PB89-215685

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INFORMATION PROFILES ON POTENTIAL OCCUPATIONAL HAZARDS: THIOUREA AND COMPOUNDS -- SECOND DRAFT

SYRACUSE RESEARCH CORPORATION
SYRACUSE, NY

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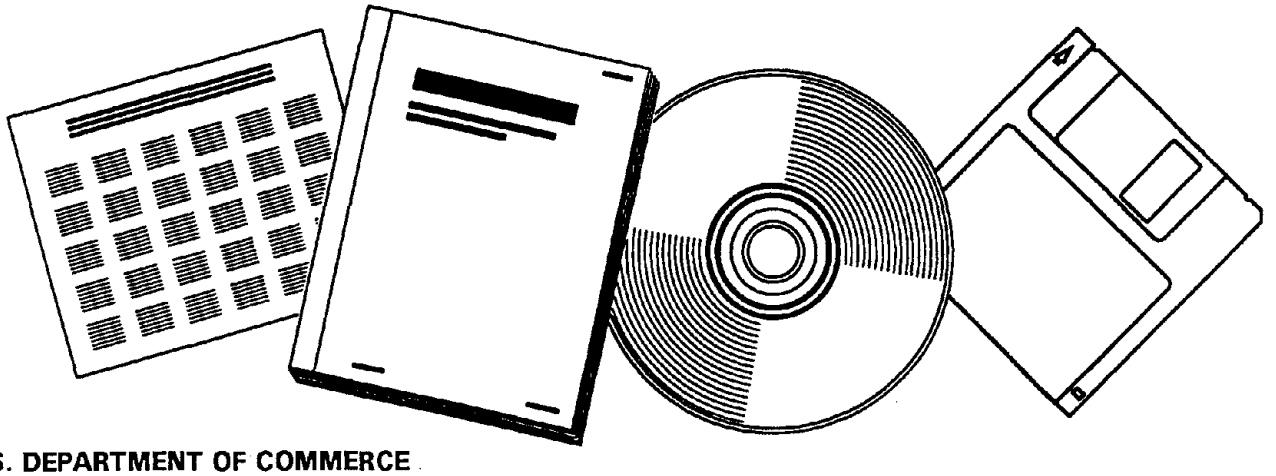

U.S. DEPARTMENT OF COMMERCE
National Technical Information Service

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SRC TR 82-500

SECOND DRAFT

Information Profiles on Potential Occupational Hazards: Thiourea and Compounds

Center for Chemical Hazard Assessment
Syracuse Research Corporation
Merrill Lane
Syracuse, New York 13210

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15. Supplementary Notes

16. Abstract (Limit: 200 words) Information profiles were presented for thiourea and the following thiourea compounds considered important in the industrial community: 1-allyl-3-(2-hydroxyethyl)-2-thiourea (105817), allylthiourea (109579), N,N'-bis(hydroxymethyl)thiourea (3084251), N,N'-bis(methoxymethyl)thiourea (51872265), 1-butyl-3-ethyl-2-thiourea (32900064), 1,3-dibutyl-2-thiourea (109466), 1,3-diisopropyl-2-thiourea (2986176), 1,3-dimethyl-2-thiourea (534134), N,N'-di-o-tolylthiourea (137973), 3-ethyl-1,1-dimethyl-2-thiourea (15361861), ethylthiourea (625536), (hydroxymethyl)thiourea (1000835), (2-methylphenyl)thiourea (614788), thiourea (62566), 1,3-diethyl-2-thiourea (105555), 1,3-diphenyl-2-thiourea (102089), ethylenethiourea (96457), 1-naphthylthiourea (86884), 1-phenyl-2-thiourea (103855), 1,1,3,3-tetramethylthiourea (2782914) and 1,1,3-trimethyl-2-thiourea (2489772). Most of the compounds were highly toxic to rodents. Positive mutagenic effects have been elicited in various assays with several of these compounds. The use of thiourea, diethylthiourea and tetramethylthiourea as antithyroid drugs indicated these compounds have antithyroidal effects in humans. Frequently observed side effects from the use of these medications have included headache, anxiety, fever, skin rash, and gastrointestinal disturbances.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms NIOSH-Publication, NIOSH-Contract, Contract-210-79-0030, Corrosion-inhibitors, Bactericides, Rodenticides, Coatings, Flame-retardants, Toxic-effects, Mutagens

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 128
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(See ANSI-Z39.18) *See Instructions on Reverse*

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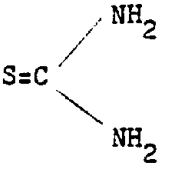
I. SCOPE OF DOCUMENT AND SUMMARY OF MAJOR FINDINGS

A. CLASS IDENTIFICATION

Thiourea is identified by the following chemical structure:



The thioureas identified in this class are the compounds in which one or more of the hydrogens attached to nitrogen are replaced with a different functional group such as an ethyl, methyl, or phenyl group.

B. CHEMICALS TO BE ADDRESSED

The following thioureas have been selected for individual profiles:

1-Allyl-3-(2-hydroxyethyl)-2-thiourea
Allylthiourea
N,N'-Bis(hydroxymethyl)thiourea
N,N'-Bis(methoxymethyl)thiourea
1-Butyl-3-ethyl-2-thiourea
1,3-Dibutyl-2-thiourea
1,3-Diethyl-2-thiourea
1,3-Diisopropyl-2-thiourea
1,3-Dimethyl-2-thiourea
1,3-Diphenyl-2-thiourea
N,N'-Di-o-tolylthiourea
Ethylene thiourea
3-Ethyl-1,1-dimethyl-2-thiourea
Ethylthiourea
(Hydroxymethyl)thiourea
(2-Methylphenyl)thiourea
1-Naphthylthiourea
Phenylthiourea
1,1,3,3-Tetramethylthiourea
Thiourea
1,1,3-Trimethyl-2-thiourea

These compounds were selected for individual profiles because all were identified to have some commercial importance in terms of production, importation, or use.

C. SUMMARY OF BIOLOGICAL ACTIVITY

There is a paucity of information on the biological effects of most of the profiled thiourea compounds. Currently available information does not suggest, however, that any member of the thiourea series considered here produces unique toxicological effects. With the exception of acute lethal dose levels, most of the published toxicity data have been for thiourea, diethylthiourea, ethylenethiourea, naphthylthiourea, and phenylthiourea.

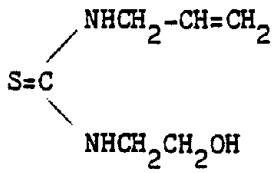
Most of the profiled thioureas are moderately to highly toxic to rodents following oral administration or i.p. injection; acute toxicity may be related to the development of pulmonary edema and pleural effusion, which has been associated with exposure to thiourea, naphthylthiourea, and phenylthiourea. Chronic feeding of thiourea, allylthiourea, diethylthiourea, phenylthiourea, tetramethylthiourea, and trimethylthiourea has produced goitrogenic effects, thyroid hyperplasia and/or tumors in rats. Positive mutagenic effects have been elicited in various assays with thiourea, ethylthiourea, ethylene thiourea naphthylthiourea, and phenylthiourea, and fetotoxic and/or teratogenic effects have been observed in rats following oral administration of thiourea, ethylene-thiourea, and tetramethylthiourea. The use of thiourea, diethylthiourea, and tetramethylthiourea as antithyroid drugs indicates that these compounds have antithyroidal effects in humans; frequently observed side effects were headache, anxiety, fever, skin rash, and gastrointestinal disturbances.

II. INFORMATION PROFILES

A. 1-ALLYL-3-(2-HYDROXYETHYL)-2-THIOUREA

1. Chemical Name: 1-Allyl-3-(2-hydroxyethyl)-2-thiourea

2. Chemical Structure:



3. Synonyms: Thiourea, N-(2-hydroxyethyl)-N'-2-propenyl-
N-Allyl-N'-(b-hydroxyethyl)-thiourea

4. Chemical Abstracts Service (CAS) Number: 105-81-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	160.24
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of 1,allyl-3-(2-hydroxyethyl)-2-thiourea and production volumes are presented in Table 1.

8. Use

Patent literature suggests uses in photography.

Table 1. Producers of 1-Allyl-3-(2-hydroxyethyl)-2-thiourea and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Fairmount Chemical Newark, NJ	Manufacturer	2-20 thousand lb
Millmaster Chemical Berkeley Heights, NJ	Importer	under 1000 lb
Rhone-Poulenc Freeport, TX	Importer	under 1000 lb
Andrews Paper and Chemical Port Washington, NY	Importer	1-10 thousand lb

9. Manufacturers and Distributors

1-Allyl-3-(2-hydroxyethyl)-2-thiourea is commercially manufactured by Fairmount Chemical in Newark, NJ (SRI International, 1980; USITC, 1980; U.S. EPA, 1980).

Distributors include (Chem Sources-USA, 1980):

Chemical Dynamics	Lachat Chem.
Chem. Procurement Lab.	Millmaster Chem.
Columbia Organics	Monomer-Polymer and Dajac Lab.
Delamar Inc.	Trans World Chem.
ICN/K and K	Tridem Chem.

10. Manufacturing Processes

Information regarding the commercial process by which 1-allyl-3-(2-hydroxyethyl)-2-thiourea is manufactured is not available from the literature searched.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 1-allyl-3-(2-hydroxyethyl)-2-thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1-allyl-3-(2-hydroxyethyl)-2-thiourea were not found in the literature searched.

14. Biological Effects

No information was found in the literature searched regarding the biological effects of 1-allyl-3-(2-hydroxyethyl)-2-thiourea.

15. Ongoing Studies

No current toxicological or environmental studies of 1-allyl-3-(2-hydroxyethyl)-2-thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1-allyl-3-(2-hydroxyethyl)-2-thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

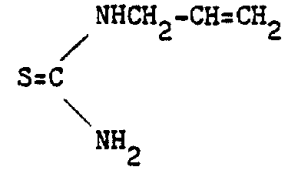
18. Other Pertinent Data

No other information that would aid in the assessment of 1-allyl-3-(2-hydroxyethyl)-2-thiourea as an occupational hazard was found in the literature searched.

B. ALLYLTHIOUREA

1. Chemical Name: Allylthiourea

2. Chemical Structure:



3. Synonyms: Allyl sulfocarbamide
Allyl sulfourea
Aminosin
Rhodalline
Thiosinamine
Thiourea, 2-propenyl
Urea, 2-propenyl-thio-

4. Chemical Abstracts Service (CAS) Number: 109-57-9

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YR8050000

6. Chemical and Physical Properties:

Description:	white crystalline solid with slight garlic odor and bitter taste
Molecular Weight:	116.20
Boiling Point:	---
Melting Point:	78°C
Vapor Pressure:	---
Solubility:	soluble in 30 parts water; soluble in alcohol; slightly soluble in ether; insoluble in benzene
Specific Gravity:	1.22
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of allylthiourea and production volumes are presented in Table 2.

Table 2. Producers of Allylthiourea and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Fairmount Chemical Newark, NJ	Manufacturer	under 1000 lb
Fike Chemical Nitro, WV	Manufacturer	none
Millmaster Chemical Berkeley Heights, NJ	Importer	1-10 thousand lb
Degussa Corp. Teterboro, NJ	Importer	1-10 thousand lb

8. Use

Allylthiourea has the following uses: chemical sensitization in photography (MacWilliam, 1968); corrosion inhibitor for citric acid against tin plating (Foley and Brown, 1979); medicine to promote absorption of fibrous tissue, and inorganic syntheses (The Merck Index, 1976; Hawley, 1977).

9. Manufacturers and Distributors

The manufacturers are listed in Table 2.

Distributors include (Chem Sources-USA, 1980):

Aldrich Chem.	Columbia Organics	Lachat Chem.
Atomergic Chemetals	Degussa	MCB Reagents
Bio-Clinical Lab	Eastern Chem.	Millmaster Chem.
Bodman Chem.	Eastman Kodak	Pfaltz and Bauer
Chemical Dynamics	EM Lab	Polysciences
Chem. Procurement Lab	Fisher Sci.	Trans World Chem.
Chem Sciences	ICN/K and K	Tridom Chem.

10. Manufacturing Processes

Allylthiourea is made by warming a mixture of equal parts of allyl isothiocyanate and absolute alcohol with 30% ammonia (Hawley, 1977).

11. Impurities or Additives

There is no evidence in the literature searched to indicate the presence of impurities or deliberate additives in commercially produced allylthiourea.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 30 workers are potentially exposed to allylthiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to allylthoiurea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

LD50 values of 500 mg/kg (Dubois et al., 1947) and 200 mg/kg (Dieke et al., 1947) have been reported following, respectively, intraperitoneal injection in rats and oral administration in mice. Dubois and coworkers (1947) indicated that the toxicity of allylthiourea for rats at lethal levels resembles that of other thiourea compounds (i.e., pleural effusion, pulmonary edema, hyperglycemia).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

An abstract of an unpublished study (Skoryna and Ross, 1951) reported that dietary administration of allythiourea to rats at a level of 0.04-0.06% for 15 months produced thyroid hyperplasia and benign adenomas. A goitrogenic effect also has been noted in rabbits following administration of 30-40 mg/kg allylthiourea, but the route of administration and duration of exposure were not stated (Wagner-Jauregg and Koch, 1947).

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of allylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for allylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

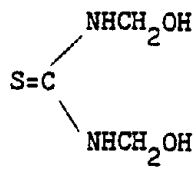
18. Other Pertinent Data

No other information that would aid in the assessment of allylthiourea as an occupational hazard was found in the literature searched.

C. N,N'-BIS(HYDROXYMETHYL)THIOUREA

1. Chemical Name: N,N'-Bis(hydroxymethyl)thiourea

2. Chemical Structure:



3. Synonyms: 1,3-Di(hydroxymethyl)-2-thiourea
Dimethylolthiourea
Thiourea, N,N'-bis(hydroxymethyl)-

4. Chemical Abstracts Service (CAS) Number: 3084-25-1

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	136.17
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of N,N'-bis(hydroxymethyl)thiourea and production volumes are presented below:

Morganton Plant (Morganton, NC)
Manufacturer
1977 Production: 1-10 thousand lbs.

