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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Ethylenethiourea: Toxicology Considerations in Relation to the Registration Standards on the Ethylenebisdithiocarbamates

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Caswell #'s 41A, 443AA, 539, 913A, 585

The attached document consists of the Toxicology Branch's position on ethylene-thiourea (ETU) in relation to the ethylenebisdithiocarbamates (EBDC's) for which Registration Standards have been generated. Tolerance reassessment was only done in one of these standards and that was for Mancozeb. Tolerance reassessments are done for the other EBDC's (Maneb, Metiram and Nabam) in this document as well as a discussion of these reassessments, including that for mancozeb, in relation to ETU.

The review, which should be considered as part of the Registration Standard for each of the EBDC's, consists of the following sections:

1. Background;

2. Discussion of toxicity and metabolism data on ETU - this discussion

is by no means a complete review of the literature on ETU but highlights the more important issues involving the toxicity of ETU;

3. Tolerance Considerations for ETU and the EBDC's;

4. Toxicological Issues;

5. Toxicology data requirements on ETU for the continued registration of each of the EBDC's;

6. DER's on ETU studies reviewed by Toxicology Branch;

7. Toxicology Branch Peer Review Committe report on ETU.

Ethylenethiourea

1. Background

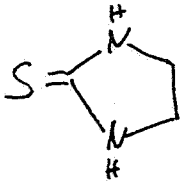
Ethylenethiourea (ETU is a contaminant/metabolite/degradation product of the ethylenebisdithiocarbamates (EBDC's). The EBDC's for which Registration Standards have been written are maneb, mancozeb, metiram and nabam. These four chemicals are also the subject for an NRDC lawsuit and resulting Data-Call-In.

Maneb is registered for control of early and late blights on potatoes and tomatoes, and many other diseases of fruits, vegetables and field crops and as a turf fungicide. Mancozeb is registered for use as a seed treatment for cotton, potatoes, corn, safflower, sorghum, peanuts, tomatoes, flax and cereal grains. Metiram contols diseases on top fruits, asparagus, cotton, peanuts, potatoes, sweat corn, grapes, vegetables and ornamentals. Nabam has several industrial uses and is also used in sugar refining. Nabam no longer has any other food uses.

Several documents have been generated by the EPA on ETU and/or the EBDC's. These include:

- Ethylene Bisdithiocarbamates. Decision Document. Final Resolution of Rebuttable Presumption against Registration. October 14, 1982.
- The Carcinogen Assessment Group's Risk Assessment on Ethylenebisdithiocarbamate (EBDC). June 7, 1979.

Structure of ETU:



2. Available Toxicity and Metabolism Data on ETU

Subchronic Toxicity

Two subchronic ETU toxicity studies in rats can be found in the open literature. The purpose of both studies was to examine in some detail the subchronic effects of ETU on the thyroid. In one study (Graham, et al., 1972) levels of 50, 100, 500 and 750 ppm were fed in the diets to male, Osborne-Mendel rats for 30, 60, 90 and 120 days. A NOEL was not determined in this study due to effects of ETU seen on thyroid weights at all dosage levels at 120 days. In the other rat (Charles River, Sprague-Dawley) study (Freudenthal, et al., 1977) a NOEL of 5 ppm was determined for the effects of ETU on the thyroid. Thyroid toxicity seen at levels above 5 ppm consisted of thyroid hyperplasia, decreased uptake of ^{125}I by the thyroid and decreased serum levels of T_3 and T_4.

The National Toxicology Program (Peters, et al., 1980) had a 90-day toxicity

study conducted in Fischer 344 rats. ETU was administered in the diet at levels of 0, 60, 125, 500 and 750 ppm. A NOEL for the effects of ETU on the liver of Fischer 344 male ras was not determined due to hepatocytic cellular atypia seen at all dosage levels. A NOEL of 60 ppm in males and 125 ppm in females was found for the effects of ETU on the thyroid (follicular hyperplasia). Judging from the results of this study it appears that the Sprague-Dawley rat is more sensitive to the effects of ETU on the thyroid than the Fischer 344 rat.

In another study done by Battelle Columbus Laboratories (Leber, et al., 1978) in Sprague-Dawley rats, it was shown that serum T_3 and T_4 levels return to normal within 2-4 weeks after discontinuing ETU in the diet. Administration of T_3 and T_4 along with ETU did not completely reverse the effects of ETU on T_3/T_4 levels.

In a 90-day mouse (Charles River CD-1, O'Hara and DiDonata, 1985) oral administration of ETU resulted in an increased incidence of follicular cell hyperplasia in male and female mice at levels of 100 ppm and higher in the diet. The NOEL for these effects was 10 ppm (equivalent to 1.72 mg/kg/day in males and 2.38 mg/kg/day in females). A NOEL of 10 ppm was established for the effects of ETU on the liver based upon increased relative liver weights in female mice at 100 ppm and 1000 ppm ETU.

A 21 week ETU subchronic toxicity study in male and female Rhesus monkeys was conduced by Battelle Columbus Laboratories (Freudenthal, et al., undated) for the EPA. The dosage levels tested were 0, 2, 10, 50, and 250 ppm. Serum thyroid hormone concentrations were measured as well as iodine uptake in the thyroid. Thyroid and pituitary were examined microscopically only at 50 and 250 ppm. Mild to moderate pituitary hypertrophy was seen at 50 and 250 ppm ETU as well as thyroid follicular lining cell hypertrophy and hyperplasia (mild, 50 ppm; moderate to severe, 250 ppm). Serum levels of T_4 were significantly decreased in the 250 ppm group. FTI, a measurement of free serum T_4 levels, was also significantly decreased in both the 50 and 250 ppm group; iodine uptake was signficantly increased at these levels; and TSH levels were significantly increased at 250 ppm.

