

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1.0 Executive Summary

Use Profile

Ethylene thiourea (ETU) is a degradate/metabolite of the ethylene bisdithiocarbamate (EBDC) fungicides mancozeb, maneb and metiram. The EBDCs are used on agricultural crops such as vegetables, fruits and nuts, on turf including golf courses and sod farms, and on ornamentals including cut flowers. The EBDCs are broad spectrum contact fungicides used to prevent a variety of fungal diseases.

Updated human health risk assessments have been conducted for mancozeb and metiram to account for proposed new uses. The proposed Section 3 uses for mancozeb are for use on almonds, broccoli, cabbage, lettuce (head and leaf), and pepper (bell and non-bell). Import tolerances on bananas and grapes were proposed for metiram. No new uses for maneb have been proposed; therefore, an updated risk assessment for maneb is not necessary at this time. The mancozeb and metiram risk assessments include exposures and risks from ETU derived from the individual EBDC.

The purpose of this assessment is to provide information on aggregate exposure and risk from ETU as a result of all EBDC usage, to describe risks from all three EBDCs in broad terms, and to identify significant sources of exposure and risk.

Sources of ETU

Crops treated with EBDCs may contain both EBDC and ETU residues; in addition, cooking and/or processing may result in conversion of EBDC residues to ETU, or in concentration or reduction of existing ETU residues. Therefore, both EBDC and ETU residues may be consumed in the diet. During application of EBDCs, workers may be exposed to ETU residues which form during degradation of the tank mix over a typical workday, and the Agency has data to reflect these potential exposures. Additional exposure to both EBDCs and ETU may occur during activities conducted in and around growing crops following treatment with EBDCs. Metabolic conversion of absorbed EBDC to ETU occurs and has been accounted for in calculating ETU doses.

Hazard Assessment

The toxicology 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 and the nervous system are targets for ETU. Thyroid toxicity in subchronic and chronic rat, mouse, and dog studies included decreased levels of T_4 (serum thyroxin), increases or decreases in T_3 (triiodothyronine), compensatory increases in levels of the thyroid stimulating hormone (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 of the fetuses because they occurred at a dose that caused minimal maternal toxicity (decreased food consumption and body weight gain).

Although the data provided evidence for increased susceptibility to fetuses following dosing with ETU, HED determined that the degree of concern or uncertainty for the qualitative susceptibility is low because the developmental 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.

The submitted data do not support the reduction or removal of the 10X Food Quality Protection Act safety factor (FQPA SF) due to the absence of required toxicological studies. HED has retained a 10X FQPA safety factor for ETU dietary, residential and aggregate risk assessments.

The doses and endpoints used for ETU are listed below. For acute ETU exposures, developmental effects were selected as the most sensitive endpoint. This same endpoint was also used for short and intermediate term exposures. For chronic exposures, the endpoint was based upon thyroid effects that were observed in the chronic dog study. ETU was classified as a probable human carcinogen based upon liver tumors observed in female mice and a unit risk value, Q_1*, of 0.0601 $(mg/kg/day)^{-1}$ was used for risk assessment.

Exposure Route, Duration	ETU Dose in mg/kg/day (study/effects)
Acute dietary (females 13-49)	NOAEL of 5 (Developmental rat/developmental brain defects)
Chronic dietary (gen. U.S. pop.)	NOAEL of 0.18 (Chronic dog/thyroid toxicity)
Incidental oral, short/int.-term (toddlers)	NOAEL of 7 (4-week Dog/thyroid toxicity)
Oral, short/int.-term (females 13-49)	NOAEL of 5 (Developmental rat/developmental brain defects)
Dermal, short/int.-term (toddlers)	NOAEL of 7 (4-week Dog/thyroid toxicity)
Dermal, short/int.-term (females 13-49)	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)

[NOAEL= No observed adverse effect level. Combined Uncertainty factors (UFs) for ETU occupational assessments are 100x; combined UFs for residential and dietary assessments are 1000x. Dermal absorption for ETU is 26%, while inhalation absorption is 100%. Dermal and inhalation exposures can be combined, since the toxic effects from these two routes of exposure are similar for similar durations.]

Drinking Water Exposure

The OPP Environmental Fate and Effects Division (EFED) prepared a drinking water exposure assessment for ETU. 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 ETU surface water estimated drinking water concentrations (EDWCs) were generated using a combined monitoring/modeling approach. The monitoring data were from a targeted surface water monitoring study conducted by the ETU Task Force, in which none of the tested water samples had concentrations above the limit of detection of 0.1 ppb. A ground water EDWC was selected from a targeted ground water monitoring

study conducted in a known EBDC use area in Florida. Acute surface water estimates were reported as a range of 0.1 ppb (monitoring) to 25.2 ppb (modeling) and chronic/cancer surface water estimates were 0.1 ppb (monitoring). Ground water estimates were 0.21 ppb (monitoring) for all durations of exposure.

Dietary Exposure and Risk Analysis

Both EBDC and ETU residues may be consumed in the diet. In this assessment the ETU food residues from each of the EBDCs are aggregated. For the acute, chronic and cancer dietary assessments, field trial or monitoring data from the EBDC/ETU Market Basket Survey, percent crop treated information, and extensive processing study results were used for existing uses. Dietary inputs for the proposed new uses and tolerances included field trial data, processing factors, projected percent crop treated information (for the proposed mancozeb new uses), and percent imported information (for the proposed metiram tolerances).

A probabilistic acute aggregate dietary assessment was conducted for ETU derived from metiram, mancozeb, and maneb uses. Aggregated acute dietary exposure and risk estimates for food alone and food and drinking water are below HED's level of concern.

The refined chronic risk estimates are below the HED's level of concern for aggregate exposure to ETU for the general U.S. population and all population subgroups for food alone and food and drinking water.

The aggregate cancer risk estimate associated with exposure to ETU from all EBDCs for both food alone and food and drinking water combined is 3.3×10^{-6} and 3.6×10^{-6}, respectively, for the general U.S. population. The greatest contributors to the dietary exposure for the cancer assessment were bananas and leaf lettuce.

Residential and Recreational Exposures and Risks

No new residential uses were added to the label as part of the current Section 3 requests. There is a potential for home gardener exposure during and after applications to home garden vegetables from the existing uses of the EBDCs. There is also a potential for golfer and toddler post application exposure on golf course turf and transplanted lawns.

The agricultural application rates were used because the rates given on the two home garden product labels for mancozeb conflicted with one another and were generally higher than the agricultural rates. The residential handler Margins of Exposure (MOEs) for ETU from use of mancozeb in gardens were not of concern because they greatly exceed the target MOE of 1000. The cancer risks were also not of concern because they were less than 1×10^{-6}.

The post application risks were also assessed for adult and youth-aged home gardeners. The ETU MOEs exceeded the target MOE of 1000 for both adult and youth home gardeners. The cancer risk for adult home gardeners was less than 1×10^{-6}.

For the ETU aggregate assessment, the turf exposures were assessed for toddlers by assuming the application conditions from the mancozeb and maneb Reregistration Eligibility Decision (RED) documents. Assuming a three day Pre-Harvest Interval (PHI) and two days to harvest, transport and install the turf, all MOEs exceeded 1000 and were not of concern.

Mancozeb is the only EBDC registered for use on golf courses. The turf exposures were assessed for golfers by using the day 0 Turf Transferable Residues (TTR) for short term exposures and the 7 day average TTR for lifetime exposures. The ETU MOE for golfers exceeded the target MOE of 1000 and is not of concern. The golfer cancer risk was 6×10^{-9} assuming that golfers played an average of 1 day per year on mancozeb treated turf.

Aggregate Risks

The aggregate exposures for adults included food, drinking water, golfing, and home gardening, while the aggregate exposures for toddlers include playing on turf, food and drinking water.

Acute aggregate risks were calculated for females 13-49 years old only because an appropriate endpoint for this exposure duration was not identified for other populations. The acute aggregate exposures including food and drinking water were not of concern as the exposure resulted in a risk that was equivalent to 89% of the aPAD at the 99.9th percentile of exposure.

The short term aggregate risks were calculated for adults by aggregating average daily food exposure, chronic drinking water exposure, and the residential exposures. The short term MOEs ranged from 6,100 to 13,000, which are not of concern. For youth gardeners, aggregate risks are not of concern. The aggregate risks for toddlers playing on turf, food, and drinking water are also not of concern.

The chronic aggregate risks were calculated using average food and drinking water exposures and were below HED's level of concern (<100% cPAD). The most highly exposed population subgroup was children 1-2 years old, with aggregate risks of 86% of the cPAD.

The cancer risks were aggregated using the average daily food, drinking water and residential exposures. The aggregate cancer risk for the U.S. population is 3.8×10^{-6}, which exceeds HED's level of concern. HED conducted sensitivity analyses to determine the commodities that provided the most contribution to the ETU exposure. The commodities that are the greatest contributors to ETU exposure are bananas, leaf lettuce, drinking water, turnip greens, grape juice and mangoes. If the proposed tolerance in/on bananas (from metiram applications) is removed from the aggregate, then the aggregate cancer risk does not exceed HED's level of concern. Note that the metiram-derived ETU residue values from crop field trials used in the aggregate assessment are considered to be overestimates. Projected percent crop treated information was not available, so percent imported information was used and it is highly unlikely that all

bananas will be treated. In general, monitoring data on other commodities show much lower residues than field trial data, so actual exposure is likely to be lower.

Occupational Exposure
The occupational aspect of the human health risk assessment has been completed for each of the EBDC fungicides in the risk assessments of the parent compound.

Environmental Justice Considerations
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.ch.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and drinking water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the United States Department of Agriculture (USDA) under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research
This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

Data Gaps
The data gaps for each individual EBDC and the corresponding exposures to ETU are discussed in the risk assessments for each parent compound. The data gaps for ETU, which were previously identified in the 2005 human health risk assessment for the RED, include the following:

Toxicology

- Guideline 870.3800 2-generation reproduction, rat
- Guideline 870.3700 Developmental toxicity, rabbit

• Guideline 870.6300	Developmental neurotoxicity
• Non-guideline	Comparative study for thyroid toxicity in adults and offspring

2.0 Ingredient Profile

ETU is a metabolite, environmental degradate, and cooking byproduct of the EBDC fungicides, metiram, maneb and mancozeb. Technical ethylenethiourea is a crystalline solid with a white to pale green color, and a faint amine odor. It has a melting point of 203-204 °C. ETU is considered soluble in water, with a water solubility of 20,000 ppm at 30 °C, but it is also slightly soluble in methanol, ethanol, ethylene glycol, pyridine, acetic acid and naphtha. When ETU is heated to decomposition, nitrogen and sulfur oxides are emitted.

