

## SCREENING-LEVEL HAZARD CHARACTERIZATION Thiuram Category

**Tetramethyl thiuram monosulfide (TMTM; CASRN 97-74-5)**

**Tetraethyl thiuram disulfide (TETD; CASRN 97-77-8)**

**Tetramethyl thiuram disulfide (TMTD; CASRN 137-26-8)**

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set<sup>1,2</sup>) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental

---

<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<b>Chemical Abstract Service Registry Number (CASRN)</b>	97-74-5 97-77-8 137-26-8
<b>Chemical Abstract Index Name</b>	<b>Thiodicarbonyl diamide ((H<sub>2</sub>N)C(S))<sub>2</sub>S), tetramethyl-Thioperoxydicarbonyl diamide ((H<sub>2</sub>N)C(S))<sub>2</sub>S<sub>2</sub>, tetraethyl-Thioperoxydicarbonyl diamide ((H<sub>2</sub>N)C(S))<sub>2</sub>S<sub>2</sub>, tetramethyl-</b>
<b>Structural Formula</b>	See Section 1

**Summary**

Thiuram category members are solids with moderate water solubility and low to moderate vapor pressure. They are expected to have high mobility in soil. Volatilization of the thiuram category members is considered moderate based on their Henry's Law constant. Hydrolysis is moderate (neutral pH) to rapid (alkaline conditions) for CASRN 137-26-8 and 97-77-8. The rate of atmospheric photooxidation is considered rapid for all category members. Although these compounds are not readily biodegradable, hydrolysis is expected to be an important environmental fate process and the weight of evidence suggests that the persistence of the compounds in the thiuram category is moderate (P2). The bioaccumulation potential for all category members is low (B1).

Acute oral toxicity of the thiuram category members in rats, and acute dermal toxicity in rabbits is low. Acute inhalation toxicity of CASRN 137-26-8 in rats is moderate. Repeated-dose subchronic toxicity studies of CASRN 97-74-5 in rats via oral routes showed reduced body weight gain and effects on hematological parameters, phospholipids, liver and kidney at 26 mg/kg/day, the lowest dose; the NOAEL for systemic toxicity was not established. Repeated-dose subchronic toxicity studies of CASRN 97-74-5 to rats via inhalation showed reduced body weight gain and effects on liver and kidney at 0.4 mg/L/day, the only dose tested; the NOAEL for systemic toxicity was not established. Repeated-dose chronic toxicity/two-year bioassays of CASRN 137-26-8 in rats via oral routes showed reduced body weight gain and liver effects at 7.5 mg/kg/day; the NOAEL for systemic toxicity was 1.5 mg/kg/day. Repeated-dose chronic toxicity/two-year bioassays of CASRN 137-26-8 in mice via oral routes showed reduced body weight gain and histopathological effects in various organ tissues at 25 mg/kg/day; the NOAEL for systemic toxicity was 2.5 mg/kg/day. Repeated-dose chronic toxicity/two-year bioassays of CASRN 97-77-8 via oral routes showed no systemic toxicity at the highest dose tested in rats (30 mg/kg/day), male mice (300 mg/kg/day) and female mice (75 mg/kg/day). A two-generation oral reproductive toxicity study with CASRN 137-26-8 showed reduced body weight and food consumption at 3.8 mg/kg/day (F0 males) and 5.1 mg/kg/day (F0 females); the NOAEL for systemic toxicity for male and female rats was 1.5 mg/kg/day and 2.3 mg/kg/day, respectively. The study showed no reproductive or developmental (pre- and post-natal) toxicity at the highest doses tested in male rats (8.9 mg/kg/day) and female rats (14 mg/kg/day). In an oral prenatal developmental toxicity study of CASRN 137-26-8 in rats at higher dose levels, no maternal toxicity was observed at 30 mg/kg/day but there was developmental toxicity at 30 mg/kg/day as demonstrated by decreased fetal weights; the NOAEL for developmental toxicity was 15 mg/kg/day. In an oral prenatal developmental toxicity study of CASRN 137-26-8 in rabbits, no maternal or developmental toxicity was observed at 5 mg/kg/day (highest dose tested). In oral

prenatal developmental toxicity studies of CASRN 97-77-8 in rats, no maternal or developmental toxicity was observed at 250 mg/kg/day (only dose tested). In oral prenatal developmental toxicity studies of CASRN 97-77-8 in mice, no maternal or developmental toxicity was observed at 4900 mg/kg/day (only dose tested). CASRN 137-26-8 and 97-77-8 induced gene mutation *in vitro* and induced chromosomal aberrations when tested *in vitro* but not *in vivo*. The category members are irritating to rabbit eyes. CASRN 97-74-5 is also a skin irritant in rabbits. CASRN 97-74-5 and 137-26-8 are skin sensitizers in humans and guinea-pigs, respectively. The category members are not carcinogenic in rats and mice. Studies in rats exhibited some evidence of neurotoxicity for CASRN 137-26-8.

For the acute hazard of thiuram category chemicals, based on CASRN 137-26-8, the measured 96-hour LC<sub>50</sub> values to fish range from 0.13 to 0.27 mg/L, the measured 48-hour EC<sub>50</sub> values to aquatic invertebrates range from 0.21 to 0.24 mg/L, and the measured 96-hour EC<sub>50</sub> to aquatic plants is 1.0 mg/L.

No data gaps were identified in the HPV Challenge Program.

The sponsors, the Rubber and Plastic Additives (RAPA) Panel of the American Chemistry Council (ACC) submitted a Test Plan and Robust Summaries to EPA for the Thiuram Category on December 12, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 14, 2002 (<http://www.epa.gov/chemrtk/pubs/summaries/thiurmct/c13348tc.htm>). EPA comments on the original submission were posted to the website on August 26, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 10, 2003, which were posted to the ChemRTK website on July 25, 2003. The Thiuram Category consists of 3 chemicals as shown in Table 1.