Jersey State Chemical Co. (Haledon, NJ)
Manufacturer
1977 Production: 10-100 thousand lbs.

8. Use

The primary manufacturer, Jersey State Chemical Co., manufactures chemical specialties for textile finishing and printing (SRI International, 1980). Patent literature indicates that bis(hydroxymethyl)thiourea is useful as a cellulosic and polyester crosslinking agent for fibers, as a tanning and forming agent, as an ingredient in bacteriocides, and as an ingredient in copper electroplating.

9. Manufacturers and Distributors

See production section above.

10. Manufacturing Processes

Information regarding the commercial process by which N,N'-bis-(hydroxymethyl)thiourea is manufactured is not available from the literature searched.

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to bis(hydroxymethyl) thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to bis(hydroxymethyl)thiourea were not found in the literature searched.

14. Biological Effects

No information was found in the literature searched regarding the biological effects of bis(hydroxymethyl)thiourea except a reported LD50 of 1000-1500 mg/kg for intraperitoneal administration of the compound in mice (Doull et al., 1962).

15. Ongoing Studies

No current toxicological or environmental studies of bis(hydroxymethyl)thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for bis(hydroxymethyl)thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

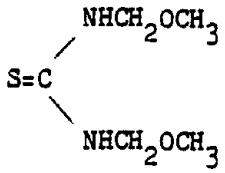
18. Other Pertinent Data

No other information that would aid in the assessment of bis-(hydroxymethyl)thiourea as an occupational hazard was found in the literature searched.

D. N,N'-BIS(METHOXYMETHYL)THIOUREA

1. Chemical Name: N,N'-Bis(methoxymethyl)thiourea

2. Chemical Structure:



3. Synonyms: Thiourea, N,N'-bis(methoxymethyl)-
1,3-Di(methoxymethyl)-2-thiourea

4. Chemical Abstracts Service (CAS) Number: 51872-26-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	solid
Molecular Weight:	164.22
Boiling Point:	---
Melting Point:	81-82°C
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of N,N'-bis(methoxymethyl)thiourea and production volumes are presented below:

Proctor Chemical Co. (Salisbury, NC)
Manufacturer
1977 Production: 10-100 thousand lbs.

8. Use

The manufacturer, Proctor Chemical Co., primarily manufactures finishing resins, dyeing assistants, and surface-active agents for use in the

textile industry, and is a custom producer of special organic chemicals (SRI International, 1980).

9. Manufacturers and Distributors

See production section above.

10. Manufacturing Processes

Information regarding the process by which bis(methoxymethyl)-thiourea is manufactured is not available from the literature searched.

11. Impurities or Additives

No data is available from literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to bis(methoxymethyl) thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to bis(methoxymethyl)thiourea were not found in the literature searched.

14. Biological Effects

No information was found in the literature searched regarding the biological effects of bis(methoxymethyl)thiourea.

15. Ongoing Studies

No current toxicological or environmental studies of bis(methoxymethyl)thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for bis(methoxymethyl)thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

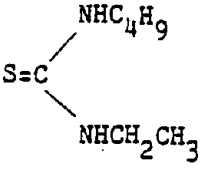
18. Other Pertinent Data

No other information that would aid in the assessment of bis-(methoxymethyl)thiourea as an occupational hazard was found in the literature searched.

E. 1-BUTYL-3-ETHYL-2-THIOUREA

1. Chemical Name: 1-Butyl-3-ethyl-2-thiourea

2. Chemical Structure:



3. Synonyms: Thiourea, N-butyl-N'-ethyl-
Urea, N-butyl-N'-ethyl-thio-

4. Chemical Abstracts Service (CAS) Number: 32900-06-4

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	192.27
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	---

7. Production

No data is available; however, in 1979, in excess of 5000 pounds or $5000 were produced or sold domestically (USITC, 1980).

8. Use

No information is available from the literature searched.

9. Manufacturers and Distributors

1-Butyl-3-ethyl-2-thiourea is manufactured on a commercial scale by Pennwalt Corp. in Wyandotte, MI (USITC, 1980).

10. Manufacturing Processes

Information regarding the process by which 1-butyl-3-ethyl-2-thiourea is manufactured is not available from the literature searched.

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 1-butyl-3-ethyl-2-thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1-butyl-3-ethyl-2-thourea were not found in the literature searched.

14. Biological Effects

No information was found in the literature searched regarding the biological effects of 1-butyl-3-ethyl-2-thiourea.

15. Ongoing Studies

No current toxicological or environmental studies of 1-butyl-3-ethyl-2-thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1-butyl-3-ethyl-2-thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

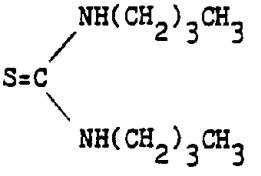
18. Other Pertinent Data

No other information that would aid in the assessment of 1,butyl-3-ethyl-2-thiourea as an occupational hazard was found in the literature searched.

F. 1,3-DIBUTYL-2-THIOUREA

1. Chemical Name: 1,3-Dibutyl-2-thiourea

2. Chemical Structure:



3. Synonyms: N,N'-Dibutylthiourea
1,3-di-n-butyl-2-thiourea
Thiourea, N,N'-dibutyl-
Urea, N,N'-dibutyl-thio-
USAF EK-2138

4. Chemical Abstracts Service (CAS) Number: 109-46-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Y58400000

6. Chemical and Physical Properties:

Description:	white to light tan powder
Molecular Weight:	188.37
Boiling Point:	---
Melting Point:	59-69°C
Vapor Pressure:	---
Solubility:	slightly soluble in water; soluble in methanol, ether, acetone, benzene, and ethyl acetate; insoluble in gasoline
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of 1,3-dibutyl-2-thiourea and production volumes are presented below:

Pennwalt Corp. (Wyandotte, MI)
Manufacturer
1977 Production: confidential

Fike Chemical (Nitro, WV)
Small Manufacturer
1977 production: confidential

In 1979, in excess of 5000 pounds or $5000 were produced or sold domestically (USITC, 1980).

8. Use

Dibutylthiourea is used as an accelerator, activator, or vulcanizing agent in rubber processing (SRI International, 1980). It is also used as a corrosion inhibitor, as a pickling agent for cast iron or carbon steel, as an agent for reducing corrosion of ferrous metals and aluminum alloys in brine, and as an intermediate (Hawley, 1977).

9. Manufacturers and Distributors

The manufacturers of dibutylthiourea are (SRI International, 1980; USITC, 1980):

Fike Chem.	Nitro, WV
Pennwalt Corp.	Wyandotte, MI

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Frinton Labs
Atomergic Chemetals	ICN/K and K
Bodman Chem.	Lachat Chem.
Chem. Procurement Lab	MCB Reagents
Degussa Chem.	Tridom Chem.
EM Lab	Vanderbilt, R.T. Co.
Faesy and Besthoff	

10. Manufacturing Processes

Dibutylthiourea can be produced by refluxing n-butylamine and ammonium thiocyanate under evolution of ammonia (Phrix-Werke A.-G., 1953).

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to dibutylthiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to dibutylthiourea were not found in the literature searched.

14. Biological Effects

The only information found in the literature searched regarding the biological effects of dibutylthiourea were three acute toxicity values. LD50 values of 800-1000 mg/kg (Doull et al., 1962) and 350 mg/kg or <1500 mg/kg (Dieke et al., 1947) have been reported, respectively, following intraperitoneal injection in mice and oral administration in wild or domestic strains of rats.

15. Ongoing Studies

No current toxicological or environmental studies of dibutylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for dibutylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

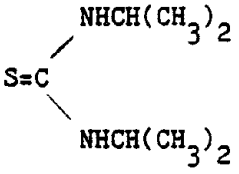
18. Other Pertinent Data

No other information that would aid in the assessment of dibutylthiourea as an occupational hazard was found in the literature searched.

G. 1,3-DIISOPROPYL-2-THIOUREA

1. Chemical Name: 1,3-Diisopropyl-2-thiourea

2. Chemical Structure:



3. Synonyms: N,N'-Diisopropylthiourea
Thiourea, N,N'-bis(1-methylethyl)-

4. Chemical Abstracts Service (CAS) Number: 2986-17-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YS9860000

6. Chemical and Physical Properties:

Description:	grayish-white solid
Molecular Weight:	160.31
Boiling Point:	---
Melting Point:	138.5-142.5°C
Vapor Pressure:	---
Solubility:	slightly soluble in water; soluble in methanol, acetone, and ethyl acetate; insoluble in ether, benzene, and gasoline
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of 1,3-diisopropyl-2-thiourea and production volumes are presented below:

Fike Chemicals (Nitro, WV)
Manufacturer
1977 Production: confidential

8. Use

1,3-Diisopropyl-2-thiourea is used as a corrosion inhibitor for ferrous metals in pickling and aluminum alloys in brine, and as an intermediate (Hawley, 1977).

9. Manufacturers and Distributors

1,3-Diisopropyl-2-thiourea is manufactured by Pennwalt Corp. in Wyandotte, MI (SRI International, 1980) and by Fike Chemicals in Nitro, WV (U.S. EPA, 1980).

Distributors include (Chem Sources--USA, 1980):

Atomergic Chemetals	EM Lab
Bodman Chem.	ICN/K and K
Chem. Procurement Lab	Pfaltz and Bauer
Chem Services	Wateree Chem.
Degussa	

10. Manufacturing Processes

The commercial process by which 1,3-diisopropyl-2-thiourea is manufactured is not available from the literature searched; it may be prepared, however, by reacting isopropylamine and a thiocyanate.

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 1,3-diisopropyl-2-thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,3-diisopropyl-2-thiourea were not found in the literature searched.

14. Biological Effects

The only information found in the literature searched regarding the biological effects of diisopropylthiourea were two acute toxicity values. LD50 values of 450 mg/kg or 500 mg/kg have been reported following oral administration in domestic or wild rats, respectively (Dieke et al., 1947).

15. Ongoing Studies

No current toxicological or environmental studies of 1,3-diisopropyl-2-thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1,3-diisopropyl-2-thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

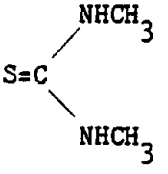
18. Other Pertinent Data

No other information that would aid in the assessment of 1,3-diisopropyl-2-thiourea as an occupational hazard was found in the literature searched.

H. 1,3-DIMETHYL-2-THIOUREA

1. Chemical Name: 1,3-Dimethyl-2-thiourea

2. Chemical Structure:



3. Synonyms: Dimethylthiocarbamide
N,N'-Dimethylthiourea
sym-Dimethylthiourea
Thiourea, N,N'-dimethyl-
Ura, N,N'-dimethyl-thio-

4. Chemical Abstracts Service (CAS) Number: 534-13-4

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	colorless, exceedingly deliquescent crystals
Molecular Weight:	104.18
Boiling Point:	268-270°C
Melting Point:	60-62°C
Vapor Pressure:	---
Solubility:	very soluble in water, alcohol, acetone, and chloroform; slightly soluble in ether and benzene; insoluble in CS_2 and petroleum ether
Specific Gravity:	1.142
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of 1,3-dimethyl-2-thiourea and production volumes are presented below:

Fike Chemicals (Nitro, WV)
Small manufacturer
1977 Production: confidential

8. Use

Dimethylthiourea has the following uses: corrosion inhibitor; accelerator and catalyst in polymerizations; and stabilizer for organic amines (various patent literature).

9. Manufacturers and Distributors

Dimethylthiourea is manufacturerd by Pennwalt Corp. in Wyandotte, MI (SRI International, 1980) and by Fike Chemicals in Nitro, WV (U.S. EPA, 1980).

In addition to the manufacturers, dimethylthiourea is distributed by (1980-81 OPD Chemical Buyers Directory, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Chem. Procurement Lab	MCB Reagents
Alfa Prod.	Degussa	Pfaltz and Bauer
Atomergic Chemetals	EM Lab	Shawnee Chem.
Biochemical Lab	ICN/K and K	Trans World Chem.
Bodman Chem.	Lachat Chem.	Wateree Chem.

10. Manufacturing Processes

Information regarding the commercial process by which dimethylthiourea is manufactured is not available from the literature searched. It may be prepared, however, from methylamine and a thiocyanate.

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to dimethylthiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to dimethylthiourea were not found in the literature searched.

14. Biological Effects

The only available information concerning the biological effects of dimethylthiourea found in the literature searched was a clinical report of contact dermatitis that developed in a textile cutter after 5 years of employment (Dooms-Goossens et al., 1979); the reaction was traced to diazo-sensitized pattern paper which contained dimethylthiourea as an additive.

15. Ongoing Studies

No current toxicological or environmental studies of dimethylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for dimethylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

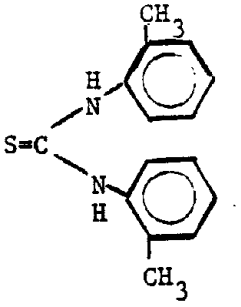
18. Other Pertinent Data

No other information that would aid in the assessment of dimethylthiourea as an occupational hazard was found in the literature searched.

I. N,N'-DI-o-TOLYLTHIOUREA

1. Chemical Name: N,N'-Di-o-tolylthiourea

2. Chemical Structure:



3. Synonyms: 1,3-bis(o-tolyl)-2-thiourea
2,2'-Dimethylthiocarbanilide
Thiourea, N,N'-bis(2-methylphenyl)-
1,3-2-tolyl)-thiourea
USAF EK-3114

4. Chemical Abstracts Service (CAS) Number: 137-97-3

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

FE0700000
YS2783000

6. Chemical and Physical Properties:

Description:	colorless crystalline leaflets with pungent odor
Molecular Weight:	256.39
Boiling Point:	216-218°C (sublimes)
Melting Point:	144-165°C
Vapor Pressure:	---
Solubility:	insoluble in water; soluble in hot alcohol, hot benzene, and chloroform; slightly soluble in ether
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of N,N'-di-o-tolylthiourea and production volumes are presented below:

Fike Chemicals (Nitro, WV)
Small manufacturer
1977 Production: confidential

8. Use

N,N'-di-o-tolylthiourea is used as a metal pickling inhibitor (Hawley, 1977).