2.1 Summary of Registered/Proposed Uses

The EBDC fungicides are used on numerous agricultural crops, including vegetables, fruit and nut trees, field and forage crops, and grapes; for seed treatment; on turf, including golf courses, and sod farms; and on ornamental trees, shrubbery, perennials and annuals. The EBDCs are broad spectrum contact fungicides used to prevent a variety of fungal diseases, including downy mildews, anthracnose, rusts, leaf spots, blights, crown rot, molds, cankers, seed rot and seedling damping off. EBDC end-use products are available as wettable powder (WP), dry flowable (DF), dust (D), emulsifiable concentrate (EC), and ready-to-use formulations.

Mancozeb and maneb have the most food uses, while metiram food uses are limited to apples and potatoes, with proposed import tolerances on bananas and grapes. In terms of annual production and uses, mancozeb is the most significant of the EBDCs, with over 6 million pounds of total domestic usage; crops with the largest market in terms of pounds active ingredient (ai) are potatoes, fresh tomatoes and apples. Maneb domestic use is estimated to be over 2 million pounds ai annually; crops with the largest markets in pounds ai are potatoes, peppers (bell and nonbell), and lettuce. Metiram domestic use is estimated at over 600,000 pounds annually, with two-thirds of the production volume applied to apples, and one-third of the production volume applied to potatoes.

Summary Tables 2.1 and 2.3 show the proposed new uses for metiram, and mancozeb, respectively. Table 2.2 shows the future harmonization pattern for grapes grown in Europe.

Table 2.1 Summary of Proposed Uses for Metiram on Bananas and Grapes [1]

Application Timing; Equipment Type [2]	Formulation	Applic. Rate [3]	Max. No. Applic/ Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Bananas (For Use in Central and South America)						
Broadcast spray to established banana crops	Polyram® 80 WG	2.0-2.5 kg/ha	Not specified (NS)	NS	7	Spray mix is to be prepared by adding 0.4 L/ha of Nu Film (surfactant) to water (spray volume not specified) and Polyram® 80 WG. Initial application may be made when disease symptoms first appear and repeated at 8-15 day intervals.
Grapes (For Use in Italy)						
Broadcast spray to established grape orchards	Polyram® DF Fungicide	150-400 g/100 L water	NS	NS	28	When mixed with other formulations, the longest waiting period must be observed. The following varieties may be sensitive to Polyram® DF: Butirra d'Estate, Conference, Coscia, Gentil Bianca, S. Maria and Spadona.
Grapes (For Use in France)						
Broadcast spray to established grape orchards	Polyram® DF Fungicide	2.0-3.5 kg/ha	NS	NS	NS	
Grapes (For Use in Germany)						
Broadcast spray to established grape orchards	Polyram® WG	0.8-3.2 kg/ha	8	NS	56	Do not apply more than 8 applications in producing plantings, of which maximally 4 with decaying flowers until start of maturing (vine stages 68-81, BBCH Code)

[1] Information included in table excerpted directly from proposed label.
[2] Type of application equipment is not specified on the labels.
[3] It could not be determined if the application rates were in terms of product or the active ingredient.

Table 2.2 Label Directions for the Use of Metiram on Grapes Grown in Europe[1]

Country	Product Name	Growth Stage & Season BBCH	No. Applic. per Season[2]	Single Applic. Rate	Implied Max. Seasonal Rate	PHI (days)
Germany[3]	Polyram® DF	15-79	6	2.24 kg ai/ha (2.0 lb ai/A)	13.44 kg ai/ha (12.0 lb ai/A)	56
EU (N+S-EU)[4]	Polyram® DF	15-79	3	1.1 kg ai/ha (1.0 lb ai/A)	3.3 kg ai/ha (2.9 lb ai/A)	56
EU (N+ S-EU)[5]	Polyram® DF	15-79	3	1.8 kg ai/ha (1.6 lb ai/A)	5.4 kg ai/ha (4.8 lb ai/A)	56
France (N + S-EU)	518 01F	60-80	3	1.1 kg ai/ha (1.0 lb ai/A)	3.3 kg ai/ha (2.9 lb ai/A)	35

[1] Information included in table excerpted directly from proposed label.
[2] Minimum retreatment interval is 12 days
[3] Exemplarily listed for a national label direction.
[4] Minimum use rate for metiram in grapes (supports also use of mix formulations)
[5] Future EU harmonized GAP.

Table 2.3 Summary of Proposed Uses for Mancozeb.

Applic. Timing, Type, and Equip.	Formul-ation	Applic. Rate (lb ai/A) [kg ai/ha]	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A) [kg ai/ha]	PHI (days)	Use Directions and Limitations
Broccoli and Cabbage						
Postemergence Broadcast	80% WP	1.6	6 (implied)	9.6	7	Applications are to be made as soon as disease is present. A minimum retreatment interval (RTI) of 7 days is specified.
Lettuce						
Postemergence Broadcast	80% WP	1.6	6 (implied)	9.6	10	Applications are to begin when disease appears. Use limited to all states except CA. A minimum RTI of 7 days is specified.
		1.6	4 (implied)	6.4	14	Applications are to begin when disease appears. Use limited to CA. A minimum RTI of 7 days is specified.
Pepper						
Postemergence Broadcast	80% WP	1.6	6 (implied)	9.6	7	Applications are to begin when disease appears. Use limited to west of the Mississippi River. A minimum RTI of 7 days is specified.

Table 2.3 Summary of Proposed Uses for Mancozeb.						
Applic. Timing, Type, and Equip.	**Formul-ation**	**Applic. Rate (lb ai/A) [kg ai/ha]**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A) [kg ai/ha]**	**PHI (days)**	**Use Directions and Limitations**
		2.4	6 (implied)	14.4	7	Applications are to begin when disease appears. Use limited to east of the Mississippi River. A minimum RTI of 7 days is specified.
Almond						
Postemergence Broadcast Ground or aerial	80% WP	4.8	3 (implied)	14.4	Last applic. to be made no later than 5 weeks after petal fall	Applications are to begin at the dormant to popcorn growth stages and continue with a minimum 7-day retreatment interval. A non-ionic surfactant or spreader sticker is to be added to the spray solution. Aerial applications are to be made in a minimum of 10 gal/A. The grazing of livestock in treated areas is prohibited.

2.2 Structure and Nomenclature

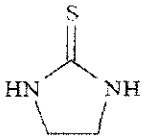
Table 2.4 ETU Test Compound Nomenclature	
Compound	
Common name	Ethylenethiourea (ETU)
Empirical formula	$C_3H_6N_2S$
Molecular weight	102.2
CAS registry number	96-45-7

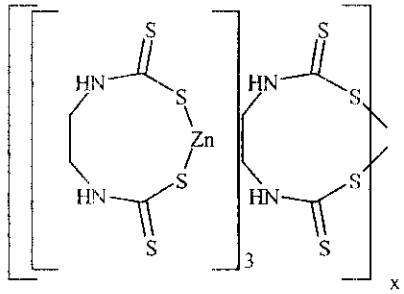
Table 2.5 Metiram Test Compound Nomenclature	
Compound	
Empirical Formula	$(C_{16}H_{33}N_{11}S_{16}Zn_3)_x$
Common name	Metiram
IUPAC name	zinc ammoniate ethylenebis(dithiocarbamate)-poly(ethylenethiuram disulfide)
CAS name	mixture of 5.2 parts by weight of ammoniates of [ethylenebis(dithiocarbamato)]zinc with 1 part by weight ethylenebis [dithiocarbamic acid] bimolecular and trimolecular cyclic anhydrosulfides and disulfides
CAS registry number	9006-42-2

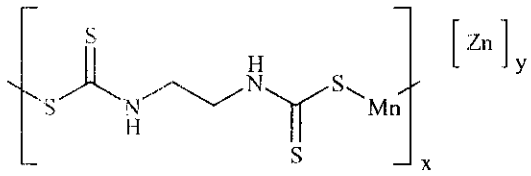
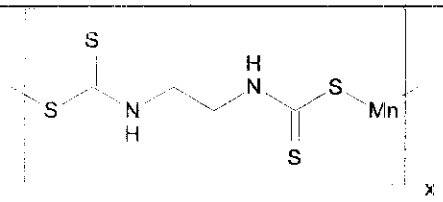
Table 2.6. Mancozeb Test Compound Nomenclature	
Chemical structure	
Common name	Mancozeb
IUPAC name	manganese ethylenebis(dithiocarbamate)(polymeric) complex with zinc salt
CAS name	[[1,2-ethanediylbis[carbamodithioato]](2-)]manganese mixture with [[1,2-ethanediylbis[carbamodithioato]](2-)]zinc
CAS registry number	8018-01-7

Table 2.7 Maneb Test Compound Nomenclature	
Chemical structure	
Common name	Maneb
IUPAC name	Manganese ethylenebis (dithiocarbamate) (polymeric)
CAS name	[[1,2-ethanediylbis[carbamodithioato]](2-)]manganese
CAS registry number	12427-38-2

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

The ETU toxicology database is considered incomplete; however by using a combination of guideline and literature information and including an additional uncertainty factor; sufficient information was available to select endpoints for ETU.

Guideline toxicological data gaps include a 2-generation reproduction studies in rats, a developmental study in rabbits, developmental neurotoxicity study and a comparative study for thyroid toxicity in adults and offspring.

3.1.2 Toxicological Effects

Acute toxicity: The acute toxicity profile for ETU is shown in Table 3.1, below. Acute oral and dermal sensitization studies with ETU were not available.

Table 3.1 Acute Toxicity of ETU

Guideline No.	Study Type	MRID Nos.	Results	Toxicity Category
870.1100	Acute Oral – rat	N/A	N/A	N/A
870.1200	Acute Dermal - rabbit	458881-01	LD_{50} > 2000 mg/kg	III
870.1300	Acute Inhalation - rat	458881-02	LC_{50} > 10.4 mg/L	IV
870.2400	Primary Eye Irritation	458881-04	No irritation[1]	IV
870.2500	Primary Skin Irritation	458881-03	No irritation	IV
870.2600	Dermal Sensitization	N/A	N/A	N/A

[1] The primary eye irritation study was classified unacceptable because a UV light was not observed with fluorescein staining, however, another study is not required (M. Lewis, 4/30/03, D289726).