### **Category Justification**

All three category members have closely related molecular structures: two alkyl groups attached to a nitrogen atom, which in turn is attached to a molecule of carbon disulfide. Two of these molecules are attached to each other through one or two sulfur atoms to form the thiuram mono- or di- sulfide respectively. The thiurams are manufactured from a secondary amine (dimethylamine or diethylamine) and carbon disulfide to form a dithiocarbamate. Two dithiocarbamate molecules are joined together through an oxidizer such as hydrogen peroxide. All three thiuram sulfides degrade to their respective dithiocarbamates when exposed to heat or alkaline conditions and to carbon disulfide and amine in acid.

The thiurams are fast-curing primary accelerators for natural and synthetic rubbers, speeding the formation of the sulfur crosslinks by donating sulfur atoms. They are also secondary accelerators for thiazole and sulfonamide accelerators. Tetramethyl thiuram disulfide is used in agriculture as a fungicide known as “thiram”. Tetraethylthiuram disulfide is also a prescription drug used in the treatment of alcoholism and is generically known as “disulfiram”. The thiuram sulfides degrade to their respective dithiocarbamates when exposed to heat or under alkaline conditions, and to carbon disulfide and the amine under acidic conditions.

EPA agreed that the category proposal was feasible and that read-across could be used between the two disulfides. However, the quality of the submission with respect to amount of detail provided in the robust summaries and the language it was submitted in allowed for limited review of the submitted data. In the revised submission, the robust summaries still lacked study details but were greatly improved with more focus on addressing the SIDS endpoints. EPA agrees that the three thiuram molecules are structurally similar and show similar physico-chemical and environmental fate properties and that the submitted data for the ecotoxicological and human health endpoints support their inclusion in thiuram category.

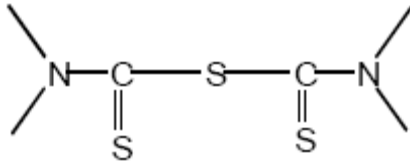
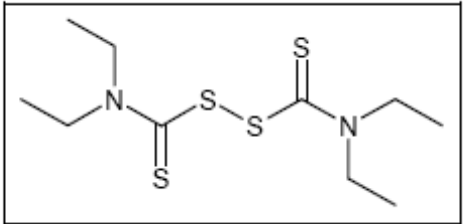
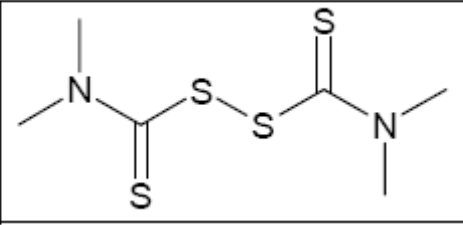
## **1 Chemical Identity**

### **1.1 Identification and Purity**

The following description is taken from the final Test Plan (2003):

The materials in this category share the basic structure: two alkyl groups are attached to a nitrogen atom, which in turn is attached to a molecule of carbon disulfide. Two of these molecules are attached to each other through one or two sulfur atoms to form the thiuram mono-

or disulfide respectively. The chemical structures of these chemicals in this category are listed in Table 1.

<b>Table 1. Chemical structures of Substituted Dipenylamines</b>		
<b>Chemical Name</b>	<b>CASRN</b>	<b>Structure</b>
Tetramethyl thiuram monosulfide (TMTM)	97-74-5	
Tetraethyl thiuram disulfide (TETD)	97-77-8	
Tetramethyl thiuram disulfide (TMTD)	137-26-8	

## 1.2 Physical-Chemical Properties

The physical-chemical properties of Thiuram category members are summarized in Table 2. Thiurams are solids with moderate water solubility and low to moderate vapor pressure.

Property	Value		
	Tetramethyl thiuram monosulfide (TMTM)	Tetraethyl thiuram disulfide (TETD)	Tetramethyl thiuram disulfide (TMTD)
CASRN	97-74-5	97-77-8	137-26-8
Molecular Weight	208.37	296.52	240.4
Physical State	Yellow solid	Solid	Solid
Melting Point	105–109.5 °C (measured)	69–73 °C (measured)	145 °C (decomposes; measured) 146 °C (measured) 155 °C (measured)
Boiling Point	301 °C (estimated) <sup>2</sup>	117 °C at 17 mm Hg (measured); 232 °C at 760 mm Hg (extrapolated) <sup>5</sup>	129 °C at 20 mm Hg (measured) 242 °C at 760 mm Hg (extrapolated) <sup>5</sup>
Vapor Pressure	$2.7 \times 10^{-4}$ mm Hg at 25°C (estimated) <sup>2</sup>	0.097 mm Hg at 25°C (estimated) <sup>5</sup>	$1.73 \times 10^{-5}$ mm Hg at 25°C (measured)
Water Solubility	15 mg/L at 20 °C (measured)	4.09 mg/L at 25 °C (measured)	16.5 mg/L at 20 °C (measured) 30 mg/L at 20 °C (measured)
Dissociation Constant (pK <sub>a</sub> )	Not applicable	Not applicable	Not applicable
Henry's Law constant	$1.7 \times 10^{-5}$ atm-m <sup>3</sup> /mole (estimated)	$8.32 \times 10^{-5}$ atm-m <sup>3</sup> /mole (estimated) <sup>2</sup>	$3.26 \times 10^{-7}$ atm-m <sup>3</sup> /mole (measured) <sup>3</sup>
Log K <sub>ow</sub>	1.17 (measured) <sup>4</sup> 0.75 (estimated) <sup>2</sup>	3.88 (measured)	1.73 (measured)

<sup>1</sup>Rubber and Plastics Additives Panel of the American Chemistry Council. July 11, 2003. Revised Robust Summary for Thiuram. <http://www.epa.gov/chemrtk/pubs/summaries/thiurmct/c13348tc.htm>.

<sup>2</sup>U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

<sup>3</sup>HSDB. 2008. Hazardous Substances Data Bank. Available via Toxnet at <http://toxnet.nlm.nih.gov/>. Accessed October 30, 2008.