9. Manufacturers and Distributors

Dimethylthiourea is manufacturerd by Fike Chemicals in Nitro, WV (U.S. EPA, 1980).

In addition to the manufacturers, N,N'-di-o-tolylthiourea is distributed by (Chem Sources--USA, 1980):

Bodman Chem.
Chem. Procurement Lab.
Degussa
ICN/K and K
Lachat Chem.
Polysciences
Trans World Chem.

10. Manufacturing Processes

N,N'-Di-o-tolylthiourea is made by the interaction of ortho-toluidine and carbon disulfide (Hawley, 1977).

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to N,N'-di-o-tolylthiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to N,N'-di-o-tolylthiourea were not found in the literature searched.

14. Biological Effects

The only available information concerning the biological effects of dimethylthiourea found in the literature searched regarding the biological effects of N,N'-di-o-tolylthiourea consisted of acute toxicity data; this information is summarized in Table 3.

15. Ongoing Studies

No current toxicological or environmental studies of N,N'-di-o-tolylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for N,N'-di-o-tolylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of N,N'-di-o-tolylthiourea as an occupational hazard was found in the literature searched.

Table 3. Acute Toxicity of N,N'-di-o-tolylthiourea

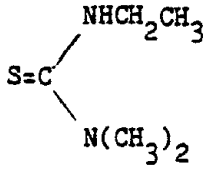
Route	Species	Dose (mg/kg)	Effect	Reference
oral	rat (domestic or wild)	>2000	LD50	Dieke et al., 1947
oral	rat	100	no symptoms of toxicity	Hanzlik and Irvine, 1921
oral	rabbit	3000	LD50 (approximate)	Hanzlik and Irvine, 1921
oral	cat	500	LD50 (approximate)	Hanzlik and Irvine, 1921
i.p.[a]	mouse	100	LD50	Doull et al., 1962

[a]intraperitoneal

J. 3-ETHYL-1,1-DIMETHYL-2-THIOUREA

1. Chemical Name: 3-Ethyl-1,1-dimethyl-2-thiourea

2. Chemical Structure:



3. Synonyms: Thiourea, N'-ethyl-N,N-dimethyl-
Urea, N'-ethyl-N,N-dimethyl-thio-

4. Chemical Abstracts Service (CAS) Number: 15361-86-1

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	132.23
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of 3-ethyl-1,1-dimethyl-2-thiourea and production volumes are presented below:

Vanderbilt Chemical Corp. (Bethel, CT)
Manufacturer
1977 Production: confidential

In 1978, in excess of 1000 pounds or $1000 were produced or sold by Vanderbilt (USITC, 1979a).

8. Use

3-Ethyl-1,1-dimethyl-2-thiourea is used as an accelerator, activator, or vulcanizing agent in rubber processing (SRI International, 1980).

9. Manufacturers and Distributors

3-Ethyl-1,1-dimethyl-2-thiourea is manufacturerd by Vanderbilt Chemical Co. in Bethel, CT and in Murray, KY (SRI International, 1980).

10. Manufacturing Processes

Information regarding the commercial process by which dimethylthiourea is manufactured is not available from the literature searched.

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 3-ethyl-1,1-dimethyl-2-thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 3-ethyl-1,1-dimethyl-2-thiourea were not found in the literature searched.

14. Biological Effects

No information was found in the literature searched regarding the biological effects of 3-ethyl-1,1-dimethyl-2-thiourea.

15. Ongoing Studies

No current toxicological or environmental studies of 3-ethyl-1,1-dimethyl-2-thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 3-ethyl-1,1-dimethyl-2-thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

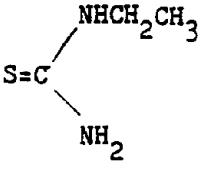
18. Other Pertinent Data

No other information that would aid in the assessment of 3-ethyl-1,1-dimethyl-2-thiourea as an occupational hazard was found in the literature searched.

K. ETHYLTHIOUREA

1. Chemical Name: Ethylthiourea

2. Chemical Structure:



3. Synonyms: Thiourea, ethyl-
Urea, ethyl-thio-

4. Chemical Abstracts Service (CAS) Number: 625-53-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	104.18
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of ethylthiourea and production volumes are presented in Table 4.

8. Use

According to various patent literature, ethylthiourea is useful as a corrosion inhibitor for metals, as a bacteriocide, as a photographic chemical agent, and as a chemical intermediate.

Table 4. Producers of Ethylthiourea and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Muskegon Chemical Co. Whitehall, MI	Small manufacturer	confidential
Millmaster Chemical Berkeley Heights, NJ	Importer	1-10 thousand lb
Degussa Corp. Teterboro, NJ	Importer	10-100 thousand lb

9. Manufacturers and Distributors

Ethylthioura is manufactured by Muskegan Chemical in Whitehall, MI (U.S. EPA, 1980).

Distributors include (Chem Sources--USA, 1980):

Bodman Chem.	Lachat Chem.
Degussa	Millmaster Chem.
Eastern Chem.	Pfaltz and Bauer
ICN/K and K	Tridom Chem.
Kennedy and Klim	

10. Manufacturing Processes

The commercial process by which ethylthiourea is manufactured is not available from the literature searched. It may be prepared, however, according to the following reaction (Schweizer et al, 1978):

$$C_2H_5NH_3Cl + KNCS \longrightarrow C_2H_5NHCNH_2$$

(S)

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to ethylthiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to ethylthiourea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

LD50 values of 100 mg/kg (Dieke et al., 1947) and >1000 mg/kg (Doull et al., 1962) have been reported following, respectively, oral administration in wild rats and intraperitoneal injection into mice.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Yamaguchi (1980) has reported recently that ethylthiourea was weakly mutagenic in S. typhimurium TA100 at a level of 150 µg/plate with microsomal activation. This finding is consistent with the earlier results of Seiler (1974), who reported weak activity in S. typhimurium his G-46 following application of 5 mg/plate (without activation) in a spot test.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of ethylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for ethylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

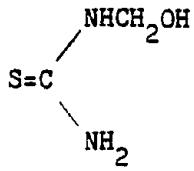
18. Other Pertinent Data

No other information that would aid in the assessment of ethylthiourea as an occupational hazard was found in the literature searched.

L. (HYDROXYMETHYL)THIOUREA

1. Chemical Name: (Hydroxymethyl)thiourea

2. Chemical Structure:



3. Synonyms: Monomethylol thiourea
Thiourea, (hydroxymethyl)-
Urea, (hydroxymethyl)-thio-

4. Chemical Abstracts Service (CAS) Number: 1000-83-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	---
Molecular Weight:	106.14
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of (hydroxymethyl)thiourea and production volumes are presented below:

Hunt Chemical OCD EP (East Providence, RI)
Manufacturer
1977 Production: 10-100 thousand lbs.

Proctor Chemical co. (Salisbury, NC)
Manufacturer
1977 Production: 10-100 thousand lbs.

8. Use

One manufacturer, Hunt Chemical in East Providence, RI, manufactures specialty organic chemicals particularly for the photographic, reprographic, and electronics industry. The other manufacturer, Proctor Chemical in Salesbury, NC, primarily manufactures finishing resins, dyeing assistants, and surface-active agents for use in the textile industry (SRI International, 1980).

Nabiev (1979) indicates that (hydroxymethyl)thiourea is useful in the finishing of cotton cellulose fabrics.

9. Manufacturers and Distributors

See production section above.

10. Manufacturing Processes

Information regarding the commercial process by which (hydroxymethyl)thiourea is manufactured is not available from the literature searched.

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to (hydroxymethyl) thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to (hydroxymethyl)thiourea were not found in the literature searched.

14. Biological Effects

No information was found in the literature searched regarding the biological effects of (hydroxymethyl)thiourea.

15. Ongoing Studies

No current toxicological or environmental studies of (hydroxymethyl)thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for (hydroxymethyl)thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

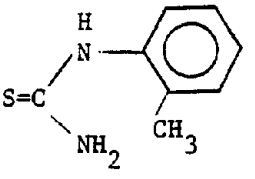
18. Other Pertinent Data

No other information that would aid in the assessment of (hydroxymethyl)thiourea as an occupational hazard was found in the literature searched.

M. (2-METHYLPHENYL)THIOUREA

1. Chemical Name: (2-Methylphenyl)thiourea

2. Chemical Structure:



3. Synonyms: Thiourea, (2-methylphenyl)-
ortho-Tolylthiourea
Urea, 2-thio-1-(2-tolyl)-

4. Chemical Abstracts Service (CAS) Number: 614-78-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Y42975000

6. Chemical and Physical Properties:

Description:	white needles
Molecular Weight:	166.25
Boiling Point:	---
Melting Point:	162°C
Vapor Pressure:	---
Solubility:	very soluble in hot water and alcohol; slightly soluble in ether
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of (2-methylphenyl)thiourea and production volumes are presented in Table 5.

8. Use

Patent literature indicates that (2-methylphenyl)thiourea is used as a corrosion inhibitor for iron and aluminum alloys.

Table 5. Producers of (2-Methylphenyl)thiourea and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Union Carbide Corp. Site No. 02-305 Ambler, PA	Manufacturer	10-1000 thousand lb
Miles Laboratories Zeeland, MI	Manufacturer - Not distributed	none
Hexcel/Fine Organics Lodi, NJ	Small manufacturer	confidential
Hexcel Corp. Zeeland, MI	Manufacturer	confidential

9. Manufacturers and Distributors

The manufacturers are listed in Table 5.

Distributors include (Chem Sources--USA, 1980):

Accurate Chem.
Chem. Procurement Lab.
Degussa, Inc.
ICN/K and K
Pfaltz and Bauer

10. Manufacturing Processes

(2-Methylphenyl)thiourea can be prepared by treating a salt of an arylamine with NH_4SCN or an alkali thiocyanate in an aqueous medium containing a hydrogen sulfur trioxide ion (Papenfuhr, 1979).

11. Impurities or Additives

No data is available from the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 292 workers are potentially exposed to (2-methylphenyl)thiourea.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to (2-methylphenyl)thiourea were not found in the literature searched.

14. Biological Effects

The only information found in the literature searched regarding the biological effects of (2-methylphenyl)thiourea were three acute toxicity values. LD50 values of 150 mg/kg (Plzak and Doull, 1969) and 5.2 mg/kg or 1.5 mg/kg (Dieke et al., 1947) have been reported following, respectively, intraperitoneal injection in mice and oral administration in wild or domestic rats.

15. Ongoing Studies

No current toxicological or environmental studies of (2-methylphenyl)thiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for (2-methylphenyl)thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

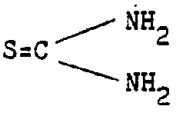
18. Other Pertinent Data

No other information that would aid in the assessment of (2-methylphenyl)thiourea as an occupational hazard was found in the literature searched.

N. THIOUREA

1. Chemical Name: Thiourea

2. Chemical Structure:



3. Synonyms: Pseudothiourea
Sulourea
Thiocarbamide
beta-Thiopseudourea
2-Thiourea
THU
Urea, thio-

4. Chemical Abstracts Service (CAS) Number: 62-56-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YU28000

6. Chemical and Physical Properties:

Description:	white lustrous crystals with a bitter taste
Molecular Weight:	76.13
Boiling Point:	decomposes
Melting Point:	176-182°C
Vapor Pressure:	---
Solubility:	9.18 g/100 ml (13°C) water; soluble in alcohol; sparingly soluble in ether to insoluble in ether
Specific Gravity:	1.405
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of thiourea and production volumes are presented in Table 6. From Table 6 it can be seen that thiourea is not currently manufactured in commercial quantities in the United States, but is imported.

Commerical production of thiourea was started in the United States by two companies in 1938; however, one of these companies transferred production to Canada in 1952, and the other stopped production in 1954. In 1959,

Table 6. Producers of Thiourea and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Brown Chemical NYC, NY	Importer	0.1 to 1.0 million lb
Graymor Chemical Pinebrook, NJ	Importer	10 to 100 thousand lb
American Cyanamid Boundbrook, NJ	Importer	10 to 100 thousand lb
Aceto Chemical Flushing, NY	Importer	zero
ABC Compounding Co. Atlanta, GA	Manufacturer	0 to 1000 lb
American Hoescht Bridgewater, NJ	Importer	confidential
American Research Products S. Euclid, OH	Manufacturer/ Small Manufacturer/ Importer	confidential
Uniroyal Chemical Naugatuck, CT	Importer	0.1 to 1.0 million lb
Sumitomo Shoji America NYC, NY	Importer	zero
Millmaster Chemical Berkeley Heights, NJ	Importer	0 to 1000 lb
Mitsui and Co. Los Angeles, CA Houston, TX	Importer Importer	0.1 to 1.0 million lb 10 to 100 thousand lb
Philipp Bros. Chemical NYC, NY	Importer	confidential
J.E. Halma Co. Lodi, NJ	Importer/ Small Manufacturer	confidential
Carroll Products Wood River Junction, RI		confidential

Table 6. Producers of Thiourea and Production Ranges (U.S. EPA, 1980) (Cont'd)

Producer and Location	Type of Production	1977 Production Range
C. Itoh and Co. NYC, NY	Importer	0.1 to 1.0 million lb
ICC Industries NYC, NY	Importer	confidential
American International Chemicals Natick, MA	Importer	confidential
Davos Chemical Fort Lee, NJ	Importer	0.1 to 1.0 million lb
Plant Site Not on File	---	0.1 to 1.0 million lb 1 to 10 million lb

production of thiourea at the U.S. supplying plant in Canada was also stopped. The U.S. requirements in 1964 were estimated to be 7.9 million pounds and were reported to be supplied exclusively from one producing company in each of the following countries: the Federal Republic of Germany (where the product was made from cyanamide), France (by the reaction of carbon disulphide with ammonia) and Japan (from cyanamide). At least two U.S. companies announced plans to start production of thiourea in the early 1960's, but no evidence was found that commercial quantities have been produced to date (IARC, 1974a).