In a six month Rhesus monkey study (Leber et al., 1978) dosage levels of 0, 50, 150 and 450 ppm ETU were used. Pituitary as well as thyroid hormone levels were measured in this study. A NOEL was not demonstrated in this study due to the effects of ETU on the thyroid as would be expected from the results of the 21 week study previously discussed. Of note in this study was the fact that the pituitary hormone levels were unaffected by ETU.

The effect of ETU on the thyroid gland of dogs was studied for 6 months at one dosage level (0.1% of the diet) by Kameda (1982). The thyroids of treated dogs increased to 30 times their normal size and not only follicular but also C-cells of the thyroid were hyperplastic and hypertrophic.

Chronic Toxicity/Oncogenicity

o Innes Study (1969)

In the Innes study two hybrid strains of mice were used, (C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1. Eighteen mice per sex per group were used

in the treatment group. Only one dose was tested which was stated to be the maximum tolerated dose. When the mice were seven days old, 215 mg/kg ETU was given by stomach tube daily. At 28 days of age, the mice were given diets containing 646 ppm of ETU. The mice were killed after a total of 83 weeks of treatment. Histopathology consisted of examination of all major organs and of all grossly visible lesions. Thyroid glands were apparently not examined.

A statistically significant increase was reported for hepatomas in both strains of mice in both males and females. Liver tumors were not classified as adenomas or carcinomas but only as hepatomas.

o Ulland Study (1972)

Groups of 26 rats (Charles River CD)/sex were administered 175 or 350 ppm of ETU in the diet for 18 month. At that time 5 rats/sex were killed and the remaining rats were placed on control diets until termination of the study at 24 months. The control group consisted of 32 male and 32 female rats. The report states that no thyroid lesions were seen in the control groups.

An increase in the incidence of thyroid follicular cell carcinomas was seen in both sexes of both dasage groups. The number of animals examined was not given; however, CAG assumed 26 rats per group for the treated group and 32 for the control group for their review. The thyroid was apparently the only tissue evaluated. The author did state that "possibly additional carcinomas could have been discovered if serial sections had been done in the goitrous gland".

o Graham Study (1975)

Five groups of 68 male and 68 female Charles River rats were placed on diets containing 0, 5, 25, 125, 250 or 500 ppm ETU. The duration of the study was 2 years. At 18 and 24 months five rats per sex from each group were given 5 uCi ^{131}I by i.p. injection, fasted for 24 hours and killed. At the end of 66 weeks 3 rats/sex/group were placed on the control diet for the remainder of the study to determine the reversibility of thyroid toxicity due to ETU.

Body weight gain was adversely affected at the highest dose tested at 18 and 24 months for both males and females. ^{131}I uptake was statistically significantly increased in male rats at 18 months in the 25 and 125 ppm groups and decreased at 500 ppm. At 24 months in male rats, ^{131}I uptake was significantly increased in the 5 ppm group and decreased in the 500 ppm group. Because of large variability in the values obtained, there were no statistically significant differences in ^{131}I uptake in female rats.

Histopathology incidence data were combined for males and females. An increase in the number of rats with cataracts/keratitis and with thyroid follicular adenocarcinoma/carcinoma was observed in the groups fed 250 ppm and 500 ppm ETU; with thyroid adenomas in the 250 ppm group; and with thyroid hyperplasia in the 5, 25, 125 and 250 ppm groups. A NOEL was not determined for the effects of ETU on the thyroid in this study.

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Interim sacrifices at 6 and 12 months were also done as a part of this study and reported elsewhere (Graham, 1973). To quote this paper, "At the 500 ppm level, carcinomas [thyroid follicular] were found in 77% of the male rats....At the 500 ppm level, carcinomas were found in 42% of the female rats".

o Gak Study (1976)

ETU did not produce any tumors in hamsters fed diets containing 0, 5, 17, 60 and 200 ppm ETU for 20 months.

Developmental Toxicity

ETU has been shown to be a teratogen in rats and hamster. In rats it produces a wide variety of anomalies in the central nervous, urogenital, and skeletal systems as well as other organs at dosages that do not produce maternal or fetotoxicity. The NOEL for these effects is 5 mg/kg (Khera, 1973). Administration of T_3/T_4 with ETU to pregnant rats appears to reduce the incidence of some but not all of these effects (Lu and Staples, 1978), indicating that the effect of ETU on the thyroid is not the only possible mechanism for teratogenicity.

The hamster is not as sensitive as the rat to the teratogenic effects of ETU. The dose resulting in abnormalities such as hydrocephalus in the hamster was 27 times that resulting in hydrocephalus in the rat. In addition fewer tissues/organs were affected in the hamster (Teramoto, et al. 1978).

ETU was not teratogenic to mice (Teramoto, et al. 1978, rabbits (Khera, 1973), guinea pigs (Chernoff, 1979) or cats (Khera and Iverson, 1978).

Mutagenicity

Extensive literature references are available on the mutagenicity of ETU. Two assays (transformation) were submitted as part of the Data-Call-In for Mancozeb. The results of the assays from the available literature references and the two transformation assays are tabulated below.

Mutagenicity of ETU

Assay System	Result	Classification	Reference
Transformation in C3H 10T 1/2 cells	negative	acceptable	McGlynn-Kreft, (1984)
Transformation for promotion in C3H 10T 1/2 cells	negative	unacceptable	McLeod (1985)
Drosophila, sex-linked recessive lethal	negative	unclassified	Molet (1975) Purchase and Ray (1981)
E. coli WP_2 Reversion	negative	unclassified	Bridges, et al. (1981)