Subchronic/Chronic toxicity: The thyroid is a target organ for ETU. Thyroid toxicity in subchronic and chronic rat, mouse, and dog studies included decreased levels of the thyroid hormone T4 (serum thyroxin), changes in the thyroid hormone T3 (triiodothyronine), compensatory increases in levels of thyroid stimulating hormone (TSH), 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.

Carcinogenicity: 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 also 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 probable human carcinogen, group B2, (Bill Sette, Ph.D., 4/16/90). The Q_1* for ETU, using a ¾ scaling factor, was determined to be 0.0601 $(mg/kg/day)^{-1}$ based upon female mouse liver tumors in a National Toxicology Program (NTP) study (Bernice Fisher and Hugh Pettigrew, 2/24/95).

Developmental/Reproductive toxicity: The nervous system is a target for ETU. The developmental defects seen in the rat developmental study with ETU included exencephaly, atrophy of brain tissue, cranial edema, dilated ventricles of the brain, compression and/or hemorrhages of the spinal cord, deficiency of tissue in the olfactory bulb, meningoencephalocele, incomplete cranial ossification, wide cranial sutures, curved clavicle, fused sternebrae, absent caudal or sacral vertebrae, fused and/or thickened ribs, wavy ribs, misshapen or incomplete ossification of hindlimb long bones, ribs and pelvis, kyphosis (abnormal spine curvature), reduced number of ribs, fused lumbar, sacral, or caudal vertebrae, abnormal pelvic limb posture, oligodactyl, agnathia, cleft palate, cleft lip, club limb, stubby tail, forelimb flexure, kinked tail, cryptorchidism (abnormal descending of the testes), ectopic kidneys, agenesis of the kidneys, hydronephrosis, reduced stomach with thickened wall, edematous fat pads, syndactyl digits, and anal atresia (closure).

Developmental defects in the rat developmental study indicated increased qualitative susceptibility since numerous and 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) a smaller dose of ETU (50 mg/kg/day) was needed 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 that occurred with mancozeb were accompanied by more severe maternal toxicity.

A developmental study in rabbits was not submitted. No reproductive toxicity was attributed to treatment in the 2-generation reproduction study in rats.

Neurotoxicity: Neurotoxicity studies for ETU are not available.

The toxicity profile of ETU is shown in Table 3.2.

Table 3.2 Toxicity Profile of ETU

Study Type [Guideline No.]	MRID No./ Classification	Results
Subchronic (13-week) feeding - rat [870.3100] 250 ppm (males: 14.28 mg/kg/day; females: 17.81 mg/kg/day)	00261536/1986 Acceptable	NOAEL = <14.28 mg/kg/day LOAEL = 14.28 mg/kg/day, based on reduced body weight, changes in thyroid hormone and TSH levels. increased thyroid and liver weight, microscopic thyroid hyperplasia and liver hypertrophy.
Subchronic (13-Week) feeding - mouse [870.3100] 0, 1, 10, 100, 1,000 ppm (males: 0, 0.16, 1.72, 18.18, 168.2 mg/kg/day; females: 0, 0.22, 2.38, 24.09, 231.1 mg/kg/day)	00259888/1985 Unacceptable	NOAEL = 1.72 mg/kg/day LOAEL = 18.18 mg/kg/day, based on microscopic thyroid hypertrophy/hyperplasia. % purity, feed concentrations were not reported. At the high dose, more microscopic thyroid changes and increases in thyroid and liver weight occurred. Unacceptable because dietary concentrations were not reported.
Subchronic (13-Week) feeding - dog [870.3100] 0, 10, 150, 2000 ppm (males: 0, 0.39, 6.02, 66.23 mg/kg/day; females: 0, 0.42, 6.51, 71.62 mg/kg/day)	42174201/1991 Acceptable	NOAEL = 0.39 mg/kg/day LOAEL = 6.02 mg/kg/day, based on elevated cholesterol. (Note: this endpoint was not considered robust enough for use in risk assessment) In high dose group: mortality, anemia, decreased activity, decreased thyroid hormone levels, increased thyroid weight microscopic thyroid hyperplasia.
Chronic tox/carcinogenicity - rat [870.4100] 0, 0.5, 2.5, 5.0, or 125 ppm	42607801/1992 Unacceptable	Concentration of ETU in feed varied widely and doses could not be determined. Microscopic thyroid hyperplasia occurred in the low-dose group. At higher doses, changes in thyroid hormone and TSH levels, increased thyroid weight, and grossly enlarged livers, occurred. Increases in thyroid follicular adenomas and pituitary adenomas in high-dose males. Unacceptable because ETU concentrations varied widely.
Chronic (24-Month) Feeding - mouse (NTP)	NA	This study was used to determine the Q1* for ETU of 6.01×10^{-2} $(mg/kg/day)^{-1}$ based upon female mouse liver adenomas and/or carcinomas.
Chronic (1-year) oral toxicity - dog [870.4100] 0, 5, 50, or 500 ppm (males: 0, 0.18, 1.99, 20.13 mg/kg/day; females: 0, 0.19, 1.79, or 20.15 mg/kg/day)	42338101/1992	NOAEL = 0.18 mg/kg/day LOAEL = 1.99 mg/kg/day, based on increased thyroid weight and microscopic changes in thyroid (hypertrophy, follicular dilatation). At the high dose, mortality, anemia, and microscopic hepatocellular necrosis.
4-Week Rangefinding - Dog 0, 196, 980, 4900 ppm (males: 0, 7.0, 34, or 172	41863401/1989 Acceptable	NOAEL = 7 mg/kg/day LOAEL = 34 mg/kg/day, based on decreased levels of thyroid hormones, gross thyroid lesions.

Table 3.2 Toxicity Profile of ETU		
Study Type [Guideline No.]	**MRID No./ Classification**	**Results**
mg/kg/day; females: 0, 8.0, 36, or 197 mg/kg/day)		
Developmental tox. - rat [870.3700] 50 mg/kg/day	00246663/1980 Acceptable/non-guideline	Maternal NOAEL = <50 mg/kg/day Maternal LOAEL = 50 mg/kg/day, based on decreased body weight gain. Developmental NOAEL = <50 mg/kg/day Developmental LOAEL = 50 mg/kg/day, based on gross developmental defects, central nervous system defects, skeletal defects, cryptorchidism, and decreased fetal weight. Only one dose was included in the study.
Developmental tox. - rat [870.3700] 0, 5, 10, 20, 40, or 80 mg/kg/day	4593760/1973 [Khera, K.S. 1973. *Teratology* 7:243-252] Acceptable non-guideline	Maternal NOAEL = 40 mg/kg/day Maternal LOAEL = 80 mg/kg/day, based on mortality. Developmental NOAEL = 5 mg/kg/day Developmental LOAEL = 10 mg/kg/day based on central nervous system and gross developmental defects of the brain including exencephaly, dilated ventricles and hypoplastic cerebellum.
2-Generation reproduction - rat [870.3800] 0, 2.5, 25, 225 ppm	42391701/1992 Unacceptable	Doses on a mg/kg/day basis could not be determined. Parental: microscopic thyroid hyperplasia/hypertrophy in mid and/or high-dose groups. No reproductive effects attributed to treatment. Unacceptable because of stability problems with test material and poor record keeping.
Dermal absorption - rat [870.7600]	40312001/1987 Acceptable	Dermal absorption = 26%

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Metiram, mancozeb and maneb degrade and/or are metabolized to ETU. In oral rat metabolism studies with radiolabelled EBDCs, an average 7.5% *in vivo* metabolic conversion of EBDC to ETU occurred, on a weight-to-weight basis. This metabolic conversion has been taken into consideration in the human health risk assessment, including the dietary exposure assessment as well as dermal and inhalation assessments. There is inherent uncertainty in assuming the metabolic conversion occurs following dermal and inhalation dosing, since dermal and inhalation exposure do not involve the GI tract. In addition to ETU, other identified decomposition products are ethylenethiuram, ethylene-bis-isothiocyanate sulfide (EBIS), carbon disulfide (CS_2), and elemental sulphur (the latter 3 being known inhibitors of mono-oxygenases). Metabolism data indicate that the EBDCs do not bioaccumulate.

3.3 FQPA Considerations

HED has evaluated the toxicology database for ETU and reviewed the potential for increased susceptibility of infants and children from exposure to ETU in accordance with the February 2002 OPP 10X guidance document. Studies available for FQPA consideration included several developmental toxicity studies from the literature, one unacceptable guideline developmental toxicity study in rats where only one dose was administered, and a 2-generation reproduction toxicity study in rats.

There is concern for prenatal toxicity resulting from exposure to ETU due to the effects seen in developmental studies. There was evidence of quantitative and qualitative susceptibility to fetuses in several developmental studies in rats:

- In a 1973 literature study (Khera), developmental defects of the brain in the fetuses occurred at a dose significantly lower than the dose at which maternal toxicity was observed;
- In a 1979 literature study (Chernoff, *et. al.*), the maternal toxicity NOAEL was twice the developmental LOAEL, at which hydrocephalus occurred. The maternal LOAEL was four times higher than the developmental LOAEL, and the effect consisted of reduced body weight gain and mortality;
- In a 1978 literature study (Teramoto, *et. al.*), developmental toxicity (dilated ventricle of the brain was seen at the lowest dose tested (10 mg/kg/day) in the absence of maternal toxicity;
- In a 1991 literature study (Saillenfait, *et. al.*), severe developmental effects (dilated ventricles of the brain, hydroureter, short/kinky tail, and dilated ureters) were seen at a dose (25 mg/kg/day) that only induced decreases in body weight gain in the dams.

Evidence of susceptibility in rabbits could not be ascertained due to the missing prenatal study in this species. The 2-generation reproduction study in rats was not adequate to evaluate susceptibility.