<sup>4</sup>Material Safety Data Sheet from Sigma-Aldrich

<sup>5</sup>NOMO5 Estimation Software

## **2 General Information on Exposure**

### **2.1 Production Volume and Use Pattern**

The three chemicals in the Thiuram Category had an aggregated production and import volume in the United States between 2 million and 20.5 million pounds during calendar year 2005.

The volumes for the category members are as follows:

CASRN 97-74-5 I	<500,000 pounds
CASRN 97-77-8	1-10 million pounds
CASRN 137-26-8	1-10 million pounds

Non-confidential information in the IUR indicated that the industrial processing and uses of CASRN 97-77-8 and CASRN 137-26-8 include process regulators used in vulcanization or polymerization processes for the manufacture of rubber products and tires. Non-confidential information in the IUR indicated that the commercial and consumer products containing CASRN 137-26-8 include rubber and plastic products. The HSDB states that these chemicals are primarily used as vulcanization accelerators. In addition, CASRN 97-77-8 and 137-26-8 are used as fungicides and disinfectants. No use information was reported for CASRN 97-74-5. The HPV submission states that the thiurams category chemicals are used as primary accelerators in natural and synthetic rubbers.

## 2.2 Environmental Exposure and Fate

No quantitative information on environmental releases is available.

The environmental fate properties of the category chemicals are provided in Table 3. Thiuram category members are expected to have high mobility in soil. Volatilization of the thiuram category members is considered moderate based on their Henry's Law constant. Hydrolysis is moderate (neutral pH) to rapid (alkaline conditions) for CASRN 137-26-8 and 97-77-8. The rate of atmospheric photooxidation is considered rapid for all category members. Although these compounds are not readily biodegradable, hydrolysis is expected to be an important environmental fate process and the weight of evidence suggests that the persistence of the compounds in the thiuram category is moderate (P2). The bioaccumulation potential for all category members is low (B1).

<b>Property</b>	<b>Value</b>		
	<b>Tetramethyl thiuram monosulfide (TMTM)</b>	<b>Tetraethyl thiuram disulfide (TETD)</b>	<b>Tetramethyl thiuram disulfide (TMTD)</b>
CASRN	97-74-5	97-77-8	137-26-8
Photodegradation Half-life	0.925 hours (estimated)	19.6 minutes (estimated)	26.6 days (estimated); 0.36 hours (estimated) <sup>2,3</sup>
Hydrolysis Half-life	No data	Expected to hydrolyze at a rate similar to that of its analog TMTD whose half-life is 2 days at pH 7. In more alkaline water at pH 9, hydrolysis will occur much faster, with a half-life of 4 to 7 hours.	2 days at pH 7 and 25°C; 4-7 hours at pH 9 and 25°C; 77 days at pH 5 and 25°C
Biodegradation	0% in 28 days (not readily biodegradable) <sup>4</sup>	No data	100% in 28 days (readily biodegradable); 0% in 28 days (not readily biodegradable); Half-lives of 27.4 days and 14.4 days for bareground and turf plots of sandy loam soil <sup>5</sup>
Bioconcentration	BCF = 2 (estimated)	BCF = 194 (estimated)	BCF = 91 (measured)
Log K <sub>oc</sub>	1.0 (estimated)	1.967 (estimated)	1.0 (estimated)
Fugacity (Level III Model) <sup>2</sup>	Air = 0.266% Water = 56.3% Soil = 43.3% Sediment = 0.109%	Air = 0.0678% Water = 23.7% Soil = 73.7% Sediment = 2.52%	Air = 0.0499% Water = 36.8% Soil = 63% Sediment = 0.109%

Property	Value		
	Tetramethyl thiuram monosulfide (TMTM)	Tetraethyl thiuram disulfide (TETD)	Tetramethyl thiuram disulfide (TMTD)
CASRN	97-74-5	97-77-8	137-26-8
Persistence <sup>6</sup>	P2(moderate)	P2(moderate)	P2(moderate)
Bioaccumulation <sup>6</sup>	B1 (low)	B1 (low)	B1 (low)

<sup>1</sup>Rubber and Plastics Additives Panel of the American Chemistry Council. July 11, 2003. Revised Robust Summary for Thiuram, <http://www.epa.gov/chemrtk/pubs/summaries/thiurmct/c13348tc.htm>.

<sup>2</sup>U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

<sup>3</sup>The submitter estimated photooxidation half-lives for tetramethyl thiuram monosulfide and tetraethyl thiuram disulfide using AOPWIN v. 1.90, but for tetramethyl thiuram disulfide using the GEMS program. The EPA calculated photooxidation half-lives using AOPWIN v. 1.92 which were in agreement with the submitter's values for tetramethyl thiuram monosulfide and tetraethyl thiuram disulfide but not for tetramethyl thiuram disulfide. As the concentration of atmospheric hydroxyl radicals was not significantly different between the scenarios used by the submitter and the EPA, the disparity is likely due to differences between the two models. Using the EPA's calculations, the rate of atmospheric photooxidation is considered rapid for the thiuram category members.

<sup>4</sup>IUCALID Chemical Data Sheets Information System. Accessed October 30, 2008. <http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=dat>.

<sup>5</sup>EPA Registration Eligibility Decision (REDS) for Thiuram. September 2004. [http://www.epa.gov/pesticides/reregistration/status\\_page\\_t.htm](http://www.epa.gov/pesticides/reregistration/status_page_t.htm).

<sup>6</sup>Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

### 3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

#### *Acute Oral Toxicity*

##### *Tetramethyl thiuram monosulfide (CASRN 97-74-5)*

Sprague-Dawley rats (5/sex/dose) were administered single doses of tetramethyl thiuram monosulfide in corn oil via gavage at 794, 1000, 1260, 1580 or 2000 mg/kg-bw and observed for 10 days. Mortality was observed from days 1-7 with most deaths occurring within 4 days.

**LD<sub>50</sub> = 1320 mg/kg-bw**

##### *Tetraethyl thiuram disulfide (CASRN 97-77-8)*

Sprague-Dawley rats (5/sex/dose) were administered tetraethyl thiuram disulfide in corn oil via gavage at 2500, 3606, 5200 or 7500 mg/kg-bw. One male at 5200 mg/kg-bw and three females at 5200 mg/kg-bw died following traumatic intubations.