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Chromosomal aberrations in Chinese hamster DON cells	negative	unclassified	Teramoto, (1977)
Mouse dominant lethal	negative	unclassified	Sram (1975) Schupbach and Hummer (1976)
Chromosomal aberrations in bone marrow - mice	positive	unclassified	Sram (1975)
UDS - HeLa cells	positive	unclassified	Ashby and Kilbey (1981)
UDS - human fibroblasts	negative	unclassified	Ashby and Kilbey (1981)
Transformation BHK 21 cells	positive	unclassified	Brookes and Preston (1981)
Sister chromatid exchange in CHO cells	negative	unclassified	Brookes and Preston (1981)
Cytogenetics in CHO cells	negative	unclassified	ibid, (1981)
Gene mutation - mouse lymphoma cells	negative	unclassified	ibid, (1981)
Gene mutation - CHO-HGPRT assay	negative	unclassified	ibid, (1981)
S. cerevisiae - mitotic recombinants			
Strain JD1 & D7	positive	unclassified	deSerres and Hoffman (1981) . Wilkie and Gooneskera (1980)
Strain T1, T2, D4	negative	unclassified	
Ames Assay			
his G-46, TA 1535	positive/		
TA 98, 100, 1537, 1538	negative	unclassified	Tchinotsubo et al. (1981) & Bridges et al. (1981)
Micronucleus, mouse bone marrow	negative	unclassified	Purchase and Ray (1981)

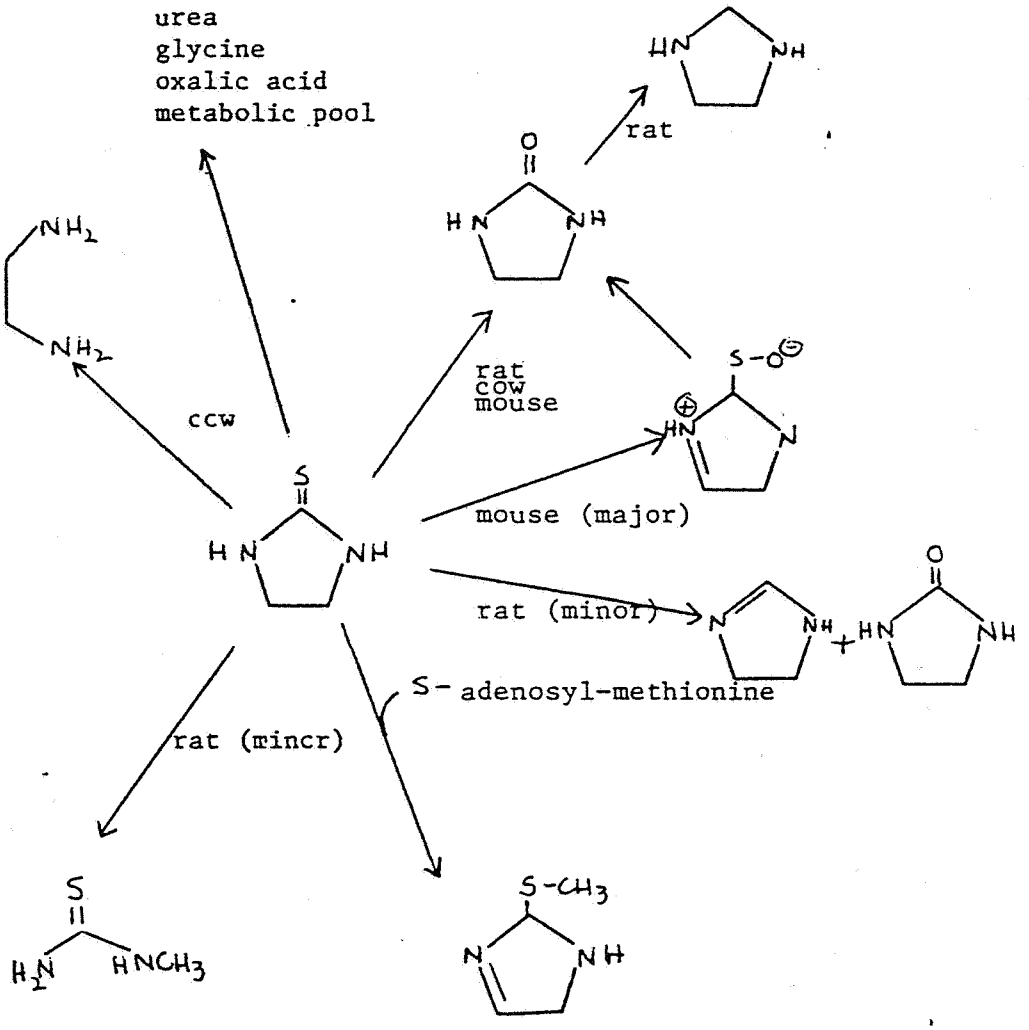
The results of mutagenicity assays on ETU are mixed with most of the assays being negative.

Metabolism

A scheme of known metabolic pathways for ETU can be found in figure 1.

In Rhesus monkeys, 50% of an administered dose of ^{14}C-ETU was excreted in the urine within 24 hours and 90 % within 72 hours. Only 0-0.68% of the

Figure 1. Metabolism of ETU



label was eliminated in the feces at 24 hours and no radioactivity was found at the 48 and 72 hour sampling periods (Emmerling, 1978).

In Wistar rats ^{14}C-ETU is predominately excreted in the urine (Saxton, 1972). The ratio of urine to fecal excretion varies with dose, i.e. 0.1 ppm ETU the ratio was 55/25, at 10 ppm ETU the ratio was 70/10. Minimal radioactivity was recovered as $^{14}CO_2$ ($\leq$0.5%). The level of radioactivity plateaued in the thyroid gland after eight days of dosing and declined rapidly once dosing was terminated.

The NTP (Peters, 1982) conducted a study entitled "Maximum Neonatal Dose Studies with Ethylenethiourea" in which ^{14}C-ETU was given to pregnant rats and mice. ETU equivalents were determined in maternal blood and liver, in fetal tissues and maternal milk. Differences were found in the pharmacokinetic behavior of ETU in rats and mice:

1. The mouse is more efficient in eliminating ETU and its metabolites;

2. ETU and its metabolites accumulated in mouse liver more so than in rat liver. This was true for dams and neonates;

3. The level of ETU equivalents in rat neonatal blood was about equal to those in milk; however, mouse neonatal blood levels were 13 times less than milk levels; and

4. There is no dose-dependency in tissue disposition of ETU equivalents in the mouse. In the rat there is a dose-dependent decrease in tissue levels of ETU equivalents with increasing exposure of the dam to ETU.