Since there is evidence of increased susceptibility of fetuses following exposure to ETU in the rat developmental studies, HED evaluated the level of concern for the effects observed when considered in the context of all available toxicity data. In addition, the database was examined to determine if there were residual uncertainties after establishing toxicity endpoints and uncertainty factors to be used in the ETU risk assessment. HED determined that the degree of concern for the susceptibility seen in ETU developmental studies was low because:

- The developmental effects have been well-characterized in numerous studies in the published literature, as well as in a guideline study submitted by the registrant;
- There is a clear NOAEL for these effects and the dose-response relationship, although steep, it is well characterized in the numerous developmental studies in rats.
- The developmental endpoint with the lowest NOAEL was selected for deriving the acute reference dose.

- The target organ toxicity (thyroid toxicity) was selected for deriving the chronic reference dose as well as endpoints for non-dietary exposures (incidental oral, dermal, and inhalation).

3.3.1 Recommendation for a Developmental Neurotoxicity Study

HED concluded that a developmental neurotoxicity study for ETU was required, based on severe central nervous system defects observed in the developmental toxicity study in rats including: exencephaly, atrophy of brain tissue, cranial edema, dilated ventricles of the brain, compression and/or hemorrhages of the spinal cord, deficiency of tissue in the olfactory bulb, and meningoencephalocele. A comparative thyroid toxicity study in adults and offspring was also required.

3.3.2 Safety Factor for Infants and Children

Although there are no residual uncertainties for pre- and/or post-natal toxicity, the FQPA Safety Factor of 10X was retained due to database uncertainties for ETU. In addition to the required DNT study, there are data gaps for a developmental toxicity study in rabbits, a 2-generation reproduction study in rats and a study evaluating the comparative thyroid toxicity in adults and offspring. HED determined that the FQPA SF must be retained to account for the lack of these studies, since the available data provide no basis to support reduction or removal of the factor.

3.4 Hazard Identification and Toxicity Endpoint Selection

HED evaluated the toxicology database of ETU and selected the doses and endpoints for risk assessment based on a variety of exposure pathways resulting from use of the EBDC fungicides. These doses and endpoints are summarized in Table 3.4.

3.4.1 Acute Reference Dose (aRfD) - Females age 13-49

The ETU acute dietary endpoint for females 13-49 years old was selected from a non-guideline developmental toxicity study in rats (Khera, K.S.; Teratology 7:243-252, 1973, MRID No. 45937601). The LOAEL was 10 mg/kg/day based on developmental effects of the brain, including exencephaly, dilated ventricles and hypoplastic cerebellum. The NOAEL for the study was 5 mg/kg/day. Application of the combined standard 10X UFs to account for intraspecies variability and interspecies extrapolation as well as the FQPA 10X database uncertainty factor (UF_{DB}) results in an acute reference dose of 0.005 mg/kg/day. The acute population adjusted dose is equal to the acute RfD, 0.005 mg/kg/day

3.4.2 Acute Reference Dose (aRfD) - General Population

HED concluded that an acute reference dose for the general population is not needed, since there was no appropriate endpoint attributable to a single dose in the available toxicity studies.

3.4.3 Chronic Reference Dose (cRfD)

The ETU chronic reference dose for the general population was selected 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 FQPA 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 equivalent to the chronic RfD.

3.4.4 Incidental Oral Exposure (Short- and Intermediate-Term)

A non-guideline 4-week range-finding toxicity study conducted in dogs was used to select incidental oral endpoints and doses for risk assessment. The 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 the short- term duration of exposure (up to 30 days). In addition, the study can be used for intermediate-term incidental oral risk assessment, since it is also 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 the FQPA 10X UF_{DB}. An additional uncertainty factor 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.

3.4.5 Oral Exposure (Short- and Intermediate-Term)

The ETU oral endpoint for females 13-49 years old was selected from a non-guideline developmental toxicity study in rats (Khera). The study NOAEL was 5 mg/kg/day based on developmental effects of the brain, including exencephaly, dilated ventricles, and hypoplastic cerebellum, observed at the LOAEL of 10 mg/kg/day. The target MOE for residential exposures is 1000, which includes the standard 100X combined UFs, as well as the 10X FQPA UF_{DB}.

3.4.6 Dermal Absorption

Dermal Absorption Factor: 26%.
The ETU dermal absorption factor is 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 residues were detected in organs at all three dermal doses, and were highest in the thyroid.

3.4.7 Dermal and Inhalation Exposure (Short- and Intermediate-Term)

Females 13-49 years old, dermal and inhalation exposure
In the absence of adequate dermal and inhalation toxicity studies for ETU, the non-guideline oral study in rats (Khera) was used to select endpoints for short- and intermediate-term dermal and inhalation risk assessments. The study NOAEL was 5 mg/kg/day based on developmental effects of the brain, including exencephaly, dilated ventricles, and hypoplastic cerebellum, observed at the LOAEL of 10 mg/kg/day; the endpoint is considered applicable for females 13-49 years old. Because an oral toxicity study was chosen, the 26% dermal absorption factor (relative to oral absorption) for ETU should be used in the dermal exposure assessment, and 100% absorption should be assumed for calculating inhalation exposure and risk, i.e. inhalation absorption is equivalent to oral absorption. The target MOE for residential exposures is 1000, which includes the standard 100X combined UFs, as well as the 10X FQPA UF_{DB}. The target MOE for occupational assessments is 100.

Toddlers, dermal exposure
The non-guideline 4-week range-finding toxicity study conducted in dogs was also used to select short- and intermediate-term dermal endpoints for risk assessment for infants/children. 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 combined UF applied to both short- and intermediate-term dermal risk assessments is 1000X, based on the standard 100X UF, as well as the FQPA 10X UF_{DB}. An additional uncertainty factor to extrapolate from a shorter- to a longer-term study was not needed, since the NOAEL for thyroid effects in the subchronic dog study (6 mg/kg/day) was similar to that observed in the 4-week dog study.

3.4.8 Dermal and Inhalation Exposure (Long-Term)

The long-term dermal and inhalation endpoints were selected 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 (relative to oral absorption). For calculating inhalation risks, a 100% oral equivalent 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 FQPA 10X UF_{DB} for an incomplete database. For occupational exposures, the long-term target MOE for dermal and inhalation exposures is 100.

3.4.9 Classification of Carcinogenic Potential

The HED Cancer Assessment Review Committee evaluated the carcinogenicity potential of ETU and classified ETU as a probable human carcinogen, group B2, (Bill Sette, Ph.D., 4/16/90). The Q_1* for ETU, using a ¾ scaling factor, was determined to be 0.0601 $(mg/kg/day)^{-1}$ based upon female mouse liver tumors in a National Toxicology Program

study (Bernice Fisher and Hugh Pettigrew, 2/24/95.

3.4.10 Summary of Toxicological Doses and Endpoints for ETU for Use in Human Risk Assessments

Table 3.4 ETU Toxicological Doses and Endpoints for Use in Human Health Risk Assessment

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Dietary Exposure				
Acute Dietary (General Population, including Infants and Children)	There was no appropriate endpoint attributable to a single dose in the available toxicity studies.			
Acute Dietary (Females 13-49 years old)	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=10x,UF_{DB}	Acute RfD = 0.005 mg/kg/day 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
Chronic Dietary (All Populations)	NOAEL= 0.18 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x,UF_{DB}	Chronic RfD = 0.0002 mg/kg/day cPAD = 0.0002 mg/kg/day	Dog Chronic Oral Toxicity LOAEL= 1.99 mg/kg/day based on thyroid toxicity
Oral Exposure				
Incidental Oral Short-Term (1-30 days) Intermediate-Term (1-6 months) (Toddlers)	NOAEL= 7 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x,UF_{DB}	Residential MOE = 1000 Occupational MOE = N/A	4-week range-finding dog study LOAEL= 34 mg/kg/day based thyroid toxicity
Oral (Short-Term (1-30 days) Intermediate-Term (1-6 months) (Females 13-49 years old)	NOAEL= 5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x,UF_{DB}	Residential MOE = 1000 Occupational MOE = N/A	Developmental Rat Toxicity (Khera Study, MRID No. 45937601) LOAEL = 10 mg/kg/day, based on developmental defects of brain
Dermal Exposure				
Dermal Short-Term (1-30 days) Intermediate-Term (1-6 months) (Toddlers)	NOAEL= 7 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x,UF_{DB}	Residential MOE = 1000 Occupational MOE = N/A	4-week range-finding dog study LOAEL= 34 mg/kg/day based thyroid toxicity
Dermal Short-	NOAEL= 5	UF_A= 10x	Residential MOE =	Developmental Rat

Table 3.4 ETU Toxicological Doses and Endpoints for Use in Human Health Risk Assessment

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Term (1-30 days) Intermediate-Term (1-6 months) (Females 13-49 years old)	mg/kg/day	UF_H=10x FQPA SF= 10x,UF_{DB} DA= 26%	1000 Occupational MOE = 100	Toxicity (Khera Study, MRID No. 45937601) LOAEL = 10 mg/kg/day, based on developmental defects of brain
Dermal Long-Term (>6 months)	NOAEL= 0.18 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x,UF_{DB} DA= 26%	Residential MOE = 1000 Occupational MOE = 100	Dog Chronic Oral Toxicity LOAEL= 1.99 mg/kg/day based on thyroid toxicity
Inhalation Exposure				
Inhalation Short-Term (1-30 days) Intermediate-Term (1-6 months)	NOAEL=5 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x,UF_{DB}	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.
Inhalation Long-Term (>6 months)	NOAEL=0.18 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x,UF_{DB}	Residential MOE = 1000 Occupational MOE = 100	Dog Chronic Oral Toxicity LOAEL= 1.99 mg/kg/day based on thyroid toxicity
Cancer				
Cancer (oral, dermal, inhalation)	$Q_1^* = 6.01 \times 10^{-2}$ (mg/kg/day)$^{-1}$		ETU is classified as a probable human carcinogen, Group B2, with a low-dose extrapolation approach for human risk assessment, based on liver tumors in female mice.	

Note: Separate short- and intermediate-term oral and dermal endpoints were selected for toddler and adult (females 13-49 years old) population subgroups.
Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. DA = dermal absorption. N/A = not applicable.

3.5 Endocrine Disruption

EPA is required under the Federal Food, Drug, and Cosmetic Act (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 recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that

there was a scientific basis 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 additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, ETU may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

See the parent EBDC compound risk assessments for public health data, as incident data are not available for the degradate, ETU.