**LD<sub>50</sub> > 5200 mg/kg-bw (males)**

**LD<sub>50</sub> = 4573 mg/kg-bw (females)**

##### *Tetramethyl thiuram disulfide (CASRN 137-26-8)*

(1) Sprague-Dawley rats (5/sex/dose) were administered tetramethyl thiuram disulfide in corn oil via gavage at 631, 794, 1000 or 1260 mg/kg-bw and observed for 10 days.

**LD<sub>50</sub> = 1080 mg/kg-bw**

(2) In two separate studies, rats (strain and number not stated) were administered tetramethyl thiuram monosulfide (doses not stated) via gavage.

**LD<sub>50</sub> ~ 1287 – 1800 mg/kg-bw**

#### *Acute Dermal Toxicity*

##### *Tetramethyl thiuram monosulfide (CASRN 97-74-5)*

New Zealand albino rabbits (2/sex) were administered tetramethyl thiuram monosulfide (40% suspension in corn oil) dermally on to the skin at 1260, 2000, 3160 or 5010 mg/kg-bw for 24 hours and observed for 14 days. There were no mortalities at the two lowest dose levels. Mortality was observed on day 9 at 5010 mg/kg-bw and day 14 at 3160 mg/kg-bw.

**LD<sub>50</sub> > 2000 mg/kg-bw**

##### *Tetraethyl thiuram disulfide (CASRN 97-77-8)*

New Zealand white rabbits (5/sex) were administered tetraethyl thiuram disulfide dermally at 2000 mg/kg-bw under occluded conditions for 24 hours. No mortalities were reported.

**LD<sub>50</sub> > 2000 mg/kg-bw**

##### *Tetramethyl thiuram disulfide (CASRN 137-26-8)*

(1) New Zealand albino rabbits (1 female and 2 male) were administered a single dose of tetramethyl thiuram disulfide dermally on shaved skin at 5010 or 7940 mg/kg-bw as a 40% suspension in corn oil for 24 hours. No mortalities were reported.

**LD<sub>50</sub> > 7940 mg/kg-bw**

(2) Rabbits (number and strain not stated) were administered a single dose of tetramethyl thiuram disulfide dermally at 2000 mg/kg-bw. No mortalities were reported.

**LD<sub>50</sub> ≥ 2000 mg/kg-bw**

#### *Acute Inhalation Toxicity*

##### ***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) In two studies, rats (strain, number, sex not stated) were exposed to tetramethyl thiuram disulfide via inhalation for 4 hours.

**LC<sub>50</sub> = 4.42 mg/L**

(2) Rats were exposed to tetramethyl thiuram disulfide via inhalation at 0.1 mg/L for 4 hours. No mortality was observed.

**LC<sub>50</sub> > 0.1 mg/L**

#### ***Repeated-Dose Toxicity***

##### ***Tetramethyl thiuram monosulfide (CASRN 97-74-5)***

(1) In a 4-week study, Wistar rats (male and female, number not stated) were administered tetramethyl thiuram monosulfide via gavage at 0, 26, 520, or 867 mg/kg-bw/day for 28 days. At 26 mg/kg-bw/day, body weights and food consumption were decreased. There was a treatment-related decrease in red blood cell counts and hemoglobin levels in animals. Limited histopathological examination showed generalized swelling of liver cells and renal tubular epithelia. Radiolabeled palmitic acid incorporated into the phospholipids of the endoplasmic reticulum was reduced. The authors concluded that the microsomal hydroxylase enzyme system was sensitive to inhibition by tetramethyl thiuram monosulfide. The effects in other treatment groups were not reported.

**LOAEL = 26 mg/kg-bw/day** (based on reduced body weight gain, and effects on hematological parameters, liver, kidney and phospholipids)

**NOAEL = Not established**

(2) Rats (male and female, number not stated) were exposed to tetramethyl thiuram monosulfide dust via inhalation at 400 mg/m<sup>3</sup> (0.4 mg/L) 2 hours/day for 15 days. Exposed animals exhibited reduced weight gain and food consumption compared to the controls. Gross necropsy showed degenerative changes in the liver and kidneys of treated animals.

**LOAEL = 0.4 mg/L/day** (based on reduced body weight gain and effects on liver and kidney)

**NOAEL = Not established**

##### ***Tetraethyl thiuram disulfide (CASRN 97-77-8)***

(1) In a two-year bioassay, Fischer 344 rats (50/sex/dose) were administered tetraethyl thiuram disulfide via diet at 300 or 600 ppm (~15 or 30 mg/kg-bw/day, respectively) for 107 weeks. Untreated group of 20/sex/dose served as control. Mortalities were not considered treatment-related. Mean body weights of both sexes decreased throughout the study period in a dose-dependent manner. Other clinical signs and several nonneoplastic changes (degenerative, inflammatory, and cystic lesions in various organ tissues) occurred at comparative frequencies in the dosed and control groups.

**NOAEL = 30 mg/kg-bw/day**

(2) In a two-year bioassay, B6C3F1 mice (50/sex/dose) were administered tetraethyl thiuram disulfide via diet at 100 or 500 ppm (females; approximately 15 or 75 mg/kg-bw/day, respectively) and at 500 or 2000 ppm (males; approximately 75 or 300 mg/kg-bw/day, respectively) for 108 weeks. Untreated group of 20/sex/dose served as control. Mortalities were not considered treatment-related. Mean body weights of both sexes decreased throughout the study period in a dose-dependent manner. Other clinical signs and several nonneoplastic changes occurred at comparative frequencies in the dosed and control groups.