Toxicity of Metabolites

Ethylene Urea: Ethylene urea (EU) was testd for carcinogenicity at the same dosage levels as EU (see Chronic Tox./Onco. Section on ETU) in two strains of mice by Innes et al. (1969). EU at this dosage level did not induce an oncogenic response in either strain of mice. At a single dose level of 480 mg/kg EU was not teratogenic to rats (Ruddick et al., 1976a).

Imidazole: Imidazole is not teratogenic to rats (Ruddick, et al., 1976b).

o Ethylenebisisothiocyanato sulfide (EBIS)

EBIS is not a metabolite of ETU but is a common metabolite of the EBDC's and is, itself, metabolized to ETU. EBIS was not teratogenic to either rat or mouse (Chernoff, et al., 1979). In the rat it was tested at dosage levels of 0, 7.5, 25, and 30 mg/kg and in mice at 0, 50, 100 and 200 mg/kg. At 30 mg/kg in the rat a statistically significant decrease in body weight gain and an increase in liver to body weight ratio was seen in the dams. Administration of EBIS did cause a significant decrease in fetal weight and eye opening in female rats. At 200 mg/kg in mice an increase in liver to body weight ratio was seen in the dams.

Administration of 50 mg/kg day EBIS to rats by gavage for 15 days resulted in hind leg paralysis which was reversible once treatment was stopped

(Chernoff, et al., 1979). Hind leg paralysis was not seen at 25 mg/kg/day in rats nor in mice treated with up to 300 mg/kg/day. Decreased T_4 and ^{125}I thyroid uptake was also seen in rats treated with 50 mg/kg day EBIS for one week (Freudenthal, et al., 1979).

It should be noted that metiram has been reported to cause skeletal atrophy in rats at a oral dosage of 16 mg/kg/day after two years of administration. Maneb administered to mongrel dogs for a period of one year has been found to produce edema of spinal nerves with loss of myelin at levels of 2 mg/kg/day and above (see metiram and maneb Registration Standards).

3. Tolerance Considerations for ETU and the EBDC's

The establishment of a tolerance for ETU and the EBDC's on various RAC's is a complex issue. The toxicology data base on each of the EBDC's is insufficient to determine an ADI for these chemicals and also does not allow a decision as to whether the toxicity seen in the studies is due to the EBDC or to ETU. Since ETU is a metabolite, contaminant, and breakdown product of the EBDC's, since it has been shown to be an oncogen, a thyroid toxicant and a teratogen and since the total amount of exposure of the human to ETU through the use of the EBDC's on RAC's is not known, the most conservative approach to regulating the EBDC's is to assume 100% conversion to ETU and setting an ADI based on the available toxicology data base on ETU. In using such an approach, the parent EBDC, ETU and the intermediate metabolites between the EBDC and ETU would be considered in the tolerance. This approach would be reconsidered when the toxicolgy data base on the EBDC's has been completed and when adequate residue and processing data on both the EBDC's and ETU are available in order to determine the appropriate means, based upon scientific data, to regulate the use of the EBDC's.

A NOEL for the effects of ETU on the thyroid has not been determined in the rat, since at 5 ppm in the diet after 2 years of feeding a high incidence of thyroid follicular hyperplasia was seen in male and female rats (Graham, 197?). Using 5 ppm, which converts to 0.25 mg/kg/day (0.05 conversion factor for the rat), a safety factor of 1000 since this is an LEL and an additional factor of 10 since the lesion was seen at such a high incidence at the lowest dose tested and due to data gaps, a PADI based on the available data base on ETU can be calculated to be 0.00003 mg/kg/day.

Provisional ADI's and/or Preliminary Limiting Doses can also be calculated for each of the EBDC's as follows:

o Mancozeb

The study chosen to calculate a PADI for mancozeb was a 90-day dog feeding study (Cox, 1986). A NOEL of 3 mg/kg/day was determined for this study based upon decreased food consumption and body weight gain, thymic cortical lymphoid deletion and prostatic hypogenesis at the LEL of 29 mg/kg/day. A two-year dog study with a NOEL of 2.5 mg/kg/day was not used because it was of inadequate quality.

Using an uncertainty factor of 1000 for a subchronic study the PADI can be determined to be 0.003 mg/kg/day. As noted in the mancozeb registration

standard the TMRC would exceed the PADI by 940%. However, using the PADI calculated for ETU, assuming 100% conversion of mancozeb to ETU as discussed above, the TMRC would exceed the PADI by 96,120%.

o Maneb

The study chosen to calculate a PLD for maneb was a 6-month feeding study in Rhesus monkeys. A NOEL of 5 mg/kg/day was determined for this study based upon increased thyroid weights seen at the LEL of 15 mg/kg/day. The PLD can be calculated using a 100 fold safety factor and modifying factor of 10 due to extensive data gaps to be 0.005 mg/kg/day. The TMRC exceeds this PLD by 620%; however using the PADI calculated for ETU, assuming 100% conversion of maneb to ETU as was discussed above, the TMRC would exceed the PADI by 104,490%.

o Metiram

The study chosen to calculate a PADI for metiram was a rat reproduction study in which a NOEL was not established. The LEL was 5ppm or 0.25 mg/kg/day. Using a safety factor of 100 for a chronic study and an additional factor of 10 since this a LEL and there are significant data gaps, the PADI can be calculated to be 0.00025 mg/kg/day. The TMRC exceeds by 2572% this PLD; however, using the PADI calculated for ETU, assuming 100% conversion of metiram to ETU as was discussed above, the TMRC would exceed the PADI by 21,700%.

o Nabam

The study chosen to calculate a PLD for nabam was a 90-day dog study. The NOEL was established at 0.09 mg/kg/day based upon reduced body weight for males at 0.4 and 0.2 mg/kg/day and an increasingly large number of casts in the kidney of male rats. Using a safety factor of 1000 since this is a subchronic study and there are extensive data gaps, the PLD can be calculated to be 0.00009 mg/kg/day. According to SIS there are no food tolerances for nabam despite the one remaining in the CFR for melons.