5.0 Dietary Exposure/Risk Characterization

5.1 Environmental Degradation

Reference:
Estimated Drinking Water Concentrations of ETU (Ethylene-thio-urea, degradate of mancozeb, and common degradate of EBDCs "Ethene-bis-dithio-carbamates") for Use in Human Health Risk Assessment. D323143 and D323141. August 11, 2006. M.A. Ruhman and Ronald Parker.

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 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, reducing the possibility of losses from surface water due to volatilization.

5.1.1 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 at a limit of quantitation of 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 U.S. 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.

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 provides 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 default percent cropped area (PCA) value of 0.87. If 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 using the national maximum PCA.

Acute Surface Water EDWCs: The ETU surface water estimated drinking water concentrations 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 value of 0.87.

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

5.1.2 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 was 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. 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.

Table 5.1 Summary of Estimated Surface Water and Ground Water Concentrations for ETU		
Exposure Duration	**ETU**	
	Surface Water Conc.[1] (ppb)	**Groundwater Conc.[1] (ppb)**
Acute	0.1-**25.2**	0.21
Chronic (non-cancer)	0.1	**0.21**
Chronic (cancer)	0.1	**0.21**

[1] Bolded values represent drinking water estimates included in the aggregate dietary assessment.

5.2 Dietary Exposure and Risk

Reference

Aggregate Dietary Assessment of the Common Metabolite/Degradate Ethylene Thiourea (ETU) to Support New Tolerances on Imported Grapes and Bananas for Metiram and for New Tolerances for Mancozeb on Almonds, Broccoli, Cabbage, Lettuce, and Peppers. DP Barcode: D337240. April 17, 2007. Christine Olinger.

Separate dietary exposure assessments were conducted for each EBDC parent compound. In each of these assessments, human dietary exposure and health risk associated with the active ingredient were estimated, as well as dietary exposure and risk resulting from consumption of ETU residues derived from each EBDC individually. These documents are listed below:

- Metiram: Acute, Chronic, and Cancer Dietary Exposure Assessments for New Tolerances on Imported Grapes and Bananas. PP# 9E6006. D326753. April 17, 2007. Christine Olinger.
- Mancozeb Acute, Chronic, and Cancer Dietary Exposure Assessments for New Tolerances on Almonds, Broccoli, Cabbage, Lettuce, and Peppers. PP#4F4324 and 4F4333. D323878. April 17, 2007. Christine Olinger.
- Maneb and Ethylenethiourea: Revised Acute/Probabilistic, Chronic, and Cancer Dietary Exposure Assessments for the Reregistration Eligibility Decision; DP Barcode: D295410; June 2005; F. Fort.

For this assessment, ETU food residues from each of the individual EBDCs were aggregated. ETU aggregate acute, chronic and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™), Version 2.03, which used food consumption data from the United States Department of Agriculture's (USDA's) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

The ETU aggregate acute, chronic, and cancer assessments can be considered somewhat refined. Residue estimates were refined using consumer processing factors (washing, cooking), commercial processing (winemaking, juice), percent crop treated factors (existing domestic uses only), and market basket survey (monitoring) data for several of the existing uses. Projected percent crop treated information was used to refine the

estimates for the proposed new uses of mancozeb. Projected percent crop treated information is not available for the uses on imported crops (bananas and grapes), so residue estimates were refined slightly using percent imported factors. Crop field trial data were used for several of the existing uses as well as all of the proposed new uses, which are likely to provide higher estimates than actual exposures.

5.2.1 Anticipated Residue Information

Crops treated with EBDCs may contain both EBDC and ETU residues; in addition, cooking and/or processing may result in conversion of EBDC residues to ETU, or in concentration or reduction of existing ETU residues. Therefore, both EBDC and ETU residues may be consumed in the diet. In this assessment the ETU food residues from each of the EBDCs were aggregated.

When possible, market basket survey (MBS) data, generated by the ETU Task Force, were used to calculate anticipated residues. MBS data are available on the following foods: green beans (raw, frozen, canned, and baby food), dry beans (dry and canned), broccoli (raw and frozen), celery, sweet corn (raw, frozen, canned), cucumbers, lettuce, meat, milk, onion (dry bulb), potato (raw, frozen), and tomato (raw, juice, ketchup, paste, puree).

For the probabilistic acute dietary exposure analysis, the entire distributions of residue data from field trials or monitoring data were used to generate residue distribution files (RDFs) for commodities which were considered to be not blended or partially blended. For commodities considered to be blended in this analysis, the average residues incorporating the likely maximum estimated PCT was used as a point estimate. Different approaches were taken for for commodities on which more than one EBDC might be registered, depending upon the source of the residue data. It was assumed that commodities would not be treated with more than one EBDC in a season, as there were no data available to determine the relative amount of crops treated with more than one EBDC. Only data for the individual chemicals were available. When more than one EBDC was registered on any crop and the MBS data were used for the assessment, then the percent crop treated values for the individual EBDC were summed and an RDF was created in which zeroes were added proportionately. For a few commodities mancozeb field trial data were used for both mancozeb and maneb. Those commodities were treated similarly to the commodities using MBS. RDFs were created with a proportionate number of values from the relative percent crop treated for each chemical. For example, the percent crop treated for mancozeb, maneb, and metiram on apples is 35, 5, and 25, respectively. Therefore, an RDF where 35% of the values representing treated commodities were from mancozeb field trials, 5% from maneb field trials, and 25% from metiram field trials was created.

Chronic anticipated residues were also calculated from field trial or monitoring data for ETU. Averages of the field trial and MBS residue data were used. In determining the average residue when two or more EBDCs were used on a crop, the following equation was used.

(ETU from Mancozeb Residue x Mancozeb PCT/100)
+ (ETU from Maneb residue x Maneb PCT/100)
+ (ETU from Metiram residue x Metiram PCT/100)
= Chronic AR for ETU

If the sum of the PCT values for all three EBDCs exceeded 100% then the PCT values were adjusted so that the sum equaled 100%.

5.2.2 Acute Dietary Exposure/Risk

Acute dietary exposure and risk for ETU are below HED's level of concern. For females 13-49 years old, estimated dietary exposure (food only) was 0.002799 mg/kg/day, which utilized 56% of the aPAD at the 99.9th percentile. For food and water, the acute dietary exposure was 0.004437 mg/kg/day which utilized 89% of the aPAD at the 99.9th percentile of exposure. The results of the acute dietary exposure assessments for ETU are shown in Summary Table 5.2.

5.2.3 Chronic Dietary Exposure/Risk

The chronic risk estimates are below the HED's level of concern for aggregate exposure to ETU for the general U.S. population and all population subgroups. The most highly exposed population subgroup was children ages 1-2 for food alone and food and water assessments. For food only, the chronic dietary exposure was 0.000166 mg/kg/day which utilized 83% of the cPAD. For food and water combined, the chronic dietary exposure was 0.000173 mg/kg/day, which utilized 86% of the cPAD. The results of the chronic dietary exposure assessments for ETU are shown in Summary Table 5.2.

5.2.4 Cancer Dietary Risk

The cancer risk assessment for ETU was based on the same anticipated residues derived for the chronic dietary exposure assessment. The estimated chronic dietary exposure for the general U.S. population corresponds to a cancer risk of 3.3 x 10^{-6} for food alone and 3.6 x 10^{-6} for food and water combined. The results of the cancer dietary exposure assessments for ETU are shown in Summary Table 5.2.

Table 5.2 Result of Acute and Chronic Dietary Exposure and Risk Estimates for ETU Using DEEM-FCID™

Population Subgroup	ETU (food only)		ETU (food and water)	
	Exposure, mg/kg/day	% PAD	Exposure, mg/kg/day	%PAD
Acute Dietary Estimates (99.9th Percentile of Exposure)				
Females 13-49 yrs	0.002799	56	0.004437	89
Chronic Dietary Estimates				
U.S. Population	0.000055	28	0.000060	30
All infants (< 1 yr)	0.000073	37	0.000088	44
Children 1-2 yrs	0.000166	83	0.000173	86
Children 3-5 yrs	0.000112	56	0.000118	59
Children 6-12 yrs	0.000057	29	0.000061	31
Youth 13-19 yrs	0.000034	17	0.000037	19
Adults 20-49 yrs	0.000045	22	0.000049	25
Adults 50+ yrs	0.000056	28	0.000061	30
Females 13-49 yrs	0.000046	23	0.000050	25
Cancer Dietary Estimate				
U.S. Population	0.000055	3.3×10^{-6}	0.000060	3.6×10^{-6}

The dietary cancer risk including food and water is 3.6×10^{-6}, which exceeds HED's level of concern. Therefore, HED conducted a critical commodity contribution analysis for the cancer assessment and sensitivity analyses for several scenarios. The greatest contributors to the dietary exposure are bananas (approximately 17% of the exposure) and leaf lettuce (approximately 10% of the exposure). Other commodities contributing more than 3% of the total exposure were turnip greens, water, mangoes, and grape juice. The results of the critical commodity analysis and aggregate sensitivity analyses may be found in Tables 5.3 and 5.4, respectively.

Table 5.3 Summary of Commodities Contributing Greater than 3% of Total Dietary Exposure to the Chronic/Cancer Exposure Assessment

Commodity	Exposure, mg/kg bw/day	Individual Cancer Risk	Percent Contribution to Total Exposure
Bananas, uncooked[1]	0.000010	6.2×10^{-7}	17
Lettuce, Leaf	0.0000061	3.7×10^{-7}	10
Water (direct and indirect sources)	0.0000044	2.7×10^{-7}	7.4
Turnip Greens [1]	0.0000041	2.5×10^{-7}	6.8
Grape Juice (cooked and uncooked)	0.0000028	1.6×10^{-7}	4.6
Mangoes, uncooked[1]	0.000002	1.2×10^{-7}	3.3

[1]Note that this exposure value reflects the assumption of 100% crop treated.

Table 5.4 Sensitivity Analyses		
Scenario	**Exposure, mg/kg bw/day**	**Estimated Cancer Risk**
Aggregate Food and Water, excluding proposed tolerance for metiram on bananas	0.00005	3.0×10^{-6}
Aggregate Food and Water, excluding mancozeb proposed use on leaf lettuce	0.000059	3.5×10^{-6}
Aggregate Food and Water, assuming 1% crop treated for Turnip Greens	0.000056	3.4×10^{-6}

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Mancozeb: 2nd Revised ORE Assessment for the RED. D317368. May 31, 2005. Timothy Dole.
Maneb: 2nd Revised ORE Assessment for the RED. D295411. June 8, 2005. Timothy Dole.