**NOAEL = 300 (males) and 75 (females) mg/kg-bw/day**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) In a 13-week study, rats (female and male, strain and number not stated) were administered tetramethyl thiuram disulfide via diet at 50, 500 and 1000 ppm (approximately 2.5, 25 and 50 mg/kg-bw/day, respectively) for 90 days. At 25 and 50 mg/kg-bw/day, body weight and food consumption reductions were treatment-related. At the same concentrations, the following treatment-related clinical chemistry and hematological changes were also observed: reduced red blood cell count, hemoglobin and hematocrit in females; increased white blood cell, absolute neutrophil, absolute lymphocyte and absolute monocyte counts in females; reduced total protein and glucose in both sexes; reduced albumin and increased urea nitrogen and chloride in females. Absolute organ weights (specific organs not stated) were reduced while organ to body-weight ratios increased. Macroscopically, the non-glandular stomach in some animals showed areas of erosion and the mesenteric lymph nodes were diffusely red or mottled. Microscopically, treatment-related effects included focal areas of erosion/ulceration in the mucosa of the nonglandular stomach, mucosal hyperplasia, or both, accompanied by some submucosal inflammation and edema.

**LOAEL = 25 mg/kg-bw/day** (based on changes in body weight, clinical chemistry, macroscopic and microscopic effects)

**NOAEL = 2.5 mg/kg-bw/day**

(2) In a two-year bioassay, CD-1 Rats (60/sex/dose) were administered tetramethyl thiuram disulfide via diet at 0, 30, 150 or 300 ppm (approximately 0, 1.5, 7.5 or 15 mg/kg-bw/day, respectively) for 104 weeks. All surviving rats were sacrificed at week 112. At approximately 7.5 and 15 mg/kg-bw/day, rats of both sexes showed reduced body weight gain. Extramedullary hematopoiesis in the liver of males at the mid- and high-doses, and of females at the high-dose as well as steatosis of the pancreas in both sexes was also noted.

**LOAEL = 7.5 mg/kg-bw/day** (based on changes in body weight and liver effects)

**NOAEL = 1.5 mg/kg-bw/day**

(3) In a carcinogenicity study, CD-1 mice (50/sex/dose) were administered tetramethyl thiuram disulfide via diet at 0, 15, 150 or 300 ppm (males; approximately 0, 2.5, 25 or 50 mg/kg-bw/day, respectively) and 0, 15, 300 or 600 ppm (females; approximately 0, 2.5, 50 or 100 mg/kg-bw/day, respectively) for 97 weeks. At the mid- and high-doses, there was a decrease in body weight, weight gain and food consumption of treated animals of both sexes. Several effects were observed at the mid-and high-dose males and females: retinal atrophy, intracytoplasmic protein like droplets in the urinary bladder, and necrosis and inflammation in the skin. Hyperkeratosis in the nonglandular stomach was observed only in the high-dose males but in the mid-and high-dose females. Increased pigment in the inner adrenal cortex was observed in the mid-and high-dose females. Decreased mean erythrocyte count, haemoglobin, and haematocrit values were noted in the high-dose females.

**LOAEL = 25 (males) and 50 (females) mg/kg-bw/day** (based on changes in body weight and histopathological effects in various organ tissues)

**NOAEL = 2.5 (males and females) mg/kg-bw/day**

### ***Reproductive Toxicity***

#### ***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

In a two-generation reproductive toxicity study, CD-1 rats (26/sex/dose) were administered tetramethyl thiuram disulfide in the diet at 0, 30, 60 or 180 ppm (approximately 0, 1.5, 3.8 and 8.9 mg/kg-bw/day for males and 2.3, 5.1, and 14 mg/kg-bw/day for females, respectively) for 81 days continuously for the F0 generation and 84 days continuously for the F1 generation. No mortalities or clinical signs of toxicity were noted at any dose in the F0 parents. Mean maternal body weight and food consumption were reduced in the F0 females at the two high doses (5.1, and 14 mg/kg-bw/day) and in F1 females at the high dose (14 mg/kg-bw/day). Mean food consumption was reduced in the F0 males at the two high doses (3.8 and 8.9 mg/kg-bw/day). There was no treatment-related effect on either the male and female copulatory, fertility or gestation indices.

**LOAEL (systemic toxicity) = 5.1 (females) and 3.8 (males) mg/kg-bw/day** (based on changes in body weight)

**NOAEL (systemic toxicity) = 8.9 (males) and 2.3 (females) mg/kg-bw/day**

**NOAEL (reproductive toxicity) = 8.9 (males) and 14 (females) mg/kg-bw/day** (highest dose tested)

### ***Developmental Toxicity***

#### ***Tetramethyl thiuram disulfide (CAS No. 137-26-8)***

(1) In a two-generation reproductive toxicity study described above, survival indices, necropsy findings, or mean number of stillborn were unaffected by treatment for the F1 and F2 offspring. No development toxicity was observed at all doses.

**NOAEL (development toxicity) = 8.9 (males) and 14 (females) mg/kg-bw/day** (highest dose tested)

(2) Pregnant female CD-1 rats were administered tetramethyl thiuram disulfide via gavage at 7.5, 15 or 30 mg/kg-bw/day during days 6 – 15 of gestation. There was a slight but transient decrease in maternal body weight gain during some days of the treatment period. Placental and fetal weights were decreased at 30 mg/kg-bw/day. The incidence of reduced 13<sup>th</sup> ribs in fetuses was increased slightly at 15 and 30 mg/kg-bw/day but this was not considered treatment-related by the study author.

**NOAEL (maternal toxicity) = 30 mg/kg-bw/day**

**LOAEL (developmental toxicity) = 30 mg/kg-bw/day** (based on decreased fetal weights)

**NOAEL (developmental toxicity) = 15 mg/kg-bw/day**

(3) Pregnant New Zealand white rabbits were administered tetramethyl thiuram disulfide via gavage at 0, 1.0, 2.5 or 5.0 mg/kg-bw/day during days 6 – 19 of gestation. No maternal toxicity was observed. Litter parameters, survival, growth and morphological development *in utero* were unaffected.