4. Toxicological Issues

ETU has been classified as a B2 oncogen (probable human carcinogen) by the Toxicology Branch Peer Review Committee. The Committee stated the following in their final report on ETU:

> ETU induced an increased incidence of thyroid follicular cell adenomas and adenocarcinomas in Charles River CD rats (two separate studies) and of hepatomas in two strains of mice [(C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1] which meets criteria a of this category as defined in the proposed EPA Guidelines (Draft Jan. 7, 1986) for classifying a carcinogen. Also criteria c is met in that ETU induces thryoid tumors in rats after one year or less of treatment and that it induces both thyroid tumors in rats and hepatomas in mice to an unusual degree in a single experiment with regard to high incidence. This classificatin is also supported by positive structure-activity data since several other thyroid inhibitors (i.e. thiouracil and thiourea) have been found to induce hepatomas and/or thyroid tumors in rodents. The Committee

also noted that in the Graham rat study evidence of progression of the neoplastic process in the thyroid was present. Results of available mutagenicity data were mostly negative and, therefore, could not be used as supportive information.

The CAG in their document on the ethylenebisdithiocarbamates calculated an oncogenic potency estimate for ETU of 0.1428 mg/kg/day based upon the liver tumors seen in mice in the Innes (1969) study.

Also of toxicological concern is the teratogenic potential of ETU. ETU has been shown to be a teratogen in rats causing meningoencephalocele, meningorrhagia, meninhorrhea, hydrocephalus, obliterated neural canal, abnormal pelvic limb posture with equinovarus, and short or kinky tail at dosages of 10 mg/kg and higher. The NOEL for these effects was 5 mg/kg. A concern for the exposure of applicators was expressed in the Decision Document, 1982. This still remains as a possible concern since the exact amount of ETU that the applicator is exposed to is not known.

b. Toxicological Data Requirements on ETU for the Continued Registration of the EBDC's

Toxicology Branch feels that two additional studies on ETU should be required. These consist of a chronic dog study and a 2-generation reproduction study in the rat. The reasons for requesting these studies are as follows:

- o No adquate study is available for the effects of ETU in the dog;
- o Mancozeb and nabam have been found to cause kidney effects in the dog and the question needs to be answered as to whether these effects are due to ETU or to the EBDC, itself;
- o No study is available that addresses the possible reproductive effects of ETU; and
- o Metiram caused decreased litter size and reduced fertility in rats and mancozeb also caused reduced fertility in rats in reproduction studies on each of these EBDC's. Again the question of whether these effects are due to ETU or to the EBDC needs to be addressed.

In addition Toxicology Branch recommends that a chronic toxicity study in the Sprague-Dawley rat be done to determine the NOEL for the effects of ETU on the thyroid. The results of such a study could result in raising the ADI of ETU to a higher level.

No testing will be required at this time on the metabolites of ETU since from the available data, ETU appears to be more toxic than some of its metabolites and since its metabolites are formed in animals, it is assumed that they were tested through autoexposure in the ETU toxicity studies. No testing will be required on EBIS, a common metabolite of each of the EBDC's, at this time since the EBDC's, metiram and maneb appear to cause neurological toxicity at doses lower that that produced by EBIS and since EBIS is an animal metabolite of the EBDC's, it is assumed that EBIS was tested through autoexposure in the EBDC toxicity studies.

TOXICOLOGY BRANCH ADI PRINTOUT Date: 10/22/86

Maneb
Caswell #539
CFR No. 180.110
6mo feeding- monkey
NOEL = 5.0000 mg/kg
LEL = 15.0000 mg/kg
PADI = 0.005000 mg/kg/day
Safety Factor = 1000
Status: TOX complete 10/15/86. ORD verified 12/2/85. TOX, ORD values need be reconciled.

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
1	Almonds	0.100		0.03	0.000045000
2	Apples	7.000		2.53	0.265650000
3	Apricots	10.000		0.11	0.016500000
7	Bananas	0.500		1.42	0.010650000
9	Beans	10.000		2.04	0.306000000
19	Broccoli	10.000		0.10	0.015000000
20	Brussel sprouts	10.000		0.03	0.004500000
22	Cabbage, sauerkraut	10.000		0.74	0.111000000
24	Carrots	7.000		0.48	0.050400000
27	Cauliflower	10.000		0.07	0.010500000
28	Celery	5.000		0.29	0.021750000
37	Collards	10.000		0.08	0.012000000
40	Corn, sweet	5.000		1.43	0.107250000
44	Cranberries	7.000		0.03	0.003150000
46	Cucumbers, including pickles	4.000		0.73	0.043800000
53	Eggplant	7.000		0.03	0.003150000
56	Escarole/endive	10.000		0.03	0.004500000
57	Figs	7.000		0.03	0.003150000
66	Grapes, including raisins	7.000		0.49	0.051450000
75	Kale	10.000		0.03	0.004500000
76	Kohlrabi	10.000		0.03	0.004500000
84	Lettuce	10.000		1.31	0.196500000
92	Melons	4.000		2.00	0.120000000
99	Mustard greens	10.000		0.06	0.009000000
100	Nectarines	10.000		0.03	0.004500000
105	Onions	7.000		0.83	0.087150000
109	Papayas	10.000		0.03	0.004500000
114	Peaches	10.000		0.90	0.135000000
120	Peppers	7.000		0.12	0.012600000
127	Potatoes	0.100		5.43	0.008145000
131	Pumpkin, including squash	7.000		0.11	0.011550000
136	Rhubarb	10.000		0.05	0.007500000
150	Spinach	10.000		0.05	0.007500000
153	Chestnuts	45.000		0.03	0.020250000
163	Tomatoes	4.000		2.87	0.172200000
165	Turnips	7.000		0.05	0.005250000
166	Turnip greens	10.000		0.03	0.004500000
177	Chinese cabbage	10.000		0.03	0.004500000

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
TMRC				%PADI
0.031001 mg/kg/day (60kg BW, 1.5kg diet)				620.030000

RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No tox-approved tolerances are listed in the file.