No new residential uses are being added to the mancozeb or maneb labels as a result of this action, however there are existing residential uses registered. There are no uses of metiram that will result in exposure in residential settings.

The document entitled ***Mancozeb:*** *2nd Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document* cited above provides a detailed summary of the exposure and risk assessment for the existing residential uses of mancozeb. The document entitled ***Maneb:*** *2nd Revised Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document* cited above provides a detailed summary of the exposure and risk assessment for the existing residential uses of maneb.

Exposures and risks from the various residential scenarios are briefly summarized here since those values are required for the ETU aggregate risk assessments.

The existing residential handler scenario identified for mancozeb is for the application of mancozeb in home gardens. The anticipated use patterns and current labeling indicate that backpack and low pressure handwand sprayers could be used by the homeowner to make mancozeb applications. Residential risks are assumed to be of short-term and intermediate-term in duration for home garden scenarios and for adults on treated turf. HED notes that there are no direct homeowner applications of mancozeb to turf; however, there is a registered use to permit treatment of sod on sod farms with subsequent transplantation to a residential setting. Residential scenarios are considered to be of short-term duration for toddlers on treated turf since it is unlikely that sod would be installed more than once per year and since subsequent to installation, turf is watered which would contribute to a more rapid dissipation of residues. There are no long-term residential exposure scenarios associated with mancozeb at this time. In the previous aggregate assessment, exposure to athletes from treated playing fields was considered. However, the application to athletic field has been voluntarily cancelled, so is not considered in this assessment.

Maneb is used on sodfarms 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 Sodfarms 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. Therefore, the only residential scenario considered for maneb is toddlers playing on turf transplanted from sod farms.

6.1 Residential Handler Exposures and Risks

There are no residential handler scenarios for maneb.

The existing residential handler scenario identified for mancozeb is for the application of mancozeb in home gardens. The anticipated use patterns and current labeling indicate that backpack and low pressure handwand sprayers could be used by the homeowner to make mancozeb applications. Since the endpoints selected for the short- and intermediate-term assessment are identical, short- and intermediate-term risk assessments yield the same MOEs; one value is shown in the tables below for each application method. Based on tank mix studies, it was assumed that 0.2% of the mancozeb would convert to ETU, additionally; a 7.5% *in vivo* conversion of mancozeb to ETU was also considered in the exposure calculations.

Both dermal and inhalation exposures and risks for mancozeb-derived ETU were calculated for residential handlers. Since the short/intermediate-term dermal and short/intermediate-term inhalation endpoints were taken from the same study, dermal and inhalation exposures were added to calculate a combined absorbed mancozeb-derived ETU daily dose. That dose was then compared to the NOAEL from the rat developmental toxicity study. Short/intermediate-term combined dermal and inhalation MOEs for residential handlers using both backpack sprayers and low pressure handwand sprayers far exceeded the level of concern (LOC) of 1000; therefore, HED has no concern short-term risks to residential handlers exposed to mancozeb-derived ETU. Short-term dermal and inhalation exposures and combined risk for residential handlers are summarized in Table 6.1, below.

Table 6.1 Home Gardener Handler Exposure and Short/Intermediate-Term Risks for Mancozeb-Derived ETU

Exposure Scenario	Absorbed ETU Daily Dose (mg/kg/day)		Combined Absorbed ETU Daily Dose (mg/kg/day)	ETU MOE[1]
	Dermal	Inhalation		
Backpack	5.9×10^{-6}	2.1×10^{-6}	8.1×10^{-6}	620000
Low Pressure Handwand	4.4×10^{-5}	6.4×10^{-7}	4.5×10^{-5}	110000

[1] NOAEL is 5 mg/kg/day

As previously noted, mancozeb's potential for carcinogenicity is due to the formation of the metabolite ETU. Cancer risks from exposure to ETU as a result of application of

mancozeb are calculated by estimating exposure to mancozeb-derived ETU and using the ETU Q_1^* of 0.0601 $(mg/kg/day)^{-1}$ to provide a quantitative estimate of risk. Residential handler estimated cancer risks were calculated for applicators using a backpack sprayer and a low pressure handwand sprayer. For applicators using backpack sprayers the estimated cancer risk from mancozeb-derived ETU was 4.1×10^{-9}. Residential handlers using low pressure handwand sprayers had an estimated cancer risk of 2.3×10^{-8}.

Because of the uncertainties in the cancer hazard quantification methodology, risk estimates ranging from 1×10^{-6} to 3×10^{-6} are generally considered indistinguishable. Generally, cancer risk estimates which do not exceed 3×10^{-6} are below HED's level of concern. Therefore, cancer risks to residential handlers as a result of exposure to mancozeb-derived ETU from the existing home garden use are not of concern. Cancer risks for home garden handlers are summarized in Table 6.2 below.

Table 6.2 Home Garden Handler Exposure and Cancer Risk for ETU from Mancozeb

Exposure Scenario	Application Rate (lbs ai/acre)	Absorbed Daily Dose (mg/kg/day)[1]	Lifetime Average Daily Dose[2]	Cancer Risk[3]
Backpack	2.4	6.9×10^{-6}	6.8×10^{-8}	4.1×10^{-9}
Low Pressure Handwand	2.4	3.7×10^{-5}	3.8×10^{-7}	2.3×10^{-8}

[1] ADD = Absorbed Daily Dose from dermal and inhalation exposure
[2] LADD = Lifetime Average Daily Dose = ADD * (5 exposure days per year/365 days per year)*(50 years of exposure/70 years of life)
[3] Risk = (LADD * Q_1^*), where $Q_1^* = 0.0601$ $(mg/kg/day)^{-1}$

6.2. Residential Postapplication Exposure

6.2.1 Residential Postapplication Exposure – Mancozeb

Mancozeb can be used in areas that can be frequented by the general population including residential areas (e.g., home lawns and gardens) and golf courses. As a result, individuals can be exposed by entering these areas if the areas have been previously treated. The residential postapplication exposure and risk assessments conducted included the following:

- Adult dermal exposure from contact with treated home gardens
- Adult dermal exposure from contact with treated turf (golfer scenario)
- Youth (ages 10 - 12) dermal exposure from working in treated home gardens
- Toddler incidental oral exposure from hand-to-mouth transfer of resides, object-to-mouth transfer of residues and soil ingestion from contact with treated turf
- Toddler dermal exposure from contact with treated turf

The residential postapplication exposure and risk assessment are detailed in the mancozeb ORE (occupational and residential exposure) memorandum. Results of the residential postapplication exposure and risk assessment are summarized in the subsequent sections.

6.2.1.1 Home Garden Postapplication Scenarios

Table 6.3, below summarizes the post application risks from mancozeb-derived ETU for adults and youth exposed to treated home gardens on Day 0 (the day of application). Exposures are shown for low, medium and high contact activities and also for representative commodities that might be found in a home garden. The scenario with the greatest risk is shown in bold. MOEs for all scenarios for both subpopulations on Day 0 exceed the LOC of 1000 and, therefore; are not of concern.

Table 6.3 Mancozeb-derived ETU Postapplication Short/Intermediate-Term Exposure and Risks for Adult and Youth Home Gardeners

Crop Group	Application Rate (lb ai/acre)	ETU MOE on Day 0 (Adults/Youth)[1]			
		Low	Medium	High[2]	Very High
Cut Flowers	1.2	53000/97000	33000/61000	19000/35000	N/A
Vegetable, cucurbit – West[3]	2.4	80000/150000	27000/49000	**16000/29000**[4]	N/A
Vegetable, cucurbit - East[3]	2.4	94000/170000	31000/57000	19000/34000	N/A
Vegetable, fruiting - West	1.6	120000/220000	86000/160000	60000/110000	N/A
Vegetable, fruiting - East	2.4	87000/160000	62000/110000	43000/79000	N/A

[1] Low, medium and High refer to low, medium and high contact activities.
[2] The highest exposure/risk scenario is shown in bold.
[3] While the application rates are the same for west and east cucurbit, the dislodgeable foliar residue values used for east and west are different, which explains the different exposures and risks from the same application rate.
[4] The adult dose for this scenario = 3.1×10^{-4} mg/kg/day and the youth dose for this scenario = 2.4×10^{-4} mg/kg/day taken from the ORE chapter cited above.

Cancer risks from exposure to mancozeb-derived ETU from home garden exposure scenarios are summarized in Table 6.4, below. As in the table above, the scenario with the highest risk is shown in bold. Postapplication cancer risks for adult home gardeners are not of concern.

Table 6.4 Mancozeb-derived ETU Postapplication Cancer Risks for Adult Home Gardeners

Crop Group	Application Rate (lb ai/acre)	Cancer Risk on Day 0 Assuming Five Exposure Days per Year Over a Lifetime			
		Low	Medium	High[2]	Very High
Cut Flowers	1.2	4.7×10^{-8}	7.5×10^{-8}	1.3×10^{-7}	NA
Vegetable, cucurbit – West[1]	2.4	3.1×10^{-8}	9.4×10^{-8}	**1.6×10^{-7}**	NA
Vegetable, cucurbit - East[1]	2.4	2.7×10^{-8}	8.0×10^{-8}	1.3×10^{-7}	NA
Vegetable, fruiting - West	1.6	2.1×10^{-8}	2.9×10^{-8}	4.2×10^{-8}	NA
Vegetable, fruiting – East	2.4	2.9×10^{-8}	4.1×10^{-8}	5.8×10^{-8}	NA

[1] While the application rates are the same for west and east cucurbit, the dislodgeable foliar residues for east and west are different, which explains the different exposures and risks from the same application rate.
[2] The highest exposure/risk scenario is shown in bold.

6.2.1.2 Treated Turf Postapplication Scenarios for Toddlers

Toddlers can be exposed to ETU when in contact with turf treated with mancozeb. Incidental oral exposures and risks are shown below. HED notes that there are no direct

homeowner applications of mancozeb to turf; however, there is a registered use to permit treatment of sod on sod farms with subsequent transplantation to a residential setting. In calculating treated turf risks for mancozeb and its metabolite, ETU, HED used the outcome of the RED risk mitigation negotiations which provides for a 3-day PHI and includes an additional two days for harvesting, shipment and installation for a total of 5 days between treatment on a sod farm and exposure in a residential setting.