**NOAEL (maternal toxicity) = 5 mg/kg-bw/day** (based on no effects at the highest dose tested)

**NOAEL (developmental toxicity) = 5 mg/kg-bw/day** (based on no effects at the highest dose tested)

#### ***Tetraethyl thiuram disulfide (CAS No. 97-77-8)***

(1) Four pregnant Sprague-Dawley rats were administered tetraethyl thiuram disulfide via gavage at 250 mg/kg-bw/day during days 3 – 21 of gestation. No maternal or developmental toxicity was observed. No further details are provided in the robust summary.

**NOAEL (maternal toxicity) = 250 mg/kg-bw/day** (only dose tested)

**NOAEL (developmental toxicity) = 250 mg/kg-bw/day** (only dose tested)

(2) Pregnant CD-1 mice (50/dose) were administered tetraethyl thiuram disulfide in corn oil via gavage at 4900 mg/kg-bw/day during days 6 – 13 of gestation. No maternal or developmental toxicity was observed. The parameters evaluated were litter size, birth weight, neonatal growth, survival of pups and developmental toxicity. No toxic effects on the treated dams or offspring were observed.

**NOAEL (maternal toxicity) = 4900 mg/kg-bw/day**

**NOAEL (developmental toxicity) = 4900 mg/kg-bw/day**

#### ***Genetic Toxicity – Gene Mutation***

##### ***In vitro***

##### ***Tetramethyl thiuram monosulfide (CASRN 97-74-5)***

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Saccharomyces cerevisiae* (D4) were exposed to tetramethyl thiuram monosulfide at concentrations of 0.1, 1.0, 10, 100 and 500 µg/plate in the presence and absence of metabolic activation. Tetramethyl thiuram monosulfide was cytotoxic at 10 (TA98) and 500 µg/plate (all other strains) with and without metabolic activation. The response of the positive controls was not reported. No mutagenic activity was observed without metabolic activation in any strain. In the presence of metabolic activation, TA1535 exhibited a mutagenic response at doses ≥10 µg/plate. No other strains showed mutagenic activity.

**Tetramethyl thiuram monosulfide was not mutagenic in this assay except with metabolic activation in strain TA1535.**

(2) Mouse lymphoma L5178Y cells were exposed to tetramethyl thiuram monosulfide at concentrations of 2.5 – 5.0 µg/mL in the presence and absence of metabolic activation. DMSO was the solvent. A yellow precipitate formed when the test substance in solution was added to culture medium at final concentrations of 320 µg/mL. Concentrations greater than 10 µg/mL were cytotoxic without metabolic activation and more toxic with metabolic activation. The positive controls responded appropriately. No mutagenic activity of the test substance was observed.

**Tetramethyl thiuram monosulfide was not mutagenic in this assay.**

***Tetraethyl thiuram disulfide (CASRN 97-77-8)***

(1) In several bacterial reverse mutation assays, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *Saccharomyces cerevisiae*, D4 were exposed to tetraethyl thiuram disulfide at concentrations up to 5000 µg/plate (500 µg/plate for *Saccharomyces cerevisiae*, D4) in the presence and absence of metabolic activation. Tetraethyl thiuram disulfide was cytotoxic at 500 µg/plate in all strains, with and without (100 µg/plate for D4) metabolic activation. The responses of the negative and positive controls were not reported. No mutagenic activity was observed with or without metabolic activation in all strains tested.

**Tetraethyl thiuram disulfide was not mutagenic in these assays.**

(2) Mouse lymphoma L5178Y cells were exposed to tetraethyl thiuram monosulfide at concentrations up to 5 mg/kg in the presence and absence of metabolic activation. Positive results were reported.

**Tetraethyl thiuram disulfide was mutagenic in these assays.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) In several bacterial reverse mutation assays, *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, TA1537 and TA1538 were exposed to tetramethyl thiuram disulfide at concentrations up to 1000 µg/plate in the presence and absence of metabolic activation. The response of the controls was not reported. Mutagenic activity was consistently observed in all assays.

**Tetramethyl thiuram disulfide was mutagenic in these assays.**

(2) V79 Chinese Hamster Cells were exposed to tetramethyl thiuram disulfide at 1 to 56 µg/mL in the presence and absence of metabolic activation. Tetramethyl thiuram disulfide did not increase the mutation frequency at any concentration up to cytotoxic concentrations. The response of the controls was not reported.

**Tetramethyl thiuram disulfide was not mutagenic in these assays.**

***Genetic Toxicity – Chromosomal Aberrations***

***In vitro***

***Tetraethyl thiuram disulfide (CASRN 97-77-8)***

Chinese hamster ovary (CHO) cells were exposed to tetraethyl thiuram disulfide at concentrations of 0.005, 0.016, 0.05, 0.36, 1.15 or 3.6  $\mu\text{g}/\text{mL}$  in the presence or absence of metabolic activation. Increases in the number of cells with chromosomal aberrations were observed with and without metabolic activation. The positive and negative controls responded appropriately.

**Tetraethyl thiuram disulfide induced chromosomal aberrations in this assay.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) Chinese hamster ovary (CHO) cells were exposed to tetramethyl thiuram disulfide at concentrations of 0.56, 1.8 or 5.6  $\mu\text{g}/\text{mL}$  in the presence and absence of metabolic activation. Increases in the number of cells with chromosomal aberrations were observed with and without metabolic activation at the 10-hour harvest time. The response of controls was not reported.

**Tetramethyl thiuram disulfide induced chromosomal aberrations in this assay.**

(2) Chinese hamster ovary (CHO) cells were exposed to tetramethyl thiuram disulfide at concentrations of 0.003 – 0.023  $\mu\text{g}/\text{mL}$  and 0.2-1.5  $\mu\text{g}/\text{mL}$  in the absence and presence of metabolic activation, respectively. Cells with metabolic activation were harvested at 16 hours due to cell-cycle delay, while those without metabolic activation were harvested at 10 hours. The response of controls was not reported. Tetramethyl thiuram disulfide did not induce chromosomal aberrations with or without metabolic activation in this assay.