TMRC				%PADI
0.031001 mg/kg/day (60kg BW, 1.5kg diet)				620.030000

RESIDUE CONTRIBUTION OF NEW (PENDING) TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No new tolerances are listed in the file.

TMRC				%PADI
0.031001 mg/kg/day (60kg BW, 1.5kg diet)				620.030000

TOXICOLOGY BRANCH ADI PRINTOUT Date: 10/22/86

Metiram 3gen reprod.- rat PADI = 0.000250 mg/kg/day
Caswell #041A NOEL = 0.0000 mg/kg Safety Factor = 1000
CFR No. 180.217 LEL = 0.2500 mg/kg
Status: TOX complete 10/15/86. ORD not scheduled.

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
2	Apples	2.000		2.53	0.075900000
23	Cantaloupe	4.000		0.52	0.031200000
28	Celery	5.000		0.29	0.021750000
46	Cucumbers, including pickles	4.000		0.73	0.043800000
118	Pecans	0.500		0.03	0.000225000
127	Potatoes	0.500		5.43	0.040725000
163	Tomatoes	4.000		2.87	0.172200000

TMRC %PADI
0.006430 mg/kg/day (60kg BW, 1.5kg diet) 2572.000000

RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No tox-approved tolerances are listed in the file.

TMRC %PADI
0.006430 mg/kg/day (60kg BW, 1.5kg diet) 2572.000000

RESIDUE CONTRIBUTION OF NEW (PENDING) TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No new tolerances are listed in the file.

TMRC %PADI
0.006430 mg/kg/day (60kg BW, 1.5kg diet) 2572.000000

TOXICOLOGY BRANCH ADI PRINTOUT Date: 10/22/86

Nabam
Caswell #585
CFR No. 180.152
Status: TOX complete 10/15/86. ORD not scheduled.

90d feeding- dog
NOEL = 0.0840 mg/kg
LEL = 0.1700 mg/kg

PLD = 0.000300 mg/kg/day
Safety Factor = 1000

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
92 Melons	25.000		2.00	0.750000000

TMRC
0.012500 mg/kg/day (60kg BW, 1.5kg diet) % PLD 4166.666667

RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No tox-approved tolerances are listed in the file.

TMRC
0.012500 mg/kg/day (60kg BW, 1.5kg diet) % PLD 4166.666667

RESIDUE CONTRIBUTION OF NEW (PENDING) TOLERANCES

CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No new tolerances are listed in the file.

TMRC
0.012500 mg/kg/day (60kg BW, 1.5kg diet) % PLD 4166.666667

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DER

Chemical: Ethylenethiourea

Study: Effects of One-Year Administration of Ethylenethiourea upon the Thyroid of the Rat. S. L. Graham, W. H. Hansen, K.J. Davis and C.H. Perry. J. Agr. Food Chem. 21: 324-329, 1973. Submitted by Rohm and Haas under the Data-Call-In for Mancozeb. Accession No.: 259905; Caswell No. 913A

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Study Type: Chronic Toxicity - One Year

Animals: Charles River rats

Total Animals: Five groups of 68 male and 68 female rats

Age: 5 weeks

Route of Administration: Orally in the diet.

Dosage Levels: 0, 5, 25, 125, 250 and 500 ppm

Study Duration: 2, 6 and 12 months

Study Design: At 2, 6 and 12 months, ten rats per sex were killed. Twenty-four hours prior to sacrifice they were given 5uCi of ^{131}I.

Parameters Studied:

1. Body weights at 2, 6 and 12 months;
2. Organ weights - thyroids, heart, liver, kidneys, spleen, brain and testes;
3. ^{131}I uptake in the thyroid;
4. Hemoglobin, hematocrit, leukocyte count and leukocyte differential counts at 3 and 11 months on 10 rats/sex/group; and
5. Thyroids, brain, Harderian gland, eye with retina and iris, extra-orbital lacrimal gland, salivary gland, salivary lymph node, heart, lung, liver, kidney, urinary bladder, ovary, uterus, spleen, pancreas, adrenal, squamous and glandular stomach, duodenum, jejunum, ileum, colon, bone, bone marrow, pituitary and skeletal muscle were examined histologically.

Results:

1. Body Weights

After two months of dosing, body weights of male rats in the 250 and 500 ppm ETU groups were significantly lower than those of the controls; body weights of females were significantly lower in the 25, 125, 250 and 500 ppm groups. At six months, body weights were significantly lower than controls for the 25, 250 and 500 ppm dosed male rats and for the 125, 250 and 500 ppm female rats. By twelve months only males in the 500 ppm group had significantly lower body weights than the controls; however, female body weights were still significantly reduced at 125, 250 and 500 ppm.

2. Organ Weights:

The most significant and consistent effects of ETU were seen on thyroid to body weight ratios. At all time points studied this ratio was statistically significantly greater for males in the 250 and 500 ppm groups and for females in the 125, 250 and 500 ppm groups. Liver to body weight ratios were also consistently elevated to a statistically significant level in the 250 and 500 ppm female groups.

3. Uptake of ^{131}I:

^{131}I uptake in the thyroids of male rats was statistically significantly increased at 2 months in the 5, 25, and 125 ppm groups, not significantly changed at 6 months, significantly increased at 12 months in the 25, 125 and 250 ppm groups and decreased by 67% in the 500 ppm group. In female rats there were no statistically significant changes in ^{131}I uptake in any ETU-treated groups at 2 months. At 6 months, the 125 and 500 pm groups had statistically significant decreases in ^{131}I uptake. This effect of ETU was reversed at 12 months in that the uptake was substantially elevated (statistically significant) in the 125, 250 and 500 ppm groups over the controls.

