Ethylene thiourea (ETU); CASRN 96-45-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR ETU

File First On-Line 05/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	05/01/1991
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Ethylene thiourea (ETU)
CASRN — 96-45-7
Last Revised — 05/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Increased incidence of thyroid hyperplasia **Rat 24-Month Feeding Study** **Graham et al., 1975**	NOAEL: None LOAEL: 0.25 mg/kg/day (5 ppm in feed)	3000	1	8E-5 mg/kg/day

*Conversion Factors -- 5 ppm (mg/kg of feed) x 0.05 (assumed rat food consumption per body weight) = 0.25 mg/kg/day

I.A.2. Principal and Supporting Studies (Oral RfD)

Graham, S.L., K.J. Davis, W.H. Hansen and C.H. Graham. 1975. Effects of prolonged ethylene thiourea ingestion on the thyroid of the rat. Food Cosmet. Toxicol. 13: 493-499.

The oral toxicity of ethylene thiourea (ETU) was investigated in a chronic feeding study in which Charles River CD-1 rats were fed 0, 5, 25, 125, 250 and 500 ppm of the test substance for 24 months. These doses provided 0, 0.25, 1.25, 6.25, 12.5 and 25 mg/kg/day based on the assumption that rats consume 5% of their body weight of food each day. Groups of rats (68/sex) were assigned to each of the dose groups. The major endpoints of this study were histological examination of endocrine organs and other major tissues, organ weights and thyroidal uptake of Iodine-131. A significant incidence of thyroid carcinomas and adenocarcinomas was observed among rats receiving 250 and 500 ppm. Thyroid hyperplasia was observed among rats receiving 5, 25, 125 and 250 ppm with increased incidence at the higher doses. A significant decrease in body weight was found among rats receiving 500 ppm at both 18 and 24 months. A statistically significant decrease in liver-to-body weight ratio was seen in females receiving 5 or 25 ppm. Significant increases in thyroid- to-body weight ratios were seen in males and females receiving 500 ppm, and in females receiving 250 ppm. Studies of Iodine-131 uptake performed at the end

of the study did not show a significant dose-response relationship. The LOAEL derived from this study based upon detection of thyroid hyperplasia was 5 ppm (0.25 mg/kg/day).

Thyroid hyperplasia does not inevitably lead to development of adenomas and carcinomas. Thyroid hyperplasia can develop in response to many forms of physiologic stress and often regresses spontaneously. In the Graham et al. (1975) study many rats in the 5-ppm dose group exhibited thyroid hyperplasia following 2 years of dosing, but none of these rats showed thyroid adenomas or carcinomas. In addition, Iodine-131 uptake tests were not significantly different for the 5-ppm dose group when compared with control rats, suggesting that the thyroids of the 5-ppm rats were functionally normal. The occurrence of thyroid hyperplasia at this dose is not considered to be preneoplastic since carcinomas were not seen at higher doses (25 or 125 ppm).

An interim report of the findings from the first year of the previous study was published separately by Graham et al. (1973); that study also involved feeding 0, 5, 25, 125, 250 and 500 ppm of ETU. Body weight, thyroid and other organ weights, thyroidal Iodine-131 uptake, hematology and histology were the endpoints that were determined. There were significant decreases in total body weight and increases in thyroid weight for rats receiving 125, 250 and 500 ppm of ETU. At the time intervals for which interim determinations were made (2 and 6 months), hyperplasia of the thyroid was observed only at 500 ppm. The NOAEL for 6 months ETU treatment was 25 ppm (1.25 mg/kg/day). At 1 year of treatment the lowest level of ETU tested, 5 ppm or 0.25 mg/kg/day was the LOAEL for thyroid hyperplasia.

The NTP (1989) performed a chronic feeding study to determine the toxicity and carcinogenicity of ETU in F344 and B6C3F1 mice. This study combined a perinatal exposure with the traditional NTP chronic bioassay. A complicated 4x4 study design involving adult-only exposure, perinatal-only exposure, and combined perinatal-adult exposure was used. In the rats receiving adult-only exposure at 83 and 250 ppm of ETU in the diet for 36 and 105 weeks there was a dose-related increase in the incidence and severity of thyroid follicular cell hyperplasia, an increase in TSH levels, and a decrease in serum thyroxin levels. Perinatal-only exposure resulted in an increased incidence of thyroid follicular cell hyperplasia only at the highest tested level of 90 ppm. The lowest dietary level of ETU tested in adult-only exposure for rats, 83 ppm (4.1 mg/kg/day), was considered the LOAEL.