**Tetramethyl thiuram disulfide did not induce chromosomal aberrations in this assay.**

(3) L5178Y mouse lymphoma cells were exposed to tetramethyl thiuram disulfide at concentrations up to 20  $\mu\text{g}/\text{mL}$  in the presence and absence of metabolic activation in several studies. Tetramethyl thiuram disulfide showed weak activity in some assays and was equivocal in others.

**Tetramethyl thiuram disulfide was equivocal in these assays.**

***In vivo***

***Tetramethyl thiuram monosulfide (CASRN 97-74-5)***

In a bone marrow cytogenetics assay, Sprague-Dawley rats (male and female, number not stated) were administered single gavage doses of tetramethyl thiuram monosulfide at concentrations of 750 mg/kg-bw (females) and 1300 mg/kg-bw (males). Positive and negative control groups were included. Bone marrow samples were collected at 6, 24 and 48 hours sacrifice intervals after dosing. Slides were scored for proportion of aberrant metaphases and the frequency of aberrations/cell. Hypoactivity was the major clinical signs among the treated animals. Treatment-related decreases in mean body weight were also observed for both sexes at 24 and 48 hours. No treatment-related increases in the proportion of aberrant cells or aberrations/cell were observed at the 6, 24 and 48 hour time points. The positive control responded appropriately.

**Tetramethyl thiuram monosulfide did not induce chromosomal aberrations in this assay.**

***Tetraethyl thiuram disulfide (CASRN 97-77-8)***

(1) In a cytogenetic assay, Wistar rats (females, number not stated) were administered tetraethyl thiuram disulfide in the diet at 350 or 750 mg/kg-bw/day or via gavage at 3300 mg/kg-bw/day

for 5 days. The rats were sacrificed 24 hours post exposure. A minimum of 100 metaphases were scored per animal.

**Tetraethyl thiuram disulfide was not clastogenic in this assay.**

(2) Balb/c mice were administered single doses of tetraethyl thiuram disulfide via gavage at 625, 1250 or 2500 mg/kg-bw. Bone marrow samples were collected following sacrifice at 24 or 48 hours post exposure. There was no genotoxic response in the bone marrow of these animals.

**Tetraethyl thiuram disulfide did not induce micronuclei in this assay.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

CD-1 mice (male and female) were administered a single dose of tetramethyl thiuram disulfide intraperitoneally at 38, 189 or 377 mg/kg-bw. No positive controls were used. Bone marrow samples were collected from all test groups at 24, 48 or 72 hours post exposure. No increase in micronuclei in either sex was found.

**Tetramethyl thiuram disulfide did not increase micronuclei in this assay**

***Genetic Toxicity – Other effects***

***Tetraethyl thiuram disulfide (CAR N 97-77-8)***

In an *in vitro* sister chromatid exchange assay, CHO cells were exposed to tetramethyl thiuram monosulfide at three concentrations up to 5 mg/L in the presence and absence of metabolic activation. Vehicle and positive controls behaved as expected.

**Tetramethyl thiuram monosulfide did not induce sister chromatid exchange in this assay.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) In an *in vitro* DNA damage and repair assay, monolayer cultures of rat hepatocytes were exposed to 0.005 µg/mL up to 1 mg/mL tetramethyl thiuram disulfide. At concentrations  $\geq$  0.02 mg/mL tetramethyl thiuram disulfide was cytotoxic. At lower concentrations, no DNA repair was observed. No information on controls was provided in the robust summary.

**Tetramethyl thiuram disulfide was not considered genotoxic in this assay.**

(2) In an *in vitro* unscheduled DNA synthesis assay, primary cultures of rat hepatocytes were exposed to 0.03, 0.10, 0.3, 1.0, 3.0 or 10 µg/plate tetramethyl thiuram disulfide in the absence of metabolic activation. No information on controls was provided in the robust summary.

**Tetramethyl thiuram disulfide was not genotoxic in this assay.**

***Additional Information***

***Skin Irritation***

***Tetramethyl thiuram monosulfide (CASRN 97-74-5)***

Six New Zealand albino rabbits (sex not stated) were applied 0.5 mg finely ground tetramethyl thiuram monosulfide powder dermally on to the shaved skin for 24 hours. The animals were examined and scored on a scale of 1-8 at 4, 24, 48, 72 and 168 hours after application. The animals exhibited erythema at 24 and 72 hours.

**Tetramethyl thiuram monosulfide was slightly irritating in this study.**

***Tetraethyl thiuram disulfide (CASRNo. 97-77-8)***

Six rabbits (sex not stated) were applied tetraethyl thiuram disulfide dermally on to the skin for 4 hours. No effects were observed at 48 hour-interval.

**Tetraethyl thiuram disulfide was not irritating in this study.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) When applied to the skin of rabbits for 4 hours, tetramethyl thiuram disulfide was not irritating.

**Tetramethyl thiuram disulfide was not irritating to rabbit skin.**

(2) When applied to the skin of rabbits for 24 hours, tetramethyl thiuram disulfide was moderately irritating.

**Tetramethyl thiuram disulfide was moderately irritating to rabbit skin.**

***Eye Irritation***

***Tetramethyl thiuram monosulfide (CASRN 97-74-5)***

Six New Zealand albino rabbits (male/female, number per sex not stated) were instilled in to one eyes 100 mg tetramethyl thiuram monosulfide for 24 hours. The other eye was untreated and served as control. The cornea, iris and conjunctivae were examined and scored on a scale of 1-10 immediately after application, 10 minutes and 1, 24, 48, 72 and 168 hours after application. The animals exhibited slight to moderate erythema and copious discharge after application which did not clear till 72 hours post exposure.

**Tetramethyl thiuram monosulfide was slightly irritating to rabbit eyes in this study.**

***Tetraethyl thiuram disulfide (CASRN 97-77-8)***

(1) Six rabbits (strain, sex not stated) were instilled into one eye 100 mg tetraethyl thiuram disulfide; the other eye was untreated and served as the control. The eyes of three of the treated animals were washed 20-30 seconds after exposure. The eyes of the other animals remained unwashed. No effects were observed in the washed eyes. In the other animals, slight irritation was noted.