4. Hematology:

No significant differences were noted between the control and dosed animals; however, raw and/or mean data were not presented for the various parameters studied.

5. Histopathology:

Hisopathology data on the thyroid is summarized in the table below.

Incidence of Histologic Changes in the Thyroids of ETU-Treated Rats

Dose Group	Increased Vascularity	Hyperplasia			Adenocarcinoma
		diffuse[1]	nodular[2]	diffuse and nodular	
			Males		
0	4/13	6/13	0/13	0/13	0/13
5	10/11	4/11	0/11	0/11	0/11
25	10/11	7/11	0/11	0/11	0/11

125	10/11	5/11	0/13	3/11	0/11
250	10/13	3/13	3/13	4/13	3/13
500	10/13	0/13	2/13	0/13	10/13
		Females			
0	1/9	1/9	0/9	0/9	0/9
5	10/10	5/10	0/10	0/10	0/10
25	9/10	5/10	0/10	0/10	0/10
125	10/11	8/11	0/11	0/11	0/11
250	10/10	5/10	0/10	0/10	0/10
500	10/12	0/12	6/12	0/12	5/12

[1] microfollicular
[2] adenoma

The paper also states that the pituitary was "moderately hyperplastic" at the 500 ppm level.

Conclusions:

Increased vascularity was seen in the thyroids of male and female rats of all ETU-treated groups. Therefore, a NOEL for the effects of ETU was not determined in this study.

Core Classification: Supplementary

DER

Chemical: Ethylenethiourea (ETU)

Study: NTP Three-Month Study A.C. Peters, P. J. Kurtz, D.J. Donorrio, D. C. Thake and C. L. Cottrill. Prechronic Studies of Ethylenethiourea: Acute, Repeated Dose, and Subchronic in Rats. Project No. G-7186. Report submitted by Battelle Laboratories, Columbus, OH. to National Institute of Environmental Health Sciences, October 14, 1980. Submitted by Rohm and Haas under the Data-Call-In on Mancozeb. Acession No.: 259905 Caswell No.: 913A

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Study Type: 90 Day Rat Study

Animals: Fischer 344 rats

Total Animals: 10 rats/sex/group

Age: 6-7 weeks when started on study

Caging: No more than five per sex in polycarbonate cages

Route of Administration: orally in the diet

Dosage Levels: 0,60, 125, 500 and 750 ppm

Study Duration: 13 weeks

Parameters Studied:

1. Clinical observations were recorded twice daily.
2. Body weights were recorded pretest, weekly and at necropsy.
3. Food consumption data were taken weekly on a per cage basis.
4. All animals on test were necropsied.
5. All control and high dose animals were submitted for complete histopathologic evaluation. Only "target organs", namely bone marrow, esophagus, liver, pituitary, non-glandular portion of the stomach and the thyroid, were examined at all dosage levels.

Results:

1. At 750ppm, 8/10 males and 9/10 females were lethargic, all exhibited pilo-erection and 5/10 males had red exudate on the nose coat.
2. Although statistics were not done, body weight gain was depressed in

the males at 500 ppm and 750 ppm, females at 750 ppm and marginally in females at 500 ppm.

	Average Body Weights at Week 13 (g)	
Dose (ppm)	Males	Females
0	332 (+149)[1]	217 (+78)
60	324 (+148)	194 (+55)
125	326 (+143)	197 (+58)
250	323 (+142)	199 (+60)
500	300 (+121)	191 (+51)
750	226 (+46)	157 (+19)

! Number in parentheses indicates the increase in body weight in grams over the course of the study.

3. Food consumption was adversely affectd by treatment. This effect was most pronounced at 500 and 750 ppm ETU in male and female rats and slightly effected in females at 250 ppm when comparing average food intake/rat in each group. Again statistics were apparently not done.

4. Histopathology

Pertinent histopathological lesions due to ETU treatment were tabulated as follows:

Histopathology Incidence Data

	Dose Group					
Organ/Lesion	0	60	125	250	500	750
No. Animals examined	10	10	10	10	10	10
			Males			
Bone Marrow hemopoietic elements, depletion	0	0	0	0	1	9
Esophagus hyperkeratosis	0	0	0	0	0	5
Liver cholangitis, granulomatous	0	0	0	0	0	4

	0	60	125	250	500	750
hepatocytes, centrilobular cellular atypia	0	10	8	7	6	10
Pituitary pars distalis, cellular vacuolar change	0	0	0	5	6	9
Stomach nonglandular, epithelium hyperkeratosis	0	0	0	0	0	2
Thyroid adenoma	0	0	0	7	5	7
folicules, hyperplasia	0	0	1	10	10	10
			Females			
Bone Marrow hemopoietic elements, depletion	0	0	0	0	1	8
Esophagus hyperkeratosis	0	0	0	0	0	6
hyperkeratosis, multifocal	0	0	0	0	0	1
Liver hepatitis	0	0	0	0	0	2
hepatocytes, centrilobular cellular atypia	0	0	0	0	0	10
Lymph Node mesenteric, lymphoid hyperplasia	0	0	0	0	0	4
pancreatic, lymphoid hyperplasia	1	0	0	0	0	3
thoracic, lymphoid hyperplasia	0	0	0	0	0	2
Pituitary pars distalis, cellular vacuolar change	0	0	0	0	2	9
Thyroid adenoma	0	0	0	0	4	6
follicles, hyperplasia	0	0	0	6	10	10

In the bone marrow, hemopoietic depletion was observed in both males and females of the 500 and 750 ppm ETU dosage groups. Hyperkeratosis was seen in the stomach and esophagus of the high dose males and in the esophagus of the high dose females.