From an analysis of import records at principal U.S. ports of entry it is estimated that 2.6 million pounds of thiourea were imported in 1972 and 3.7 million pounds were imported in 1973 (IARC, 1974a).

8. Use

The available literature on the uses of thiourea is characterized by frequent mention of the lack of information about which applications are the most important and which are only recommended uses that have not found commercial acceptance. The following list of certain uses during certain years was taken from IARC (1974a):

1960: 1.25 million lbs. used in production of coatings for copy paper as an anti-yellowing agent

1961: about 400,000 lbs. reported used as an intermediate in the manufacture of fire-retardant resins for lacy fabrics; use in boiler-water treatment to remove copper scale increased.

1964: use in photo-sensitive papers was estimated to account for over 50% of the U.S. market for thiourea, which was estimated to be about 4 million lbs. The second largest U.S. application was in the production of flame-retardant textile sizes, and use in boiler-water was believed to be the third largest.

1966: Approximately 3.75 million lbs. reportedly were being used in the United States for the treatment of nylon to prevent running and to improve the handling properties of the final nylon-based products.

1970: Two U.S. companies were reported to be marketing thiourea-formaldehyde resins for use as flame-retardant treatments on nylon netting used for wedding gowns and window decorations.

In addition to the data from IARC (1974), thiourea has a variety of commercial uses; however, the relative importance of each application was not available. Thiourea is used as a rubber antiozonant, in combination with dithio-acid and metal salts, in a trade-named product called Robac (Nicholas et al., 1978). Typical rubber applications include tires, belts, hoses, and gaskets. Thiourea is also used as a toning agent in photography (Thirtle and Zwick, 1979) where it is normally applied in a solution containing 0.1% thiourea and 0.4% sodium hydroxide (MacWilliam, 1968). Together with thiodiglycol and ammonium sulfite, thiourea is used as a "universal assistant combination" that simplifies the process of printing of nylon with dyes (Miller, 1966).

Thiourea is used as an additive to aid in cathode deposition in copper electrodeposition (Tuddenham and Dougall, 1979). It is used also as a corrosion inhibitor in metal pickling (Foley and Brown, 1979).

Thiourea is used as a chemical intermediate in the preparation of medicines and pharmaceuticals and in the preparation of other thiourea compounds. Thiourea derivative drugs are useful as antithyroid agents (Jones, 1969). Thiourea was used in the production of amino resins and plastics; however, this use has been eliminated (Updegraff et al., 1978). Recently, thiourea has been used as a fertilizer additive to inhibit nitrification (Merritt, 1976). According to Young (1966), thiourea is sometimes used as a liquefier in liquid animal glues.

Other suggested uses include synthesis of hair preparations, as a mold inhibitor, as an analytical reagent for bismuth and selenite ions, for use in galvanic cells, for use in silver cleaning, and in paper making and in paper whiteners (Hawley, 1977; IARC, 1974a).

9. Manufacturers and Distributors

Data available from the U.S. EPA (1980) regarding producers of thiourea and production volumes are presented in Table 6.

The following companies are among the many distributors of thiourea (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Accurate Chem.	Crampton and Knowles	MCB Reagent
Aceto Chem.	Davos Chem.	Milijac Inc.
Advent Chem.	Delamar Inc.	Millmaster
Aldrich Chem.	Eastern Chem.	Mitsui and Co.
Alfa Prod.	Eastman Kodak	New England Nuclear
Alpha International	EM Lab	Norris Chem.
American Hoescht	Fairfield Chem.	Orlex Chem.
American International	Fairmount Chem.	Pacific Chem. Lab
American Research	Fisher Sci.	Pfaltz and Bauer
Anachemia Chem.	Gallard-Schelsinger	Philipp Bros. Chem.
Apache Chem.	Graymor Chem.	Polysciences
J.T. Baker Chem.	Hach Chem.	Research Organics
Balflour, MacKine	ICC Indus.	Sigma Chem.
Bentley Chem.	ICD Group	Signs Trading
Biochemical Lab	ICN/K and K	G. Fredrick Smith Chem.
Bio-Clinical Lab	ICN Nutritional	Thorson Chem.
Browning Chem.	Independent Chem.	Trans World Chem.
Calbiochem-Behring Corp.	Kennedy and Klim	Tridom Chem.
Captree Chem.	Kingsley and Keith	Univar (Van Waters and Rogers)
Centerchem	Kum Yang Co.	Universal Preservachem
Chem. Dynamics	Lachat Chem.	U.S. Biochemical
Chem. Procurement Lab.	LaPine Sci.	Vega Biochem.
Chem Services	Lawchem	Westco Chem.
Columbia Organics	Mallinkrodt	Worth Chem.

10. Manufacturing Processes

Thiourea can be produced commercially by several processes. In one process, ammonium thiocyanate is formed by digesting concentrated ammonia with carbon disulfide; upon heating, the thiocyanate is converted to thiourea (Timmerman, 1978). In practice, the ammonium thiocyanate is dehydrated with an inert gas prior to thermal conversion to the thiourea (Koppers Co., 1950). The thiocyanate is then heated to conversion and the resulting product mixture is then subjected to an aqueous separation in which the thiourea is isolated and the

unreacted thiocyanate is carried over in the mother liquor and recovered by distillation for recycle.

Other production routes involve the reaction of calcium cyanide, ammonia, or cyanamide with hydrogen sulfide (according to various patent literature). In these processes, the product thiourea is commonly precipitated from the reaction solutions, separated by filtration, and purified by washing, distillation, and/or ion-exchange resins.

Figure 1 outlines the general thiourea manufacture operations.

11. Impurities or Additives

Thiourea is available in the United States as a laboratory chemical containing 99% active ingredient (IARC, 1974a). The specifications for a West German commercial product were as follows: 99% minimum active ingredient, 0.15% maximum water, 0.1% maximum ash, 0.4% maximum dicyanodiamide and traces of sulphate ion.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 213,340 workers are potentially exposed to thiourea.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to thiourea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxicity of thiourea is summarized in Table 7. When thiourea was injected intraperitoneally into adult rats, Dieke and Richter (1945) found a wide difference in LD50 values depending upon species:

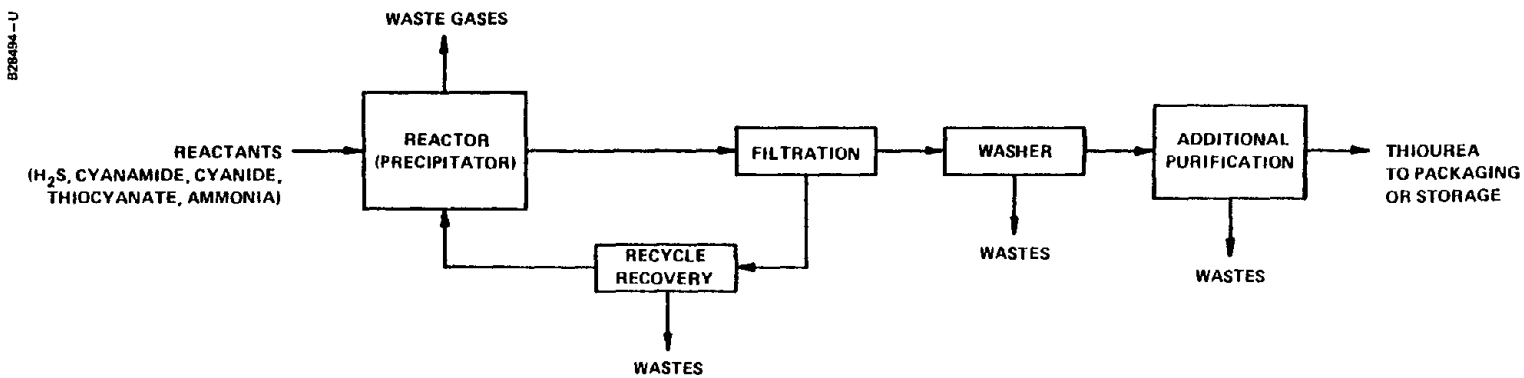


Figure 1. General Manufacture Operations of Thiourea

Table 7. Acute Toxicity of Thiourea

Route	Species	Dose (mg/kg)	Response	Reference
oral	mouse	8500	LD50	Korablev, 1965
i.p.[a]	rat	4-1830[b]	LD50	Dieke and Richter, 1945
i.p.	rat	1300 (male)	LD50	Wiberg and Grice, 1965
i.p.	rat	3650 (female)	LD50	Wiberg and Grice, 1965
i.p.	rat	3442	LD50	Zhislin et al., 1971
i.p.	mouse	100-200	LD50	Doull et al., 1962

[a] intraperitoneal

[b] wide species variations noted (see text)

values ranged from 4 mg/kg in domestic "Hopkins" rats to approximately 1800 mg/kg in a strain of wild Norway rats.

(2) Subchronic Exposures

Inhalation exposure of rats to thiourea for 3 months at unspecified levels has been reported to produce an increase in thyroid weight and a lowered hemoglobin level (Zhislin et al., 1971).

(3) Chronic Exposures

Goitrogenic effects have been reported in rats following administration of 0.25% thiourea in drinking water for 2 years (Purves and Griesbach, 1947). Deichmann and coworkers (1967) observed hydropic swelling and centrolobular necrosis of the liver, slight tubular congestion in the kidneys, and congestion and lymphoreticular hyperplasia of the spleen following 26 months of feeding rats at a 50 ppm dietary level of thiourea. Hartzell (1940) was unable to demonstrate, however, major toxic effects in rats fed 27.5 mg/kg thiourea for 53 weeks.

(4) Carcinogenicity

IARC (1974a) has reviewed numerous animal studies that investigated the carcinogenic activity of thiourea administered orally and parenterally (Table 8). Thiourea produced liver, thyroid, and zymbal gland tumors in rats following oral administration, but failed to show carcinogenic activity in mice following oral or subcutaneous administration.

(5) Mutagenicity

As detailed in Table 9, thiourea has been reported to be both mutagenic and non-mutagenic in the Ames Salmonella assay and in host-mediated assays in mice with S. typhimurium and S. cerevisiae indicator species. Thiourea has also been reported to induce petite mutations in S. cerevisiae, but

Table 8. Incidence of Tumors in Experimental Animals Treated with Thiourea (IARC, 1974a)

Route[a]	Species[b]	Dose	Exposure[c]	Tumors	Reference
oral	mouse	2%	81 wk	-	Gorbman, 1947
oral	mouse	0.25-0.37%	63 wk	-	Dalton et al., 1948
oral	mouse	0.2-0.3%	30 wk	1 thyroid adenoma	Casas and Koppisch, 1952
oral	rat, M	0.25%	12-24 mo	7 thyroid adenoma 4 thyroid carcinoma	Purves and Greisbach, 1947
oral	rat, F	0.25%	12-24 mo	8 thyroid adenoma 3 thyroid carcinoma	Purves and Greisbach, 1947
oral	rat	0.1%	24 mo	5 hepatic adenoma	Fitzhugh and Nelson, 1948
oral	rat	0.2%	14-23 mo	7 zymbal gland carcinoma	Unger and Rosin, 1960
oral	rat	0.2%	26-44 wk	5 zymbal gland carcinoma	Rosin and Rachmilewitz, 1954
s.c.	mouse	2500 mg/kg	single injection	No increase in lung adenoma	Gargus et al., 1969
i.p.	rat	10%	26 wk	5 zymbal gland carcinoma	Rosin and Rachmilewitz, 1954

[a] s.c. = subcutaneous; i.p. = intraperitoneal

[b] M = male; F = female

[c] wk = week; mo = month

Table 9. Mutagenicity of Thiourea

Type of Assay	Organism	Strain	Activation	Dose	Result	Reference
Reverse mutation	S. typhimurium	TA1535, TA1537, TA98, TA100	yes and no	<76 μg/plate	-	McCann et al., 1975
Reverse mutation	S. typhimurium	TA1535, TA1536, TA1537, TA1538, TA98, TA100	yes and no	125 μg/plate	-	Simmon, 1979a
Reverse mutation	S. typhimurium	TA1535, TA1538	yes	1-100 μg/plate	-	Kawalek et al., 1979
Reverse mutation	S. typhimurium	TA1535, TA1538	yes and no	50-250 μg/plate	-	Rosenkranz and Poirer, 1979
Reverse mutation	S. typhimurium	G-46	no	5 μg/plate	-	Seiler, 1974
Reverse mutation	S. typhimurium	TA100	yes	150 μg/plate	+	Yamaguchi, 1980
Mitotic, recombination	S. cerevisiae	D3	yes and no	5%	-	Simmon, 1979b
Petite mutation	S. cerevisiae	19 heploid strains	no	4.0 mg/mℓ	+	Egilsson et al., 1979
Host-mediated	S. typhimurium	TA1530, TA1538	mouse	125 mg/kg, i.m.	+	Simmon et al., 1979
Host-mediated	S. typhimurium	TA1535	mouse	1000 mg/kg, oral	-	Simmon et al., 1979
Host-mediated	S. cerevisiae	D3	mouse	1000 mg/kg, oral	-	Simmon et al., 1979
DNA-modifying activity	E. coli	pol A^-	yes	500 μg/plate	-	Rosenkranz and Poirer, 1979

not mitotic recombination, and did not inhibit the growth of DNA polymerase deficient E. coli (pol A^-).

(6) Teratogenicity

Oral administration of thiourea (240 mg/kg) to pregnant rats on day 12 of gestation has been reported to produce minor skeletal defects (incomplete fusion of sternebrae, wavy ribs, retarded ossification) in fetuses. One incidence of a major defect, spina bifida, was also noted (Ruddick et al., 1976).

Kertai and Remenar (1975) observed increased thyroid weights and decreased serum protein-bound iodine levels in 20-day old fetuses and newborn rats following oral maternal administration of 0.2% thiourea solution during the second and third weeks of pregnancy.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Thiourea is absorbed rapidly from the gastrointestinal tract of rats (Williams and Kay, 1945) and through the skin (Golikova, 1977). Hollinger and coworkers (1974) have shown that following intraperitoneal injection of radiolabeled thiourea in rats, liver, kidney, and lungs bind the compound producing a tissue half-life 10-fold higher (≈0 hours) than that observed for plasma levels.

b. Human Studies

(1) Pharmacokinetics

Previous human use of thiourea as an antithyroid agent indicates that the compound is well absorbed from the gastrointestinal tract (Williams and Kay, 1945).