In mice, exposure to 330 or 1000 ppm for 105 weeks resulted in dose-related increases of thyroid follicular cell hyperplasia with associated increases in TSH levels. Hepatic hypertrophy was also observed. For mice 1000 ppm (0.15x1000=150 mg/kg/day) was considered the LOAEL.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 100 was used to account for inter- and intra- species differences. An additional uncertainty factor of 3 is used since limited developmental toxicological and multi-generation data are available. An additional UF of 10 was used since the RfD was establised from a LOAEL rather than a NOAEL.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

The teratogenicity of ETU has been investigated in mice, rats, and rabbits in the gavage studies of Khera (1973) which show LOAELs for developmental toxicity of around 5 mg/kg/day.

In perinatal studies carried out by NTP (1989), ETU was administered in the diet of F344/N rats and C57Bl/6N mice from 2 weeks prior to breeding through gestation, lactation, and up to 9 week post-weaning. Rats were fed 0, 8, 25, 83 or 250 ppm and mice 0, 33, 100, 330 or 1000 ppm. No external gross fetal anomalies or other developmental effects were noted in any dosage group of rats. Based on decreased survival of rat pups between postnatal days 0 and 4 and reduction in body weight gains in male weanling rats at 250 ppm, this dose (approximately 0.075 [weanling rats consume 0.075% of their body weight in feed each day] x 250=18.8 mg/kg/day) was considered a LOAEL and the next lowest dose 83 ppm (approximately 0.075x83=6.2 mg/kg/day) was the NOAEL. No external gross fetal anomalies or other developmental effects were noted in any dosage group of mice. Based on reduced survival of mouse pups at postnatal day 28 and lower mean body weights at 1000 ppm (approximately 0.15x1000=150 mg/kg/day), this dose was considered the LOAEL and the next lowest dose, 330 ppm (approximately 0.15x330=49.5 mg/kg/day), was the NOAEL.

In an unpublished study reviewed by Rohm and Haas (1985), CD-1 mice (15/sex/group) were given ETU in the diet at 0, 1, 10, 100 or 1000 ppm for 90 days. The NOAEL was considered 10 ppm (1.72 mg/kg/day for males and 2.38 mg/kg/day for females). At 100 ppm, both sexes had increased incidences of thyroid hyperplasia and females had increased liver weights.

In a study reported by Graham and Hansen (1972) male Osborne-Mendel rats (20/dose/duration) received 0, 50, 100, 500 or 750 ppm ETU in the diet for 30, 60, 90 or 120 days. Histology results were reported only for rats in the 90- day dosing period. No thyroid changes were seen in the 50-ppm group and slight hyperplasia was seen in the 100-ppm group. A NOAEL of 50 ppm was established from this study and a LOAEL of 100 ppm. Fredenthal et al. (1977) performed a study in which Sprague-Dawley rats (20/dose/duration) received 0, 1, 5, 25, 125 or 625 ppm of ETU in the diet for 30, 60 or 90 days. At 25 ppm, an increase in serum thyroxin and some degree of

thyroid hyperplasia were seen at 60 days but not at 30 or 90 days. Because only slight transient histological changes were seen at 25 ppm the authors considered this dose the NOAEL for the 90-day study.

Two unreported studies in rhesus monkeys, both of approximately 6-months duration, showed mild thyroid follicular cell hyperplasia at 50 ppm and moderate to severe hyperplasia was seen at 250 ppm. Doses of 0, 2, 10, 50 and 250 ppm were tested. Serum T4 levels were decreased in the 250 ppm group. No serum chemistry or histological changes were reported for the lower dosage groups. The results of these studies indicated that a NOAEL had not been demonstrated.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

A medium degree of confidence for the RfD is determined since the chronic rat study of Graham et al. (1975) provides sufficient data with multiple appropriate end points. There were adequate group sizes with many test dose groups. Additional data for chronic studies performed in mice were reported in the NTP study and the unpublished study by Rohm and Haas (1985). Seven studies in rats, three studies in mice, one study in cats, and one study in rabbits have explored the developmental effects of ETU. Adequate group sizes were used in the critical rat and mouse studies and dose levels ranging from 10-80 mg/kg/day were used in the Khera (1973) study. Thus, medium confidence in the database is appropriate. Medium confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA. 1984. Health and Environmental Effects Profile for Ethylene Thiourea (2-imidazolidinethione). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/X-84/131. NTIS PB 88-120621/AS.