Since there are no direct home lawn uses for mancozeb, toddlers would only be exposed to mancozeb in a residential setting from turf transplanted from a sod farm. Since it is unlikely that sod would be installed more than once per year, and the installation process includes watering-in which will tend to increase the dissipation of residues, HED considered risks to toddlers exposed to treated lawns to be of short-term duration only.

To assess risks to toddlers from incidental oral exposure, HED summed the total exposure from residue transfer from hand-to-mouth, object-to-mouth and soil ingestion. The level of concern for both the ETU incidental oral and dermal risk assessments is 1000.

Mancozeb-derived ETU incidental oral exposures and risks to toddlers in contact with treated turf were calculated based on a 3-day PHI for sod farm turf. The MOE for combined oral incidental risk to toddlers in contact with treated turf subsequent to installation exceeds 1000 and is therefore, not of concern. Incidental oral exposures and risk are summarized in Table 6.5, below.

Table 6.5 Summary of ETU Incidental Oral Exposures and Risks for Toddlers Exposed to Turf Treated with Mancozeb

Exposure Pathway	ETU TTR[1]	Dose (mg/kg/day)	MOE
Hand-to-Mouth	0.0085 ug/cm^2	0.0030	2300
Object-to-Mouth	0.034 ug/cm^2	0.00075	9300
Soil Ingestion	0.11 ppm	0.00001	700000
Total		**0.00376**	**1900**

[1] Based upon the existing PHI of 3 days and including an additional 2 days to account for harvesting, shipping and installation.

Short-term dermal risk to toddlers in contact with treated turf with a 3-day PHI was above 1000 and is not of concern. Short-term dermal exposures and risks for toddlers exposed to treated grass are summarized in Table 6.6, below.

Table 6.6 Summary of ETU Short-Term Dermal Exposures and Risks for Toddlers Exposed to Turf Treated with Manzozeb

Exposure Pathway	ETU TTR[1]	Dose (mg/kg/day)	MOE
Dermal	0.0085 ug/cm^2	0.0022	3100

[1] Based upon the existing PHI of 3 days and including an additional 2 days to account for harvesting, shipping and installation.

6.2.1.3 Treated Turf Postapplication Scenario for Adults

Adults may be exposed to mancozeb-derived ETU through dermal contact with turf

treated directly with mancozeb. The MOE for short/intermediate-term dermal risk for the adult golfer exposed to ETU from contact with mancozeb treated golf courses exceeds 1000 and is not of concern. Exposure and risk for adult golfers is summarized in the table below.

Table 6.7 ETU Short/Intermediate-Term Dermal Postapplication Risks for Adults Exposed to Turf

Activity	Application Rate (lb ai/acre)	Mancozeb TTR (ug/cm^2)	ETU TTR (ug/cm2)	Transfer Coefficient (cm^2/hr)	Hours per Day Exposure	ETU Dose (mg/kg/day)	MOE
Golf	17.4	9.76	0.060	500	4.0	0.00076	6600

The cancer risk to adult golfers from exposure to mancozeb-derived ETU is summarized in Table 6.8. Postapplication cancer risks for adult golfers are not of concern.

Table 6.8 Summary of ETU Postapplication Cancer Risks for Adults Exposed to Turf

Activity	Application Rate (lb ai/acre)	Mancozeb TTR (ug/cm2)	ETU TTR (ug/cm2)	Transfer Coefficient (cm^2/hr)	Hours per Day Exposure	Days Per Year Exposure	Years of Exposure per Lifetime	LADD (mg/kg/day)	Cancer Risk
Golf	10.5	3.2	0.020	500	1.0	1	50	1.0×10^{-6}	6×10^{-6}

6.2.2 Residential Postapplication Exposure - Maneb

Like mancozeb, toddlers can be exposed to ETU when in contact with turf treated with maneb. Incidental oral exposures and risks are shown below. HED notes that there are no direct homeowner applications of maneb to turf; however there is a registered use to permit treatment of sod on sod farms with subsequent transplantation to a residential setting. In calculating treated turf risks for maneb-derived ETU, HED used the outcome of the RED risk mitigation negotiations which provides for a lower application rate (8.7 lb ai/A) and a 3-day PHI, which includes an additional two days for harvesting, shipment and installation, for a total of 5 days between treatment on a sod farm and exposure in a residential setting.

Since there are no direct home lawn uses for maneb, toddlers would only be exposed to maneb in a residential setting from turf transplanted from a sod farm. Since it is unlikely that sod would be installed more than once per year, and the installation process includes watering-in which will tend to increase the dissipation of residues, HED considers risks to toddlers exposed to treated lawns to be of short-term duration only.

To assess risks to toddlers from incidental oral exposure, HED summed the total exposure from residue transfer from hand-to-mouth, object-to-mouth and soil ingestion The level of concern for both the ETU incidental oral and dermal risk assessments is 1000.

Maneb-derived ETU incidental oral exposures and risks to toddlers in contact with treated turf were calculated based on a 3-day PHI for sod farm turf. The MOE for combined oral incidental risk to toddlers in contact with treated turf subsequent to

installation exceeds 1000 and is not of concern. Incidental oral exposures and risk are summarized in Table 6.9, below.

Table 6.9 Summary of ETU Incidental Oral Exposures and Risks for Toddlers Exposed to Turf Treated with Maneb

Exposure Pathway	ETU TTR[1]	Dose (mg/kg/day)	MOE
Hand-to-Mouth	0.0151 ug/cm^2	0.0014	5000
Object-to-Mouth	0.0605 ug/cm^2	0.00044	16000
Soil Ingestion	0.203 ppm	0.000066	110000
Total		**0.0019**	**3700**

[1] Based upon the existing PHI of 3 days and including an additional 2 days to account for harvesting, shipping and installation.

Short-term dermal risk to toddlers in contact with treated turf with a 3-day PHI exceeds 1000 and is not of concern. Short-term dermal exposures and risks for toddlers exposed to treated grass are summarized in Table 6.10.

Table 6.10 Summary of ETU Short-Term Dermal Exposures and Risks for Toddlers Exposed to Turf Treated with Maneb

Exposure Pathway	ETU TTR[1]	Dose (mg/kg/day)	MOE
Dermal	0.0151 ug/cm^2	0.0034	2000

[1] Based upon the existing PHI of 3 days and including an additional 2 days to account for harvesting, shipping and installation.

6.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for the EBDCs. 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. On a chemical by chemical basis, 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 database 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 with specific products with significant risks associated with drift. It is noted that the application rate for turf was modeled to estimate postapplication residential exposure of toddlers. As this rate is higher than many of agricultural application rates, this scenario is protective of any exposure of farm children via spray drift from agricultural applications.

7.0 Aggregate Risk Assessments and Risk Characterization

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.

The proposed new uses of mancozeb and tolerances of metiram can result in exposures to ETU from food and drinking water. The existing uses of metiram, mancozeb and maneb may result in exposures to ETU from food, water, and residential sources. The mancozeb uses in home gardens result in handler exposure for adults and postapplication uses to adults and youth working in the garden. The mancozeb and maneb sod farm turf uses could result in postapplication exposure to toddlers playing on treated turf. The use of mancozeb on golf courses could result in postapplication exposures to golfers.

The aggregate risk assessments are intended to be representative of exposures that are likely to co-occur. For the purpose of this risk assessment, HED only aggregated scenarios that they believed are likely to co-occur.

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

The following aggregate risk assessments have been completed:

- ETU Acute Aggregate which considers acute exposure to ETU from food and drinking water
- ETU Short/Intermediate-Term Home Garden Aggregate which combines handler exposures (inhalation and dermal) and post application garden exposures (dermal) plus average daily food and drinking water exposure for adults and post application garden exposures (dermal) plus average daily food and drinking water exposure for youth
- ETU Short-Term Treated Turf Aggregate (Toddlers) which combines treated turf post application exposures (incidental oral and dermal) plus average daily food and drinking water exposure for toddlers
- ETU Short/Intermediate-Term Treated Turf Aggregate (Adults "Golfers") which considers short-term residential exposures (dermal) plus average daily food and drinking water exposure for adults participating in activities such as golfing on treated turf
- ETU Long-Term (Chronic, Non-Cancer) Aggregate which considers chronic

exposure from food and drinking water only

- ETU Cancer Aggregate which combines handler garden exposures (dermal and inhalation), post application garden exposures (dermal), post application treated turf exposures (dermal) and average daily food and drinking water exposure for adults

7.1 Acute Aggregate Risk

The acute aggregate risk assessment for ETU considers acute exposure from food and drinking water. An acute endpoint was selected only for the subpopulation, females 13-49 years old, so an acute aggregate assessment is required only for this subpopulation. Since HED usually considers only dietary (food and drinking water) contributions to ETU acute aggregate risk, the ETU acute aggregate risk assessment is equivalent to the ETU acute dietary (food and drinking water) risk assessment detailed in Section 5.2.2.

7.2 Short- and Intermediate-Term Aggregate Risk

7.2.1 ETU Short- and Intermediate-Term Home Garden Aggregate

The ETU short/intermediate-term home garden aggregate combines handler inhalation and dermal exposures and post application garden dermal exposures plus average daily food and drinking water for adults exposed to ETU. For youth exposed to ETU, the assessment combines post application garden dermal exposures with average food and drinking water. Only mancozeb is registered for use in home garden settings. Average food and drinking water exposure values reflect the most highly exposed adult or youth subpopulation from the average daily dietary assessment, and consider ETU derived from mancozeb, metiram, and maneb applications. The existing and proposed food uses were included in the food and drinking water exposure estimates.

The ETU short/intermediate-term home garden aggregate MOEs for adults and youth exceed 1000, the level of concern for this risk assessment, and are not of concern. Aggregate risk results are shown in Table 7.1.