(2) Health Effects

In a survey of 525 patients who used thiourea as an antithyroid drug, the most frequently observed side effects were fever, skin rash, and gastrointestinal disturbances. Four cases of leukopenia were noted, as well as a single incidence of agranulocytosis (Vanderlaan and Storrie, 1955).

(3) Target Organ Toxicity

The effective use of thiourea in patients with Graves' disease indicates that the compound has antithyroid effects (Vanderlaan and Storrie, 1955).

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Mammalian metabolic studies on the fate of the thiono-sulfur group in thioureas are currently under way at Vanderbilt University, School of Medicine (Investigator: R. Neal; Grant No. RO1-ES-00075-15; sponsored by U.S. Dept. of Health, Education, and Welfare) (SSIE, 1980).

Evaluation of the mutagenic effects of thiourea in a dominant lethal assay conducted in wasps is in progress at the University of Delaware (Investigators: A. Clark, L. Smucker, and D. Hamilton; Grant No. 263-73D-0035; sponsored by U.S. Dept. of Health, Education, and Welfare) (SSIE, 1980).

16. Exposure Standards

No recommended or promulgated occupational exposure standards for thiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

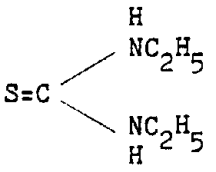
18. Other Pertinent Data

No other information that would aid in the assessment of thiourea as an occupational hazard was found in the literature searched.

0. 1,3-DIETHYL-2-THIOUREA

1. Chemical Name: 1,3-Diethyl-2-thiourea

2. Chemical Structure:



3. Synonyms: Diethylthiourea
N,N'-Diethylthiourea
NCI-C03816
Robac DET4
Thiourea, N,N'-diethyl-
USAF EK-1803

4. Chemical Abstracts Service (CAS) Number: 105-55-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YS9800000

6. Chemical and Physical Properties:

Description:	buff-colored solid
Molecular Weight:	132.25
Boiling Point:	decomposes
Melting Point:	68-71°C
Vapor Pressure:	---
Solubility:	slightly soluble in water; soluble in methanol, ether, acetone, benzene, and ethyl acetate; insoluble in gasoline
Specific Gravity:	---
Stability:	---

7. Production

In excess of 5000 pounds or $5000 were produced or sold in 1979 (USITC, 1980).

8. Use

Diethylthiourea is used as a vulcanization accelerator in rubber processing (SRI International, 1980). It is also used as a corrosion inhibitor for metal pickling (Hawley, 1977).

9. Manufacturers and Distributors

The U.S. EPA (1980) lists the following manufacturers; production ranges are not available:

Pennwalt Corp.	Wyandotte, MI
Fike Chemicals	Nitro, WV
Vanderbilt Chemical	Bethel, CT

SRI International (1980) lists Pennwalt and Fike as manufacturers, while USITC (1980) lists Fike and Pennwalt as producers.

Distributors of diethylthiourea include (1980-81 OPD Chemical Buyers Directory, 1980):

Atomergic Chemetals	Lachat Chem.
Bodman Chem.	LaPine Sci.
Chem. Procurement Lab.	MCB Reagents
Degussa Corp.	Pacific Chem. Lab
EM Lab	Tridom Chem.
Faesy and Besthoff	R.T. Vanderbilt
ICN/K and K	Wateree Chem.

10. Manufacturing Process

Information regarding the commercial process by which diethylthiourea is manufactured is not available from the literature searched. Diethylthiourea is made, however, from ethylamine (Chemical Economics Handbook, 1975) and, possibly, an isothiocyanate.

11. Impurities or Additives

There is no data available in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 11,186 workers are potentially exposed to diethylthiourea.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to diethylthiourea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Litton (1973) has determined an approximate LD50 of 316 mg/kg for diethylthiourea administered orally to rats, and an approximate LD50 of 681 mg/kg for the compound administered by the same route to mice. An approximate LD50 of 500-1000 mg/kg has been reported for diethylthiourea injected intraperitoneally into mice (Doull et al., 1962).

(2) Subchronic Exposures

Mice administered 500 ppm dietary levels of diethylthiourea showed depressed body weight within 30 weeks, while rats fed 250 ppm levels of the compound did not show significant weight loss in this period (NCI, 1979).

(3) Chronic Exposures

Dietary administration of 250 ppm levels of diethylthiourea to rats for 2 years has produced thyroid hyperplasia of both follicular and cystic cell types (NCI, 1979).

(4) Carcinogenicity

Results of an NCI bioassay of diethylthiourea for carcinogenic effects, following dietary administration of the compound for 2 years, indicate that thyroid tumors were increased in high-dose (250 ppm) rats (NCI, 1979). Follicular cell adenomas and carcinomas were increased in rats treated with 250 ppm levels of the compound, while those administered 125 ppm levels did not show significant increases in thyroid tumors. Mice treated with dietary

diethylthiourea at 250 and 500 ppm levels for the 2-year bioassay period did not show any dose-related tumor increases.

(5) Mutagenicity

No information was found in the literature searched. Diethylthiourea is scheduled, however, for mutagenicity testing in Salmonella by the NTP during fiscal year 1981 (NTP, 1980).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Williams (1945) has indicated that following equal oral doses of diethylthiourea and thiouracil, rats develop higher blood levels of the thiourea compound.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

The only available information on the effects of diethylthiourea in humans is the clinical report of Williams (1945) describing side effects in patients who used the compound as an anti-thyroid drug. Four thyrotoxic patients were initially administered 0.2 g of diethylthiourea 3 times daily. Symptoms described in these patients included headache, anxiety, anorexia, palpitations, and tachycardia. One patient developed an urticaria after 4 weeks of treatment, but this disappeared while the drug treatment continued.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of diethylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for diethylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

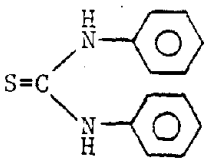
18. Other Pertinent Data

No other information that would aid in the assessment of diethylthiourea as an occupational hazard was found in the literature searched.

P. 1,3-DIPHENYL-2-THIOUREA

1. Chemical Name: 1,3-Diphenyl-2-thiourea

2. Chemical Structure:



3. Synonyms: Carbanilide, thio-
Thiocarbanilide
S-Diphenylthiocarbamide
Diphenylthiourea
N,N'-Diphenylthiourea
sym-Diphenylthiourea
Sulfocarbanilide
Thiourea, N,N'-diphenyl-
Urea, 1,3-diphenyl-2-thio-
USAF EK-245

4. Chemical Abstracts Service (CAS) Number: 102-08-9

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

FE1225000

6. Chemical and Physical Properties

Description:	gray powder to crystal leaflets
Molecular Weight:	228.33
Boiling Point:	decomposes
Melting Point:	146-154°C
Vapor Pressure:	---
Solubility:	almost insoluble in water; soluble in alcohol and ether
Specific Gravity:	1.32
Stability:	combustible

7. Production

Data available from the U.S. EPA (1980) regarding producers of diphenylthiourea and production volumes are presented in Table 10.

According to the U.S. International Trade Commission, 22 thousand pounds and 88 thousand pounds of diphenylthiourea (thiocarbanilide) were imported in 1975 and 1974, respectively (USITC, 1977a, 1976).

Table 10. Producers of Diphenylthiourea and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Producer	1977 Production Range
Brin-Mont Chemicals Greensboro, NC	Manufacturer	0.11.0 million lb
Fike Chemicals Nitro, WV	Manufacturer	confidential
Mobay Chemicals Pittsburg, PA	Importer	01 thousand lb

8. Use

Diphenylthiourea was an extensively used rubber vulcanization accelerator in the past and is still used in a few specialty recipes (Shaver, 1968). For high modulus polychloroprene latexes, diphenylthiourea (thiocarbanilide) is the preferred accelerator (Johnson, 1979).

Diphenylthiourea also has the following uses: as a dye intermediate for indigo, methyl indigo, and sulfur dyes, as a flotation agent, as a pharmaceutical intermediate, and as an acid-inhibitor (Lawler, 1977; Hawley, 1977).

9. Manufacturers and Distributors

SRI International (1980) lists American Cyanamid in Bound Brook and Linden, NJ, as a manufacturer. Producers cited by the U.S. EPA (1980) are shown in Table 10. Distributors of diphenylthiourea include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Fisher Sci.
Anachemia Chem.	ICN/K and K
J.T. Baker Chem.	MCB Reagents
Carroll Products	Millmaster Chem.
Chem. Procurement Lab	Monsanto
Degussa Corp.	Pfaltz and Bauer
Eastern (Guardian) Chem.	Wateree Chem.
Eastman Kodak	

10. Manufacturing Processes

Diphenylthiourea is formed by reacting carbon disulfide with an excess of boiling aniline; the reaction is represented as (Timmerman, 1978):

$$CS_2 + 2C_6H_5NH_2 \longrightarrow SC(NHC_6H_5)_2 + H_2S$$

According to patent literature, the carbon disulfide may be replaced by potassium ethylxanthate or carbonyl sulfide. The reaction is catalyzed on the commercial scale; a catalyst such as a zeolite-exchanged silica-alumina gel is employed (Drier and Wise, 1966).

The reaction products are separated and the diphenylthiourea must be purified via distillation or crystallization techniques. The general process operations are outlined in Figure 2.

11. Impurities or Additives

There is no data available in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 6117 workers are potentially exposed to diphenylthiourea.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to diphenylthiourea were not found in the literature searched.

14. Biological Effects

a. Animals Studies

(1) Acute Exposures

The acute toxicity of diphenylthiourea is summarized in Table 11.

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Diphenylthiourea did not show mutagenic activity in Salmonella typhimurium strains TA1535 or TA1538 at levels of 1-100 µg/plate with metabolic activation (Kawalek et al., 1979), or in S. typhimurium tester strains TA98, TA100, TA1535, and TA1537 with or without activation (NTP, 1980).

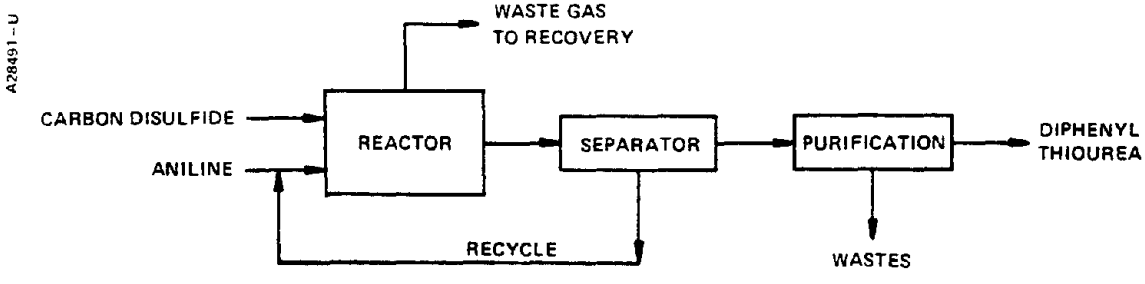


Figure 2. General Manufacture Operations of Dipehnylthiourea

Table 11. Acute Toxicity of Diphenylthiourea

Route	Species	Dose (mg/kg)	Response	Reference
oral	rat	>1500	LD50	Dieke et al., 1947
oral	rabbit	1500	LD50	Hanzlik and Irvine, 1921
oral	cats	720	LD50	Hanzlik and Irvine, 1921
i.p.[a]	mice	500-1000	LD50	Doull et al., 1962

Diphenylthiourea is scheduled for mutagenicity testing in Drosophila by the NTP during fiscal year 1981 (NTP, 1980).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or enviromental studies of diphenylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for diphenylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

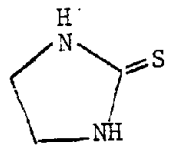
18. Other Pertinent Data

No other information that would aid in the assessment of diphenylthiourea as an occupational hazard was found in the literature searched.

Q. ETHYLENETHIOUREA

1. Chemical Name: Ethylenethiourea

2. Chemical Structure:



3. Synonyms: 4,5-Dihydroimidazole-2(3H)-thione
Ethylenethiourea
N,N'-Ethylenethiourea
1,3-Ethylene-2-thiourea
ETU
Imidazole-2(3H)-thione,4,5-dihydro-
2-Imidazolidinethione
2-Imidazoline-2-thiol
2-Mercaptiomidazoline
NA-22
NA-22-D
Pennac CRA
2-Thiol-dihydroglyoxaline
Urea,1,3-ethylene,2-thio-
Warecure C

4. Chemical Abstracts Service (CAS) Number: 96-45-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

NI9625000

6. Chemical and Physical Properties:

Description:	white to pale green crystals with a faint amine odor
Molecular Weight:	102.17
Boiling Point:	---
Melting Point:	199-204°C
Vapor Pressure:	---
Solubility:	2 g/100 ml water (30°C); 9 g/100 g water (60°C); moderately soluble in methanol, ethanol, ethylene glycol, and pyridine; insoluble in acetone, ether, chloroform, and benzene
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of ethylenethiourea and production volumes are presented in Table 12.

Data on U.S. imports and exports are not available.

8. Use

Ethylenethiourea has been widely used since 1948 as an accelerator for neoprene (polychloroprene) rubber. It is also recommended for use as part of a curing system for polyacrylate rubber. Although the curing of these rubbers converts almost all of the ethylenethiourea to other compounds, traces are still present in the cured products (IARC, 1974b).

The various types of neoprene rubber are used almost exclusively in industrial applications. The following U.S. consumption pattern was reported for 1973 (IARC, 1974b): 25% in industrial and mechanical goods; 20% in automotive products; 20% exported; 10% in wire and cable production; 10% in construction; 10% in adhesives; and 5% in miscellaneous applications. Consumer products containing neoprene include shoes and closures for containers (e.g., aerosol dispensers) (IARC, 1974b).