The Health and Environmental Effects Profile for Ethylene Thiourea received limited peer review and extensive Agency-wide review in 1984.

Other EPA Documentation — U.S. EPA, 1985, 1990

Agency Work Group Review — 12/09/1986, 10/15/1987, 01/21/1988, 02/25/1988, 02/20/1991

Verification Date — 02/20/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Ethylene thiourea (ETU) conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Ethylene thiourea (ETU)
CASRN — 96-45-7

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Ethylene thiourea (ETU)
CASRN — 96-45-7

Not available at this time.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Ethylene thiourea (ETU)
CASRN — 96-45-7

VI.A. Oral RfD References

Freudenthal, R.I., G. Kerchner, R. Persing and R.L. Baron. 1977. Dietary subacute toxicity of ethylene thiourea in the laboratory rat. J. Environ. Pathol. Toxicol. 1: 147-161.

Graham, S.L. and W.H. Hansen. 1972. Effects of short-term administration of ethylenethiourea upon thyroid function of the rat. Bull. Environ. Contam. Toxicol. 7: 19-25.

Graham, S.L., W.H. Hansen, K.J. Davis and C.H Perry. 1973. Effects of one- year administration of ethylenethiourea upon the thyroid of the rat. J. Agric. Food Chem. 21(3): 324-329.

Graham, S.L., K.J. Davis, W.H. Hansen, and C.H. Graham. 1975. Effects of prolonged ethylene thiourea ingestion on the thyroid of the rat. Food Cosmet. Toxicol. 13: 493-499.

Khera, K.S. 1973. Ethylenethiourea: Teratogenicity study in rats and rabbits. Teratology. 7: 243-252.

NTP (National Toxicology Program). 1989. NTP Technical Report on the perinatal toxicity and carcinogenicity studies of ethylene thiourea (CAS No. 96-45-7) in F/344 rats and B6C3F1 mice (feed studies). NTP-TR-388. NIH Publ. No. 90-28-43.

Rohm and Haas Company. 1985. MRID No. 00154192. HED Doc. No. 005038, 005370. Available from EPA. Write to FOI, EPA, Washington, DC. 20460.

U.S. EPA. 1984. Health and Environmental Effects Profile for Ethylene Thiourea (2-imidazolidinethione). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/X-84/131. NTIS PB 88-120621/AS.

U.S. EPA. 1985. Reportable Quantity Document for Ethylene Thiourea. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1990. Drinking Water Quantification of Toxicologic Effects of Ethylene Thiourea (ETU). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Ethylene thiourea (ETU)
CASRN — 96-45-7

Date	Section	Description
05/01/1991	I.A.	Oral RfD summary now on-line
10/28/2003	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Ethylene thiourea (ETU)
CASRN — 96-45-7
Last Revised — 05/01/1991

- 96-45-7

- 2-Imidazolidinethione
- ETHYLENE THIOUREA
- Ethylenethiourea
- ETU
- HSDB 1643
- IMIDAZOLE-2(3H)-THIONE, 4,5-DIHYDRO-
- Imidazolidinethione
- IMIDAZOLINE-2(3H)-THIONE
- Imidazoline-2-thiol
- L'ETHYLENE THIOUREE [French]
- Mercaptoimidazoline
- Mercazin I
- N,N'-Ethylenethiourea
- NA-22
- NA-22-D
- NCI-C03372
- Nocceler 22
- Pennac CRA
- RCRA WASTE NUMBER U116
- Rhenogran ETU
- Rhodanin S 62
- RODANIN S-62 [Czech]
- SODIUM-22 NEOPRENE ACCELERATOR
- Soxinol 22
- Tetrahydro-2H-imidazole-2-thione
- Thiourea, N,N'-(1,2-ethanediyl)-
- UREA, 1,3-ETHYLENE-2-THIO-
- USAF EL-62
- Vulkacit NPV/C
- Warecure C
- 1,3-ETHYLENE-2-THIOUREA
- 1,3-ETHYLENETHIOUREA
- 2-IMIDAZOLIDINETHIONE
- 2-IMIDAZOLINE-2-THIOL
- 2-MERCAPTO-2-IMIDAZOLINE
- 2-Mercaptoimidazoline
- 2-MERKAPTOIMIDAZOLIN [Czech]
- 2-THIOL-DIHYDROGLYOXALINE
- 4,5-DIHYDRO-2-MERCAPTOIMIDAZOLE
- 4,5-DIHYDROIMIDAZOLE-2(3H)-THIONE