Cellular atypia of hepatocytes occured in males in all ETU treatement groups and increased in severity with increasing dose. This effect was only observed in the females at 750 ppm ETU.

Cellular vacuolar changes were seen in the pars distalis of the pituitary in male rats at 250, 500 and 750 ppm. These changes were more pronounced as the dosage of ETU increased.

There was an increase in the incidence of thyroid adenomas in males at 250, 500, and 750 ppm and in females at 500 and 750 ppm. Thyroid follicular hyperplasia due to ETU was seen at 125 ppm ETU and higher in male rats and at 250 ppm and higher in female rats.

Conclusions:

A NOEL for the effects of ETU on the liver of Fischer 344 male rats was not found in this study due to hepatocytic cellular atypia seen at all dosage levels. A NOEL of 60 ppm in males and 125 ppm in females was found for the effects of ETU on the thyroid (follicular hyperplasia). In contrast in a 90 day study in Charles River Sprague-Dawley rats (Freudenthal et al. J. Environ. Path. Tox. 1:147-161, 1977), a NOEL of 5 ppm in the diet was determined for the effects of ETU on the thyroid. Thyroid toxicity seen at levels of 25 ppm and above consisted of thyroid hyperplasia, decreased uptake of ^{125}I by the thyroid and decreased serum levels of T_3 and T_4. The liver was not examined in this study.

Classification: Supplementary - i.e. hematology, clinical chemistries and urinalysis were not performed; statistics were not done on the reported data (body weights, food consumption); measurements of thyroid function would have been valuable in light of the known effects of ETU on the thyroid.

DER

Chemical: Ethylene Thiourea

Study: Effects of Prolonged Ethylene Thiourea Ingestion on the Thyroid of the Rat. S. L. Graham, K. J. Davis, W. H. Hansen and C. H. Graham. Food and Cosmetic Toxicology 13: 493-499, 1975. Submitted by Rohm and Haas under the Data-Call-In for Mancozeb. Accession No. 259905; Caswell No. 913A

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Study Type: Chronic Toxicity - Two Year

Animals: Charles River Rats

Total Animals: five groups of 68 male and 68 female rats

Age: 5 weeks

Route of Administration: Orally in the diet

Dosage Levels: 0, 5, 25, 125, 250 and 500 ppm in the diet

Study duration: 2, 6, 12, or 24 months

Study Design:

	No. of Animals/Group (males + females)[1]				
	Months				
Dosage Level (ppm)	2	6	12	18[2]	24[2,3]
0	20	20	20	20	56
5	20	20	20	20	56
25	20	20	20	20	56
125	20	20	20	20	56
250	20	20	20	20	56
500	20	20	20	20	56

[1] No. males = no. females

2 5/sex/group were injected with 5uCi ^{131}I and killed after being fasted for 24 hours and 5/sex/group were killed for biochemistry.
3 3/sex/group were returned to the control diet at week 66.

Parameter Studied(or Reported):

1. ^{131}I uptake in 5 rats/sex/group at 18 and 24 months
2. Body weights at 18 and 24 months
3. Organ/body weight ratio at 18 and 24 months
4. Hemoglobin,hematocrit, red blood cell count, leucoctyte and differential leucocyte counts
5. Tissues for gross and microscopic examination (exact tissues were not specified).

Results:

1. Body weights - The body weights of male and female rats were significantly decreased ($p<0.001$ at 18 months and $p<0.01$ at 24 months) in the 500 ppm ETU dosage group at 18 and 24 months.
2. Organ to Body Weight Ratios - Statistically significant differences are shown in the following table.

Organ Weight Changes

Organ/Body Weight Ratio	18 months		24 months	
	Change	p	Change	p
Thyroid	increase:		increase:	
	males, 500 ppm	<0.05	males, 500 ppm	<0.01
	females, 250 ppm	<0.05	females, 250 ppm	<0.01
Heart	-	-	increase:	
			males, 500 ppm	<0.01
Liver	-	-	decrease:	
			females, 5, 25 ppm	<0.05

3. Uptake of ^{131}I:

^{131}I uptake was statistically significantly increased in male rats at 18 months in the 25 and 125 ppm groups and decreased at 500 ppm. At 24 months in male rats, ^{131}I uptake was significantly increased in the 5 ppm group and decreased in the 500 ppm group. Because of large variability in the values obtained, there were no statistically significant differences in ^{131}I uptake in female rats.

4. Hematology:

No significant differences were noted between the control and dosed animals; however, raw and/or mean data were not presented for the various parameters studied.

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5. Histopathology:

Histopathology incidence data were combined for males and females in the table presented in the paper. Relevant data from this table are summarized in the following table.

Parameter	Data for rats given ETU in the diet at a level (ppm) of:					
	0	5	25	125	250	500
# of rats/group						
on test at 1 year	72	75	73	73	69	70
sacrificed at 18 mons.	10	10	10	10	10	10
two-year survivors	32	39	43	37	32	18
Pathological Lesions						
Cataracts/keratitis	2	1	0	2	6	12
Thyroiod carcinoma/ adenoma(follicular)	2	2	1	2	16	62
Thyroid adenomas	2	-	5	1	21	3
Thyroid hyperplasia (follicular)	4	20	41	44	27	3
Parathyroid hyperplasia	6	11	8	2	3	0
Hepatoma	1	1	1	2	1	5

Statistics were not reported on the histopathological data.

Thyroid hyperplasia seen in the 5 and 25 ppm dosage groups was described as slight and was not reversible in those rats in each group that were placed on the control diet at week 66 of the study.

Conclusion: A NOEL was not determined for the adverse effects of ETU in this study. At the lowest dose tested, thyroid hyperplasia was observed in a total of 20 male and female rats compared to four in the control group.

Core Classification: Supplementary - i.e. raw data on many of the parameters studied was not available for evaluation; histopathologic data were presented for male and female rats combined; the number of rats/sex/group for a chronic toxicity study was insufficient.