Polyacrylate rubbers are also used for industrial purposes. Products such as seals, o-rings, and gaskets for automotive and aircraft applications are believed to account for almost all the consumption (IARC, 1974b).

Although ethylenethiourea has been proposed for a variety of uses and although numerous patents have been issued, no evidence was found that it is being used commercially for other than rubber-curing purposes (IARC, 1974b).

Other suggested uses include applications in electroplating baths and as an intermediate for antioxidants, pesticides, pharmaceuticals, and synthetic resins (Hawley, 1977).

Table 12. Producers of Ethylenethiourea and Production Ranges (U.S. EPA, 1980)

Producer and Location	Type of Production	1977 Production Range
Akron Chemical Co. Akron, OH	Importer	10 to 100 thousand lb
Henley and Co. NYC, NY	Importer	confidential
Mobay Chemical Corp. Pittsburgh, PA	Importer	confidential
Millmaster Chemical Berkeley Heights, NJ	Importer	0 to 1000 lb
Fike Chemical Nitro, WV	Manufacturer	100 to 1000 thousand lb
Prochimie International NYC, NY	Importer	10 to 100 thousand lb
Plant Site Not on File	Manufacturer	confidential

9. Manufacturers and Distributors

SRI International (1980) lists Fike Chemicals (Nitro, WV) and Pennwalt Corp. (Wyandotte, MI) as manufacturers, while USITC (1980) lists Fike and du Pont as manufacturers. Producers cited by the U.S. EPA (1980) are listed in Table 12.

Distributors of ethylenethiourea include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Anachemia Chem.	Helm NY Chem.
Bodman Chem.	Henley and Co.
Chem. Procurement Lab	ICN/K and K
Chem Services	Lachat Chem.
Columbia Organics	MCB Reagents
Degussa Corp.	Millmaster Chem.
DuPont	Pfaltz and Bauer
Faesy and Besthoff	Prochimie International
Fallek Chem.	Tridom
Fisher Sci.	

10. Manufacturing Processes

Ethylenethiourea is prepared by reacting ethylenediamine with carbon disulfide in an alcohol solution at 60°C (Timmerman, 1978). The reaction products must then be separated, the alcohol media and unreacted materials recycled to the reactor, and the ethylenethiourea purified further and dried into a final product. The end-product ethylenethiourea is commonly sold in 150-pound fiber drums (Hawley, 1977).

11. Impurities or Additives

There is no data available in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 68,187 workers are potentially exposed to ethylenethiourea.

13. Control Technology and Work Practices

Ethylenethiourea is considered by NIOSH to present a potential carcinogenic and teratogenic hazard to workers. Control measures are warranted, therefore, for protection against this hazard, and are discussed in the recent NIOSH Special Occupational Hazard Review with Control Recommendations for Ethylenethiourea (Gregory, 1978). These recommentations include:

1. The use of engineering controls, such as process enclosure or local exhaust ventilation, to prevent airborne concentrations of ethylenethiourea or contact with the skin.

2. The use of protective clothing by employees whose work involves the possibility of skin exposure.

3. The use of respiratory protective equipment (supplied air respirators) during the time necessary to install or test the required engineering controls, as well as for nonroutine maintenance and repair operations, and during emergencies when airborne concentrations of ethylenethiourea may exceed the lowest detectable level (30 $\mu g/m^3$).

4. Counseling workers who have a history of thyroid disease, pulmonary disease, cardiovascular disease, or renal disease, and those using antithyroid drugs, about the potential health effects associated with jobs involving exposure to ethylenethiourea. Female workers of reproductive age should be advised of the potential for malformation of the developing fetus, and pregnant workers or workers breast-feeding an infant should not be exposed under any circumstances.

5. Implementation of appropriate sanitation and disposal practices (e.g., avoiding contamination of food with ethylenethiourea, regular washing of skin and changing of clothes to minimize dermal contact, prompt cleaning of spills with an alkaline solution of hypochlorite to oxidize ethylenethiourea into ethylene urea, etc.).

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

An oral LD50 of 1832 mg/kg has been determined for ethylenethiourea in mice (Graham and Hansen, 1972). Khera (1973) noted that

single oral doses of 656 mg/kg ethylenethiourea produced weight loss, marked salivation, and 25% mortality in rats; 72 and 216 mg/kg had no effect. An approximate dermal LD50 of 2250 mg/kg has also been reported for rats (Stula and Krauss, 1977).

(2) Subchronic Exposures

Oral administration of 80 mg/kg/day for 7-8 days was lethal to 9 of 11 female rats, but doses of up to 40 mg/kg/day from 42 days preconception to day 15 of gestation or on days 7-20 of gestation manifested no obvious signs of toxicity (Khera, 1973). Rabbits given up to 80 mg/kg on days 7-20 of gestation also showed no signs of general toxicity. Signs of delayed maternal toxicity were observed in cats administered toxic doses of ethylenethiourea orally during pregnancy (10-120 mg/kg/day from days 16-35 of gestation) (Khera and Iverson, 1978); those signs included ataxia, tremors, and hind limb paralysis.

Oral administration of ethylenethiourea to rats at dietary levels of 0.1% for 8 days has been reported to produce decreased weight gain, increased thyroid weight, marked thyroid hyperplasia, decreased thymus weight, and histological alteration of the thymus (Seifter et al., 1948). Feeding studies with rats at levels of 100-750 ppm for 2-12 months have also elicited increases in thyroid weight, decreases in iodine uptake, and decreases in body weight (Graham and Hansen, 1972; Graham et al., 1973); thyroid hyperplasia was observed in rats fed 500 and 750 ppm levels of ethylenethiourea for 90 days.

Similar effects (decreased body weight and thyroid hyperplasia at 625 ppm, increased thyroid weight at 125 ppm) in rats were seen by Freudenthal (1977) following 90 days of dietary administration of ethylenethiourea. In this study, iodine uptake was reduced in the rats exposed to 625 ppm

and thyroid stimulating hormone levels were elevated in the rats exposed to both levels of the compound (125 and 625 ppm).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

Five groups of investigators have reported ethylenethiourea to be carcinogenic in animals (Table 13).

Ethylenethiourea has produced hepatomas in 2 strains of mice administered 215 mg/kg levels by stomach tube from days 7-28 of age and 646 ppm levels of compound for an additional 55 days (BRL, 1968) (Table 13). The protocol of this large-scale study did not include examination of the thyroids.

Oral administration of ethylenethiourea at 350 ppm levels for 18 months (Ulland et al., 1972), at 250 and 500 ppm levels for 12 months (Graham et al., 1973), and at 500 ppm levels for 24 months (Graham et al., 1975) has been shown to produce thyroid carcinomas and adenomas in rats (Table 13). Gak et al. (1976) reported carcinogenicity in a lifetime study in rats (24 months), but not in hamsters (20 months), at 200 ppm in the diet; at 60 ppm, ethylenethiourea was carcinogenic for male rats but not females.

(5) Mutagenicity

A large number of studies have investigated the mutagenic activity of ethylenethiourea, a potential degradation product of dithiocarbamate pesticides (Table 14). Ethylenethiourea has shown weak mutagenicity in the Ames Salmonella assay and in the dominant lethal assay in Drosophilia. The compound failed to induce mutations in E. coli, did not show positive effects in the dominant lethal assay in rats, the micronucleus test in mice, and did not produce chromosome aberrations in cultured CHO cells or in rat bone marrow cells. Joint administration of ethylenethiourea and nitrite in vivo has produced

Table 13. Lowest Doses of Orally Administered Ethylenethiourea That Have Produced Neoplastic Changes (modified from Gregory, 1978)

Species and Strains	Route	Dose ppm	Dose mg/kg	Duration	Types of Tumors and Incidence Treated	Types of Tumors and Incidence Controls	Investigators
mouse (C57 B1/6 x C3H Hybrid), (C57B1/6 x AKR Hybrid	215 mg/kg levels by stomach tube from days 7-28 of age; 646 ppm (62 mg/kg)*) for an additional 55 days				Lymphomas 7/24 Hepatomas 59/68	5/172 14/338	BRL, 1968
rat (Charles River, Sprague Dawley)		500	40*	1 year	Thyroid carcinoma 15-25	0/22	Graham et al., 1973
rat (Charles River, Sprague-Dawley)		250	20*	2 years	Thyroid carcinoma 16/32	2/32	Graham et al., 1975
rat (Charles River, Sprague-Dawley)		350	28*	18 months	Thyroid carcinoma 6/52	0/64	Ulland et al., 1972
rat (unspecified strain)		60	5*	2 years	Thyroid carcinoma (actual number not given) 44.4%	3.2%	Gak et al., 1976
rat (Charles River Sprague-Dawley)		625	15*	90 days	Thyroid adenoma 7/20	0/20	Freudenthal et al., 1977

*Calculated from body weight and average food consumption. Average doses are given in both ppm and in mg/kg to allow for direct comparisons among the various studies. The assumptions in these calculations were that the purity of ETU used by the various investigators was the same, ETU was uniformly distributed in the food, and food consumption estimates were accurate.

Table 14. Mutagenicity Assays of Ethylenethiourea

Type of Assay	Organism	Strain	Activation	Dose	Results[a]	Reference
reverse mutation	S. typhimurium	TA1530	yes	20-200 mg/plate	±	Schupbach and Hummler, 1976
reverse mutation	S. typhimurium	his G-46	yes	20-80 mg/plate	-	Schupbach and Hummler, 1976
reverse mutation	S. typhimurium	his G-46	yes	100-1000 ppm	±	Seiler, 1974
reverse mutation	S. typhimurium	TA1535	no	5000-20,000 µg/plate	±	Shirasu et al., 1977
reverse mutation	S. typhimurium	TA100	yes	5000-20,000 g/plate	-	Shirasu et al., 1977
reverse mutation	S. typhimurium	TA1535	yes	5000-20,000 µg/plate	+	Teramoto et al., 1977
reverse mutation	S. typhimurium	TA100	yes	5000-20,000 µg/plate	-	Teramoto et al., 1977
reverse mutation	S. typhimurium	TA1536, TA1537, G46, TA1538	yes	10-10,000 µg/plate	-	Teramoto et al., 1977
reverse mutation	S. typhimurium	TA98, TA100, TA1535, TA1537	yes and no	not stated	-	NTP, 1980
reverse mutation	E. coli	WP2 her^+, WP2 her^-	yes	10-10,000 µg/plate	-	Teramoto et al., 1977
mitotic, recombination	B. subtilis	H17 Rec^+, M45 Rec^-	no	20-4000 µg/disk	-	Shirasu et al., 1977
petite mutation	S. cerevisiae	Group of 19 haploid strains	no	500 µg/ml	+	Egilsson et al., 1979
host-mediated	S. typhimurium	his G-46	mouse	150 mg/kg, p.o.	-	Shirasu et al., 1977

Table 14. Mutagenicity Assays of Ethylenethiourea (Cont'd.)

Type of Assay	Organism	Strain	Activation	Dose	Results[a]	Reference
host-mediated	S. typhimurium	his G-46	mouse	150 mg/kg (ETU)[a] + 50 mg/kg ($NaNO_2$), p.o.	+	Shirasu et al., 1977
host-mediated	S. typhimurium	TA1950	mouse	7.5-100 µmol/kg (ETU) + 7.5-100 µmol/kg ($NaNO_2$), gavage	+	Braun et al., 1977
host-mediated	S. typhimurium	TA1530	mouse	6000 mg/kg, oral	+	Schupbach and Hummler, 1977
host-mediated	S. typhimurium	his G-46	mouse	500-6000 mg/kg, oral	-	Schupbach and Hummler, 1977
dominant lethal	mouse	ICR	---	300 or 600 mg/kg/ day x 5 days, p.o.	-	Shirasu et al., 1977
dominant lethal	mouse	random bred	---	500, 100, or 3500 mg/kg, oral	-	Schupbach and Hummler, 1977
dominant lethal	Drosophila	NA	---	2.5%, sugar water	±	Mollet, 1975
micronucleus	mouse	Swiss albino	---	700, 1850, and 6000 mg/kg, 2 doses, oral, 24 hours apart	-	Schupbach and Hummler, 1977
micronucleus	mouse	ICR	---	150 and 450 mg/kg, 2 doses, oral, 24 hours apart	-	Seiler, 1975
micronucleus	mouse	ICR	---	600 mg/kg (ETU) + 200 mg/kg ($NaNO_2$), 2 doses, oral, 24 hours apart	-	Seiler, 1975
chromosome aberration	CHO cells in vitro	Don	NA	1000 and 3200 µg/ml	-	Shirasu et al., 1977

Table 14. Mutagenicity Assays of Ethylenethiourea (Cont'd.)

Type of Assay	Organism	Strain	Activation	Dose	Results[a]	Reference
chromosome aberration	rat bone marrow cells *in vivo*	Wistar	---	200 and 400 mg/kg, i.p.	-	Shirasu *et al.*, 1977
chromosome aberration	rat bone marrow cells *in vivo*	Wistar	---	50-400 mg/kg, i.p., 2-5 doses at 24 hour intervals	-	Shirasu *et al.*, 1977

[a] "±" = marginally positive response; "-" = negative response; "+" = positive response

[b] ETU = Ethylenethiourea

mutagenic effects in the host-mediated assay and in the micronucleus test, probably through the formation of an N-nitroso compound (Braun et al., 1977).