Table 7.1 ETU Short/Intermediate-Term Home Garden Aggregate Risk Results						
Population	Short/Intermediate-Term Scenario					
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food & Water Exposure[3] mg/kg/day	Residential Exposure[4] mg/kg/day	Aggregate MOE (food, water and residential)[5]
Adults – handler and post-application	5	1000	0.005	0.000061	0.000318	13000
Youth – post-application	7	1000	0.007	0.00017	0.000240	17000

[1] The LOC is based on $UF_A = 10$, $UF_H = 10$, $UF_{DB} = 10$ (Table 3.4).
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Average food and drinking water exposure taken from most highly exposed adult or youth subpopulation from the chronic dietary exposure assessment in Table 5.2. Food and drinking water consider ETU derived from existing and proposed uses of mancozeb, metiram, and maneb.
[4] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. Combined dermal and inhalation exposure for adult handlers is 8.1×10^{-6} mg/kg/day (Table 6.1). Dermal postapplication exposure for adults is 3.1×10^{-4} mg/kg/day (Table 6.3). Dermal postapplication exposure for youth is 2.4×10^{-4} mg/kg/day (Table 6.3). Only mancozeb is registered for use in home garden settings.
[5] Aggregate MOE = [NOAEL / (Avg Food & Drinking water Exposure + Residential Exposure)]

7.2.2 ETU Short-Term Treated Turf Aggregate (Toddlers)

The short-term treated turf aggregate risk assessment combines treated turf post application incidental oral and dermal exposures with average daily food and drinking water exposure for toddlers. Maneb and mancozeb are both registered for applications to sod farms. Average food and drinking water exposure values, including all sources of ETU, reflect the most highly exposed children's subpopulation from the chronic dietary assessment.

The ETU short-term treated turf aggregate MOE for toddlers exceeds 1000, the level of concern for this risk assessment, and is not of concern. Aggregate risk results are shown in Table 7.2.

Table 7.2 ETU Short-Term Treated Turf (Toddlers) Aggregate Risk Results

Population	Short-Term Post-Application Scenario					
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food & Water Exposure[3] mg/kg/day	Residential Exposure[4] mg/kg/day	Aggregate MOE (food and residential)[5]
Toddlers – mancozeb derived ETU	7	1000	0.007	0.00017	0.00596	1100
Toddlers – maneb derived ETU	7	1000	0.007	0.00017	0.00531	1280

[1] The LOC is based on $UF_A = 10$, $UF_H = 10$, $UF_{DB} = 10$

[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC

[3] Average food and drinking water exposure taken from most highly exposed child subpopulation from the chronic dietary exposure assessment in Table 5.2.

[4] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. For mancozeb, incidental oral exposure is 0.00376 mg/kg/day (Table 6.5). Dermal exposure is 0.0022 mg/kg/day (Table 6.6). For maneb, incidental oral exposure is 0.0019 mg/kg/day (Table 6.9). Dermal exposure is 0.0034 mg/kg/day (Table 6.10).

[5] Aggregate MOE = [(NOAEL / (Avg Food & Drinking water Exposure + Residential Exposure)]

7.2.3 ETU Short- and Intermediate-Term Treated Turf Aggregate (Adult "Golfers")

The short/intermediate-term treated turf aggregate risk assessment combines dermal exposures for adults participating in activities such as golfing on treated turf exposed to ETU with average daily food and drinking water exposures. Only mancozeb uses are relevant for this scenario.

The ETU short-term treated turf aggregate MOE for adults ("golfers") exceeds 1000, the level of concern for this risk assessment and is; therefore, not of concern. Aggregate risk results are shown in Table 7.3.

Table 7.3 ETU Short/Intermediate-Term Treated Turf (Adults "Golfers") Aggregate Risk Results

Population	Short-Term Scenario					
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food & Water Exposure[3] mg/kg/day	Residential Exposure[4] mg/kg/day	Aggregate MOE (food and residential)[5]
Adults (Golfers)	5	1000	0.005	0.000061	0.00076	6100

[1] The LOC is based on $UF_A = 10$, $UF_H = 10$, $UF_{DB} = 10$

[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC

[3] Average food and drinking water exposure taken from most highly exposed adult subpopulation from the chronic dietary exposure assessment in Table 5.2. Food and drinking water consider ETU derived from existing and proposed uses of mancozeb, metiram, and maneb.

[4] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. Adult dermal exposure is 0.00076 mg/kg/day for mancozeb treated turf (Table 6.7)

[5] Aggregate MOE = [(NOAEL) / (Avg Food & Drinking water Exposure + Residential Exposure)]

7.3 Long-Term (Chronic) Aggregate Risk

As noted above, there are no long-term residential exposure scenarios for the existing and proposed uses on the EBDCs which would result in long term residential exposures to ETU. Therefore, the long-term or chronic (non-cancer) aggregate risk for ETU includes contribution from dietary (food and drinking water) exposure alone. The chronic (non-cancer) aggregate risk assessment for ETU is equivalent to the ETU chronic dietary risk assessment discussed in Section 5.2.3 of this document.

7.5 Cancer Aggregate Risk

For the aggregate cancer risk assessment, HED combined residential handler and post application exposures for adults exposed to ETU from the home garden uses, as well as post application exposures to adults from contact with treated turf during activities such as golfing. The combined residential exposure was then aggregated with dietary exposure to ETU from food and drinking water and multiplied by the ETU Q_1^*. The existing and proposed uses of mancozeb, metiram, and mancozeb were considered for dietary exposure. The maneb residential use was not aggregated because the mancozeb residential uses will result in much higher exposures than the maneb sod farm use and exposure to an individual from sod farm uses of both chemicals is considered unlikely.

ETU aggregate cancer results are shown in Table 7.4.

Table 7.4 ETU Aggregate Cancer Results					
Population	**Q_1* (mg/kg/day)$^{-1}$**	**Negligible Risk Level[1]**	**Average daily Food & Water Exposure[2] (mg/kg/day)**	**Residential Exposure[3] (LADD)**	**Aggregate Cancer Risk (food, water and residential)[4]**
U.S. Population	6.01×10^{-2}	3×10^{-6}	6.0×10^{-5}	4×10^{-6}	3.8×10^{-6}

[1] Because of the uncertainties in the hazard quantification methodology, risk estimates ranging from 1×10^{-6} to 3×10^{-6} are generally considered indistinguishable. Generally, cancer risk estimates which do not exceed 3×10^{-6} are below HED's level of concern.
[2] From Table 5.2.
[3] Handler LADD (low pressure handwand – highest exposure scenario) is 3.8×10^{-7} from Table 6.2. Home garden post application LADD is 2.6×10^{-6} from Table 6.4 (risk/ Q_1* = exposure). Treated turf post app LADD is 1.0×10^{-6} from Table 6.8. Total residential exposure is 3.98×10^{-6}.
[4] Aggregate cancer risks are for the U.S. Population and are calculating the Q_1* (0.0601) by the total exposure.

The aggregate cancer risk is approximately 3.8×10^{-6}, which exceeds HED's level of concern. In fact, the aggregate food and drinking water risk also exceeds HED's level of concern, before aggregation with residential exposures. Therefore, HED conducted sensitivity analyses to determine the commodities that provided the most contribution to the ETU exposure. The commodities that are the greatest contributors to ETU exposure are bananas, leaf lettuce, drinking water, turnip greens, grape juice and mangoes (Table 5.3). The results of the aggregate sensitivity analyses may be found in Table 7.5. If the proposed tolerance in/on bananas (from metiram applications) is removed from the aggregate, then the aggregate cancer risk does not exceed HED's level of concern. All of the other sensitivity analyses resulted in risks exceeding the level of concern. Note that the metiram-derived ETU residue values from banana field trials used in the aggregate assessment are considered to be overestimates. Projected percent crop treated information was not available, so percent imported information was used, and it is highly unlikely that all imported bananas will be treated. In general, monitoring data on other commodities show much lower residues than field trial data, so actual exposure is likely to be lower

Table 7.5 Sensitivity Analyses for ETU Aggregate Cancer Results				
Scenario	**Negligible Risk Level[1]**	**Average daily Food & Water Exposure[2] (mg/kg/day)**	**Residential Exposure [3] (LADD)**	**Aggregate Cancer Risk (food, water and residential)[4]**
Food, Water, Residential, all proposed uses	3×10^{-6}	6.0×10^{-5}	4×10^{-6}	3.8×10^{-6}
Food, Water, Residential, excluding proposed banana tolerance	3×10^{-6}	5.0×10^{-5}	4×10^{-6}	3.2×10^{-6}
Food, Water, Residential, excluding proposed use of mancozeb on leaf lettuce	3×10^{-6}	5.9×10^{-5}	4×10^{-6}	3.8×10^{-6}
Food, Water, Residential, all proposed uses, assuming 1% crop Treated for turnip greens	3×10^{-6}	5.6×10^{-5}	4×10^{-6}	3.6×10^{-6}

[1] Because of the uncertainties in the hazard quantification methodology, risk estimates ranging from 1×10^{-6} to 3×10^{-6} are generally considered indistinguishable. Generally, cancer risk estimates which do not exceed 3×10^{-6} are below HED's level of concern.

[2] From Table 5.2.

[3] Handler LADD (low pressure handwand – highest exposure scenario) is 3.8×10^{-7} from Table 6.2. Home garden post application LADD is 2.6×10^{-6} from Table 6.4 (risk/ Q_1^* = exposure). Treated turf post app LADD is 1.0×10^{-6} from Table 6.8. Total residential exposure is 3.98×10^{-6}.

[4] Aggregate cancer risks are for the U.S. Population and are calculating the Q_1^* (0.0601) by the total exposure.

8.0 Cumulative Risk Characterization/Assessment

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."

No determination of a common toxic effect or mechanism of toxicity has been made for acute or chronic non-cancer risks from EBDCs.

9.0 Occupational Exposure/Risk Pathway

The occupational aspect of the human health risk assessment has been completed for each of the EBDC fungicides in the risk assessments of the parent compound.

10.0 Data Needs and Label Recommendations

The data gaps for each individual EBDC and the corresponding exposures to ETU are discussed in the risk assessments for each parent compound. The data gaps for ETU, which were previously identified in the 2005 human health risk assessment, include the following:

Toxicology

• Guideline 870.3800	2-generation reproduction, rat
• Guideline 870.3700	Developmental toxicity, rabbit
• Guideline 870.6300	Developmental neurotoxicity
• Non-guideline	Comparative study for thyroid toxicity in adults and offspring

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R149574

Chemical:	**ethylenethiourea**
	PC Code:
	600016
HED File Code:	**14100 Other Risk Documents**
Memo Date:	**6/14/2007**
File ID:	**DPD337241**
	DPD317416
	DPD327307
	DPD327318
	DPD317368
	DPD295411
	DPD267866
	DPD322230
	DPD289183
	DPD294203
	DPD337240
	DPD323143
	DPD323141
Accession #:	**000-00-0120**

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