(6) Teratogenicity

Teratogenic effects have been reported in rats administered 40 and 80 mg/kg levels of ethylenethiourea orally for 21-42 days before conception to day 15 of pregnancy or on days 6-15 or 7-20 of pregnancy (Khera, 1973). These effects included meningoencephalocele, meningorrhagia, meningorrhea, hydrocephalus, obliterated neural canal, abnormal limb posture, micrognathia, oligodactyly, and absent, short, or kinky tail. Lu and Staples (1978) found similarly that oral administration of 40 mg/kg of ethylenethiourea to pregnant rats on days 7-15 of gestation produced a high incidence of fetal malformations, including craniocele, clubbed foot, hydrocephalus, short tail, and kinky or wavy tail. Another study of teratogenic effects in rats following oral administration of a single dose of 240 mg/kg ethylenethiourea indicated that peak sensitivity to teratogenic effects occurred on days 12-15 of gestation (Ruddick and Khera, 1975). The same group further reported that a single oral dose of 30 mg/kg of the compound administered to rats on day 15 of gestation produced a 90% incidence of hydrocephalus and microphthalmia in offspring (Khera and Tryphonas, 1977). Stula and Krauss (1977) have reported extensive skeletal defects in all rat fetuses examined from mothers that had received dermal applications of 50 mg/kg levels of ethylenethiourea, but this level of compound produced no maternal toxicity or embryo-lethality.

Rabbits treated on days 7-20 of pregnancy at an 80 mg/kg level showed increased frequency of resorption, reduced brain weight, and microscopic degeneration of fetal renal tubules (Khera, 1973). Ethylenethiourea has also produced deformities in fetuses from pregnant cats that were moribund following oral administration of 30-120 mg/kg of ethylenethiourea on

days 16-34 of gestation (Khera and Iverson, 1978). Chernoff and coworkers (1979) were, however, unable to show teratogenic effects in hamsters or guinea pigs administered 100 mg/kg levels of the compound orally during organogenesis.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Following a single oral dose of ethylenethiourea, rats rapidly absorbed the compound from the gastrointestinal tract and excreted over 80% of the initial dose within 24 hours (Kato et al., 1976). Allen and coworkers (1978) reported that monkeys administered ethylenethiourea by gastric intubation showed longer body retention of the compound than did rats, with approximately 1/4 of the radiolabel detected in body tissues after 48 hours.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Animal studies indicate that ethylenethiourea probably exerts an antithyroidal action in man, but specific toxicity information is not available. The chronic effects of poisoning that may be expected in humans on the basis of the actions of similar antithyroidals, however, have been described (Astwood, 1970; Labhart, 1976; both summarized in Gregory, 1978). These signs (comprising a syndrome caused myxedema) include (Gregory, 1978): drying and thickening of the skin, puffy swelling of subcutaneous tissues, a yellowish or ivory pallor to the complexion, an enlarged tongue, a husky voice, and dry, brittle hair. Because all metabolic rates are depressed in myxedema, mental processes, talking, pulse rate, and breathing also may be slowed (Labhart, 1976, summarized in Gregory, 1978).

(3) Target Organ Toxicity

Stanley and Astwood (1947; summarized in Gregory, 1978) considered a group of thiol compounds, including ethylenethiourea, as possible therapeutic agents to suppress thyroid action. A single administration of 100 mg/kg to one volunteer gave a response of 2 when inhibition of radioactive iodine uptake was graded on a scale of 0 to 5. The authors estimated the activity of ethylenethiourea to be 50% of that of thiouracil, an antithyroidal agent used clinically during the 1940's. Details of the study were not reported with respect to ethylenethiourea (Gregory, 1978).

(4) Epidemiology

The only epidemiological information available is a retrospective study of rubber workers for excesses of birth defects or thyroid tumors carried out by Smith (1976). He found no excess of teratogenic effects in 699 female workers' birth records or carcinogenic effects (thyroid) in 1,929 rubber workers. The workers were exposed to small amounts of unreacted ethylenethiourea which was present on the surface of finished rubbers; the women were employed in operations such as rubber trimming, cutting, and molding.

15. Ongoing Studies

In vitro mutagenesis testing of ethylenethiourea in microbial species is currently under way at Case Western Reserve (Contract No. NO1-ES-9-2136) and Stanford Research Institute (Contract No. NO1-ES-9-0001) as part of the National Toxicology Program (NTP, 1980). Investigation of the chronic toxicity of ethylenethiourea is also under way by Batelle Columbus Laboratories (Contract No. NO1-ES-8-2151) through the National Toxicology Program (NTP, 1980).

16. Exposure Standards

No recommended or promulgated occupational exposure standards for ethylenethiourea were found.

17. Sources of Additional Relevant Information

NIOSH has published (1) a Current Intelligence Bulletin on Ethylenethiourea (NIOSH, 1978), and (2) a Special Occupational Hazard Review with Control Recommendations for Ethylenethiourea (Gregory, 1978).

A NIOSH Health Hazard Evaluation (HHE) relating to ethylenethiourea has been conducted at the St. Clair Rubber Co., Marysville, MIH (HHE No. 77-67-499).

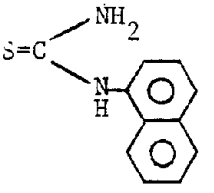
18. Other Pertinent Data

Ethylenethiourea is an *in vitro* and *in vivo* degradation product of the ethylene-bis-dithiocarbamate-type fungicides.

R. 1-NAPHTHYLTHIOUREA

1. Chemical Name: 1-Naphthylthiourea

2. Chemical Structure:



3. Synonyms: ANTU
Anturat
Bantu
Chemical 109
Kill Kantz
Krysid
alpha-Naphthylthiocarbamide
Naphthylthiourea
alpha-Naphthylthiourea
1-Naphthyl-2-thiourea
Rattrack
Rat-Tu
Thiourea, 1-naphthalenyl-
Urea, 1-naphthyl-thio-

4. Chemical Abstracts Service (CAS) Number: 86-88-4

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YT9275000

6. Chemical and Physical Properties:

Description:	odorless gray powder
Molecular Weight:	202.29
Boiling Point:	---
Melting Point:	198°C
Vapor Pressure:	---
Solubility:	0.06 g/100 g (20°C)
Specific Gravity:	---
Stability:	---

7. Production

Domestic production of naphthylthiourea on a commercial scale was terminated in 1973 (Meylan et al., 1976). It has been imported, however, in relatively small quantities in recent years, as reflected in the following figures (USITC, 1976, 1977a):

Year	Importation in Pounds
1975	1,984
1974	4,000

The following data are available from the U.S. EPA (1980):

Eastman Kodak (Rochester, NY)
Manufacturer
No manufacture or importation during 1977

Millmaster Chemical (Berkeley Heights, NJ)
Importer
1977 production of 1 to 10 thousand pounds

8. Use

Naphthylthiourea is used as a rodenticide to kill rats; it is a rat poison specific to the Norway rat (Metcalf, 1968; Spencer, 1968). Rodenticide application consists of baits of protein- or carbohydrate-rich materials formulated with a 1-3% content of naphthylthiourea (Spencer, 1968).

9. Manufacturers and Distributors

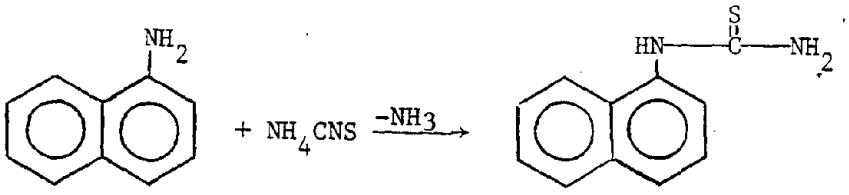
Currently, there are no commercial manufacturers of naphthylthiourea.

Distributors include (Chemical Week: 1981 Buyers Guide Issue, 1980; Chem Sources--USA, 1980):

Accurate Chem.	Eastman Kodak
Aldrich Chem.	Fisher Sci.
Atomergic Chemetals	ICN/K and K
Bio-Clinical Lab	Lachat Chem.
Chem. Procurement Lab	Millmaster Chem.
Chem Services	Pfaltz and Bauer
Eastern Chem.	Tridom Chem.

10. Manufacturing Processes

Naphthylthiourea is prepared by the interaction of 1-naphthylamine and ammonium thiocyanate (Spencer, 1968). The reaction is shown below:



The naphthylthiourea formed is probably precipitated, separated, washed, and dried by conventional operations.

11. Impurities or Additives

There is no data available in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 1146 workers are potentially exposed to naphthylthiourea.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to naphthylthiourea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of naphthylthiourea are summarized in Table 15. Rats, dogs, mice, and cats showed lethal effects of pulmonary edema and pleural effusion, while other species did not show this toxicity to the lungs (Dieke and Richter, 1946). Nephrotoxic effects, including acute glomerular nephritis, have been described in rats orally administered lethal levels of naphthylthiourea (Patil and Radhakrishnamurty, 1978).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

BRL (1968) failed to show significantly increased pneumonia in mice fed 2.1 mg/kg levels of naphthylthiourea for 18 months, probably due to the development of tolerance to the pulmonary toxicity of this compound (Boyd and Neal, 1976).

Table 15. Acute Effects of Naphthylthiourea

Route	Species	Dose (mg/kg)	Response	Reference
oral	rats (wild Norway)	6.9	LD50	Dieke et al., 1947
oral	rats (domestic)	2.5	LD50	Dieke et al., 1947
oral	dogs	≈38	LD50	Dieke and Richter, 1946
oral	cats	≈500	LD50	Dieke and Richter, 1946
oral	monkeys	≈4250	LD50	Dieke and Richter, 1946
i.p.[a]	rats	2.5-6.5	LD50	Dieke and Richter, 1946
i.p.	rats	10	LD50	Boyd and Neal, 1976
i.p.	mice	10-50	LD50	Doull et al., 1962
i.p.	mice	56	LD50	Dieke and Richter, 1946
i.p.	guinea pigs	≈350	LD50	Dieke and Richter, 1946
i.p.	monkeys	≈175	LD50	Dieke and Richter, 1946

[a] i.p. = intraperitoneal.

(4) Carcinogenicity

BRL (1968) investigated the carcinogenicity of naphthylthiourea administered orally and subcutaneously to 2 strains of mice as part as part of a bioassay for various selected pesticides. Administration of a single subcutaneous injection of naphthylthiourea to test animals (4.6 mg/kg) or oral administration of 2.1 mg/kg for 18 months failed to produce significant tumorigenic effects.

(5) Mutagenicity

Naphthylthiourea has produced positive mutagenic effects in S. typhimurium TA1535 and TA1538 at a level of 10 μg/plate in the presence of S-9 microsomal activation mixture (Kawalek et al., 1979); the compound failed to increase revertants in the absence of S-9 activation. Kawalek et al. (1979) also found that addition of naphthylthiourea to cultured hamster embryo cells at levels of 3-25 μg/ml produced transformed colonies.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Boyd and Neal (1976) have shown that naphthylthiourea is actively metabolized by microsomal drug hydroxylation in rat lung and liver extracts.

Histological examination of lung edema in rats following injection of 5 mg/kg of naphthylthiourea intraperitoneally indicates that the pulmonary edema results from damage to vascular endothelium (Cunningham and Hurley, 1972) and is maximal at 4-5 hours following injection.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of naphthylthiourea were found.

16. Exposure Standards

A Threshold Limit Value-Time Weighted Average (TLV-TWA) of 0.3 $\mu g/m^3$ (=0.04 ppm) has been recommended by the ACGIH (1980) and adopted by OSHA (1976).

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

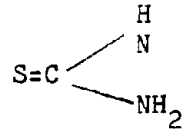
18. Other Pertinent Data

No other information that would aid in the assessment of naphthylthiourea as an occupational hazard was found in the literature searched.

S. 1-PHENYL-2-THIOUREA

1. Chemical Name: 1-Phenyl-2-thiourea

2. Chemical Structure:



3. Synonyms: NCI-C02017
Phenylthiocarbamide
Phenylthiourea
N-Phenylthiourea
PT4
Thiourea, phenyl-
Urea, phenyl-thio-

4. Chemical Abstracts Service (CAS) Number: 103-85-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YU1400000

6. Chemical and Physical Properties:

Description:	needles
Molecular Weight:	152.23
Boiling Point:	---
Melting Point:	154°C
Vapor Pressure:	---
Solubility:	slightly soluble in cold water; soluble in hot water, alcohol, and NaOH
Specific Gravity:	1.3
Stability:	---

7. Production

The following data are available from the U.S. EPA (1980):

Eastman Kodak (Rochester, NY)
Manufacturer
1977 Production of 0 to 1000 pounds

Fike Chemicals (Nitro, WV)
Manufacturer
No manufacture or importation during 1977

According to the U.S. International Trade Commission, the following quantities of phenylthiourea have been imported in recent years (USITC, 1976, 1977a, 1977b, 1979b):

Year	Importation in Pounds
1978	2,205
1976	2,260
1975	886
1974	2,359

8. Use

Phenylthiourea is used in the production of rodenticides (Metcalf, 1968) and in medical genetics (The Merck Index, 1976).

9. Manufacturers and Distributors

SRI International lists Guardian Chemical (Eastern Chem.) in Hauppauge, NY, as a manufacturer. Fike and Eastman Kodak are cited as manufacturers by the U.S. EPA (1980).

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chem Sources--USA, 1980):

Accurate Chem.
Aceto Chem.
Anachemia Chem.
Atomergic Chemetals
J.T. Baker Chem.
Bio-Clinical Lab.
Bodman Chem.
Chem Services
Degussa
EM Lab
Fisher Sci.
Gallard-Schlesinger
ICN/K and K
Lachat Chem.
LaPine Sci.
MCB Reagents
Pfaltz and Bauer
Sigma Chem.
Tridom Chem.

10. Manufacturing Processes

Phenylthiourea can be prepared by evaporating an aqueous solution of aniline hydrochloride and ammonium thiocyanate and carefully heating the residue (The Merck Index, 1976).

11. Impurities or Additives

There is no data available in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to phenylthiourea.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to phenylthiourea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxicity of phenylthiourea is summarized in Table 16. As indicated, the chemical has been shown to be highly toxic to rats following oral administration (LD50 ≈3 mg/kg). Following the administration of lethal oral doses of the compound to rats, pulmonary edema and pleural effusion have been noted in post-mortum examinations (Wheatcroft and Thornburn, 1972).

(2) Subchronic Exposures

Oral administration of phenylthiourea (0.7-12.6 mg/day) to rats for a 6-week period produced thyroid hyperplasia, atrophy of the thymus and ovaries, and a decrease in body temperature and weight (Richter and Clisby, 1942). The maximum tolerated dose of the compound, based on weight loss following 7 weeks of feeding, is 120 ppm in rats and 300 ppm in mice (Litton, 1973).

(3) Chronic Effects

Significant weight loss was noted in mice of both se es after 30 weeks of dietary administration of phenylthiourea at a 150 ppm level (NCI, 1978).

Table 16. Acute Toxicity of Phenylthiourea

Route	Species	Dose (mg/kg)	Response	Reference
oral	rat	3.1	LD50	Dieke et al., 1947
oral	rat	3.0	LD50	Wheatcroft and Thornburn, 1972
oral	mouse	≈10.0	LD50	Litton, 1973
oral	mouse	37.0	LD50	Wheatcroft and Thornburn, 1972
oral	rabbit	40.0	LD50	Wheatcroft and Thornburn, 1972
oral	chicken	≈1000.0	LD50	Scheline et al., 1961
i.p.[a]	mouse	25.0	LD50	Doull et al., 1962

[a] intraperitoneal

(4) Carcinogenicity

Lifetime feeding studies in rats and mice conducted by the NCI (1978) failed to show carcinogenic effects in either species following administration of 120 ppm levels in rats and 300 ppm levels in mice. The NCI summary of this study indicates that feeding of higher levels of phenylthiourea may be needed to establish toxic effects.

(5) Mutagenicity

Phenylthiourea failed to show mutagenic activity in S. typhimurium TA1535 or TA1538 at levels of 1-100 μg/plate, with metabolic activation (Kawalek et al., 1979). Yamaguchi (1980) recently reported, however, weak activity of phenylthiourea in S. typhimurium TA100 (with activation) at 150 μg/plate.

Phenylthiourea is scheduled for mutagenicity testing in Salmonella by the NTP during fiscal year 1981 (NTP, 1980).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Combs (1970) has reported a plasma half-life of approximately 2 hours for rats treated with phenylthiourea (dose and route of administration not specified). Scheline and coworkers (1961) confirmed this plasma half-life in rats injected intraperitoneally. These investigators have shown a 3-fold greater uptake of ^{35}S-labeled compound than ^{14}C-labeled compound by the thyroid following intraperitoneal injection of rats. Phenylthiourea was metabolized by desulphuration and ring hydroxylation in rats and rabbits.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of phenylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for phenylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

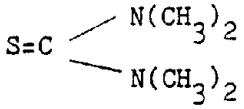
18. Other Pertinent Data

No other information that would aid in the assessment of phenylthiourea as an occupational hazard was found in the literature searched.

T. 1,1,3,3-TETRAMETHYLTHIOUREA

1. Chemical Name: 1,1,3,3-Tetramethylthiourea

2. Chemical Structure:



3. Synonyms: Tetramethylthiourea
N,N,N,N'-Tetramethylthiourea
Thiourea, tetramethyl-
TMTU
Urea, tetramethyl-thio-

4. Chemical Abstracts Service (CAS) Number: 2782-91-4

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YU2860000

6. Chemical and Physical Properties:

Description:	solid
Molecular Weight:	132.25
Boiling Point:	245°C
Melting Point:	78°C
Vapor Pressure:	---
Solubility:	slightly soluble in ether; soluble in water and alcohol
Specific Gravity:	---
Stability:	---

7. Production

The following data regarding manufacturers of tetramethylthiourea are available from the U.S. EPA (1980):

Eastman Kodak (Rochester, NY)
Manufacturer
1977 Production: none

Fike Chemical (Nitro, WV)
Manufacturer
1977 Production: confidential

8. Use

Tetramethylthiourea has been recommended as a safe processing curing agent for polychloroprenes (Johnson, 1979). Tetramethylthiourea is used as an antithyroid agent for the control of hyperthyroidism (Jones, 1969). Patent literature indicates that it can also be used in azo dye production.

9. Manufacturers and Distributors

The U.S. EPA lists Eastman Kodak and Fike Chemicals as manufacturers.

Distributors include (Chem Sources--USA, 1980):

Aldrich Chem.	ICN/K and K
Bodman Chem.	Lachat Chem.
Chem. Procurement Lab	Pfaltz and Bauer
Columbia Organics	Sigma Chem.
Eastern Chem.	Trans World Chem.
Fisher Sci.	Tridom Chem.

10. Manufacturing Processes

Tetramethylthiourea is formed by decomposition of tetramethylthiuram disulfide, which is a rubber processing chemical. The decomposition also produces carbon disulfide and sulfur.

It may be possible to prepare tetramethylthiourea from methylamines and thiocyanates.

11. Impurities or Additives

There is no data available in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 1954 workers are potentially exposed to tetramethylthiourea.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to tetramethylthiourea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Oral administration of tetramethylthiourea to rats produced lethal effects (LD50) at a level of 920 mg/kg (Stula et al., 1979). The reported LD50 for tetramethylthiourea following dermal application (in dimethylsulfoxide) to pregnant rats is 1000 mg/kg (Stula and Krauss, 1977).

(2) Subchronic Exposures

Tetramethylthiourea fed to pregnant rats from days 6-15 of gestation at 2500 ppm levels produced maternal toxicity; exposure at 100 or 500 ppm levels to dietary tetramethylthiourea did not adversely affect pregnant rats (Stula et al., 1979).

Williams (1945) has described goitrogenic effects in rats orally administered 0.1% levels of the compound for 2 weeks.

(3) Chronic Exposures

The long-term feeding (up to 2 years) of rats with 300 ppm levels of tetramethylthiourea has been reported to produce significant weight reduction in treated animals (Stula et al., 1979). Pathological findings indicated hyperplasia of the thyroid, decreased staining of the colloid, and enlargement of the lumen of the thyroid follicles (Stula et al., 1979).

(4) Carcinogenicity

Stula et al. (1979) have published the results of a long-term carcinogenesis bioassay conducted at the Haskell Laboratory in which rats (50/sex/dose level) were administered dietary tetramethylthiourea for up to 2 years. In female rats fed tetramethylthiourea at 300 ppm levels, 8 incidences of thyroid carcinoma and 6 incidences of thyroid adenoma were observed. Male rats administered this level of compound showed 2 cases of thyroid adenoma. No animals of either sex showed histological changes of the thyroid following 2

years of treatment with 30 ppm levels of tetramethylthiourea. Tetramethylthiourea was considered to be carcinogenic for the female rats at the 300 ppm dose.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

Tetramethylthiourea did not produce significant teratogenic or embryo-lethal effects when administered orally to pregnant rats (240 mg/kg) on days 12 or 13 of gestation (Ruddick et al., 1976). Stula and coworkers (1979) noted that oral administration of the compound at 2500 ppm levels on days 6-15 of gestation produced weak embryotoxic and teratogenic effects (not specified) in rats, and that this level of compound also produced maternal toxicity.

Dermal application of 250 mg/kg of tetramethylthiourea to pregnant rats produced no teratogenic effects, but did produce embryo-lethal effects when given on days 10 and 11 or 12 and 13 of gestation. Application of 500 mg/kg increased the incidence of embryo-lethality (74%) and resulted in several incidences of subcutaneous fetal hemorrhage (Stula and Krauss, 1977).

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Administration of tetramethylthiourea to rats at a 0.1% concentration in drinking water for 2 weeks produced higher blood and thyroid levels than those observed after comparable exposure to thiouracil (Williams, 1945).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

The only available information on the effects of tetramethylthiourea in humans is the clinical report of Williams (1945), who examined thyrotoxic patients who were treated 3 times daily with 0.2 g of the compound until the basal metabolic rate became normal. Three patients were treated at 0.8 to 1.0 g levels daily for 2 to 4 weeks to observe whether any toxic effects would be produced. A total of 26 female and 4 male patients were studied. A low incidence of toxic reactions to tetramethylthiourea was observed, including 1 case of leukopenia, 2 cases of rash, 3 incidences of fever, and 1 case of urticaria.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of tetramethylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational e posure standards for tetramethylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

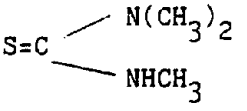
18. Other Pertinent Data

No other information that would aid in the assessment of tetramethylthiourea as an occupational hazard was found in the literature searched.

U. 1,1,3-TRIMETHYL-2-THIOUREA

1. Chemical Name: 1,1,3-Trimethyl-2-thiourea

2. Chemical Structure:



3. Synonyms: NCI-C02186
Trimethylthiourea
Thiourea, trimethyl-
Urea, thio-trimethyl-

4. Chemical Abstracts Service (CAS) Number: 2489-77-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YU4900000

6. Chemical and Physical Properties:

Description:	solid
Molecular Weight:	118.21
Boiling Point:	---
Melting Point:	87-88°C
Vapor Pressure:	---
Solubility:	very soluble in water and alcohol; soluble in benzene and chloroform
Specific Gravity:	---
Stability:	---

7. Production

Data available from the U.S. EPA (1980) regarding producers of trimethylthiourea and production volumes are presented below:

Fike Chemical (Nitro, WV)
Small manufacturer
1977 Production: confidential

In 1978, Fike produced or sold in excess of 1000 pounds or $1000 of trimethylthiourea (USITC, 1979a).

8. Use

Trimethylthiourea is used as a vulcanization accelerator in rubber processing (SRI International, 1980). It is also used as a curing agent for epichlorohydrin elastomers (Vandenberg, 1979).

9. Manufacturers and Distributors

The U.S. EPA (1980) lists Fike Chemical (Nitro, WV) as a manufacturer. SRI International (1980) lists Vanderbilt Chemical (Bethel, CT) as the only manufacturer, while USITC (1979a) lists only Fike.

10. Manufacturing Processes

The commercial process by which trimethylthiourea is manufactured is not available from the literature searched. It is possible, however, that the compound is made from mono- or diethylamine and an isothiocyanate.

11. Impurities or Additives

There is no data available in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 1061 workers are potentially exposed to trimethylthiourea.

13. Control Technology

Specific factors that may contribute to or prevent employee exposure to trimethylthiourea were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The reported LD50 values for trimethylthiourea administered orally to rats and mice are 316 mg/kg and 215 mg/kg, respectively (Litton, 1973).

(2) Subchronic Exposures

The maximum tolerated dose of trimethylthiourea, determined on the basis of weight loss in experimental animals fed the compound for 7 weeks, is 500 ppm for rats and 1000 ppm for mice (Litton, 1973).

(3) Chronic Exposures

The NCI (1979) reported significant weight losses in female mice after 25 weeks of dietary exposure to trimethylthiourea at 500 ppm levels; significant weight losses were also noted in female rats after 40 weeks of dietary exposure to 500 ppm levels of trimethylthiourea.

(4) Carcinogenicity

Life-time feeding of an 85% trimethylthiourea-15% dimethylthiourea mixture to female rats at a level of 500 ppm has produced a significant increase in thyroid carcinomas in these treated animals (NCI, 1979). No carcino genic effects were observed in similarly treated male rats or in mice of either sex administered trimethylthiourea at levels up to 1000 ppm.

(5) Mutagenicity

Trimethylthiourea is scheduled for mutagenicity testing in Salmonella by the NTP during fiscal year 1981 (NTP, 1980).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of trimethylthiourea were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for trimethylthiourea were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of trimethylthiourea as an occupational hazard was found in the literature searched.

APPENDIX - Thioureas

The following list includes all of the thioureas considered under the class definition. The compounds in the list were identified primarily from the following sources: U.S. EPA TSCA list and U.S. EPA (1980), USITC (1976-1980), SRI International (1980), Hawley (1977), and Kirk-Othmer's Encyclopedia of Chemical Technology.

CAS numbers are given to aid in identification as these types of compounds can be named by a variety of synonyms.

Allylthiourea	109-57-9
1-Allyl-3-(2-hydroxyethyl)-2-thiourea	105-81-7
N,N'-Bis(4-ethoxyphenyl)	1234-30-6
N,N'-Bis (hydroxymethyl)	3084-25-1
N,N'-Bis(4-(3-methylbutoxy)phenyl)	910-86-1
N,N'-Bis(methoxymethyl)	51872-26-5
N,N'-Bis(phenylmethyl)	1424-14-2
Butylthiourea	1516-32-1
1-Butyl-3-ethyl-2-thiourea	32900-06-4
1,3-Dibutyl-2-thiourea	109-46-6
1,3-Dicyclohexyl-2-thioures	1212-29-9
N,N'-Didecylthiourea	7614-64-4
N,N'-Diethyl-N'-2-propenylthiourea	21645-26-1
1,3-Diethyl-2-thiourea	105-55-5
N,N'-Diheptylthiourea	54244-10-9
1,3-Diisopropyl-2-thiourea	2986-17-6
1,3-Dimethyl-2-thiourea	534-13-4
1,3-Diphenyl-2-thiourea	102-08-9
N,N-Diphenylthiourea	3898-08-6
N,N'-Dioctylthiourea	109-40-0
N,N'-Di-2-propenylthiourea	6601-20-3
N,N'-Di-o-tolylthiourea	137-97-3
3-Ethyl-1,1-dimethyl-2-thiourea	15361-86-1
Ethylenethiourea	96-45-7
N-Ethyl-N-phenylthiourea	3955-58-6
N-Ethyl-N'-phenylthiourea	2741-06-2
Ethylthiourea	625-53-6
N-(2-Hydroethyl)-N'-phenylthiourea	102-12-5
N-(Hydroxymethyl)-N'-methylthiourea	15599-39-0
(Hydroxymethyl)thiourea	1000-83-5
(4-Methoxyphenyl)thiourea	2293-07-4
(1-Methylethyl)thiourea	1719-76-2
(2-Methylphenyl)thiourea	614-78-8
(4-Methylphenyl)thiourea	622-52-6

APPENDIX - Thioureas (Cont.)

1-Naphthylthiourea	86-88-4
1-Phenyl-2-thiourea	103-85-5
N,N'-1,3-Propanediyl-2-thiourea	2055-46-1
1,1,3,3-Tetramethyl-2-thiourea	2782-91-4
Thiourea	62-56-6
Tributylthiourea	2422-88-0
1,1,3-Trimethyl-2-thiourea	2489-77-2

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