**Tetraethyl thiuram disulfide was slightly irritating to rabbit eyes in this study.**

(2) Six rabbits (sex not stated) were instilled 100 mg tetraethyl thiuram disulfide (ground to a fine dust) in the conjunctival sac of one eye; the other eye was untreated and served as the control. The irritation was scored at 1 hour and 1, 2, 3, 4 and 7 days after instillation. Tetraethyl thiuram disulfide was slightly irritating; the eyes were clear by day 2.

**Tetraethyl thiuram disulfide was slightly irritating to rabbit eyes in this study.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) When applied to the eye of rabbits, tetramethyl thiuram disulfide was irritating. No further details are described in the robust summary.

**Tetramethyl thiuram disulfide was irritating to rabbit eyes in this study.**

(2) When applied to the eye of rabbits in another study, tetramethyl thiuram disulfide was not irritating. No further details are described in the robust summary.

**Tetramethyl thiuram disulfide was not irritating to rabbit eyes in this study.**

***Sensitization***

***Tetramethyl thiuram monosulfide (CASRN 97-74-5)***

(1) In a human skin patch test, 50 volunteers were applied rubber accelerator tetramethyl thiuram monosulfide. There was 1 positive reaction on initial application, 7 positive reactions during the course of 15 serial applications and 5 positive reactions on subsequent rechallenge.

**Tetramethyl thiuram monosulfide was sensitizing to human skin.**

(2) In another human skin patch test, 128 patients with Type IV allergic reactions due to rubber products were tested with tetramethyl thiuram monosulfide. 85 patients reacted positively to tetramethyl thiuram monosulfide. Patients were tested with “thiuram mix” and individual rubber compounds.

**Tetramethyl thiuram monosulfide was sensitizing to human skin.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) In two guinea-pig split adjuvant tests, Tetramethyl thiuram disulfide was concluded to be a moderate skin sensitizer.

**Tetramethyl thiuram disulfide was sensitizing in this assay.**

(2) In a guinea-pig maximization test, at 10% challenge treatment, 3 out of 10 animals showed a positive response with tetramethyl thiuram disulfide. At 5% challenge concentration 1 out of 10 animals showed a positive response.

**Tetramethyl thiuram disulfide was sensitizing in this assay**

***Carcinogenicity***

***Tetraethyl thiuram disulfide (CASRN 97-77-8)***

(1) Fischer 344 rats (50/sex/dose) were administered tetraethyl thiuram disulfide via diet at 300 or 600 ppm (~15 or 30 mg/kg-bw/day, respectively) for 107 weeks. Untreated group of 20/sex/dose served as control. Mortalities were not considered treatment-related. Mean body weights of both sexes decreased throughout the study period in a dose-dependent manner. Other clinical signs and several nonneoplastic changes occurred at comparative frequencies in the dosed and control groups. Tumor incidence was comparable to that of controls in both sexes.

**Tetraethyl thiuram disulfide was not considered carcinogenic in Fischer 344 rats.**

(2) B6C3F1 mice (50/sex/dose) were administered tetraethyl thiuram disulfide via diet at 100 or 500 ppm (females; approximately 15 or 75 mg/kg-bw/day, respectively) and at 500 or 2000 ppm (males; approximately 75 or 300 mg/kg-bw/day, respectively) for 108 weeks. Untreated group of 20/sex/dose served as control. Mortalities were not considered treatment-related. Mean body weights of both sexes decreased throughout the study period in a dose-dependent manner. Other clinical signs and several nonneoplastic changes occurred at comparative frequencies in the dosed and control groups. Tumor incidence was comparable to that of controls in both sexes.

**Tetraethyl thiuram disulfide was not considered carcinogenic in B6C3F1 mice.**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) Fischer 344 rats (male and female, number of animal not reported) were administered tetramethyl thiuram disulfide in the diet at 500 ppm (approximately 25 mg/kg-bw/day) daily for 2 years. In animals treated with the test substance alone, no increase in tumor incidence was noted.

**Tetraethyl thiuram disulfide was not considered carcinogenic in Fischer 344 rats.**

(2) Fischer 344 rats (50/sex/dose) were administered tetramethyl thiuram disulfide via diet at 0, 0.05 or 0.1% (approximately 0, 25 or 50 mg/kg-bw/day, respectively) for 104 weeks. All surviving rats were sacrificed at week 112. At approximately 50 mg/kg-bw/day, rats showed reduced body weight gain, especially in females, and liver dysfunction in biochemical examination of blood in males. Tumor incidence was comparable to that of controls in both sexes.

**Tetramethyl thiuram disulfide was not considered carcinogenic in Fischer 344 rats.**

(3) CD-1 Rats (60/sex/dose) were administered tetramethyl thiuram disulfide via diet at 0, 30, 150 or 300 ppm (approximately 0, 1.5, 7.5 or 15 mg/kg-bw/day, respectively) for 104 weeks. All surviving rats were sacrificed at week 112. At approximately 7.5 and 15 mg/kg-bw/day, rats of both sexes showed reduced body weight gain. There was a significant positive trend for hepatocellular and thyroid C-cell adenomas in both sexes. The incidences of tumors in the liver, thyroid or any other organ were not significantly increased in either sex at any of the dose levels tested as compared to the controls.

**Tetramethyl thiuram disulfide was not considered carcinogenic in male and female CD-1 rats.**

(4) CD-1 mice (50/sex/dose) were administered tetramethyl thiuram disulfide via diet at 0, 15, 150 or 300 ppm (males; approximately 0, 2.5, 25 or 50 mg/kg-bw/day, respectively) and 0, 15, 300 or 600 ppm (females; approximately 0, 2.5, 50 or 100 mg/kg-bw/day, respectively) for 97 weeks. At the mid- and high-doses, there was a decrease in body weight, weight gain and food consumption. No treatment-related increased in tumor incidence was observed in either sex.

**Tetramethyl thiuram disulfide was not considered carcinogenic in male and female CD-1 mice.**

## *Neurotoxicity*

### *Tetramethyl thiuram disulfide (CASRN 137-26-8)*

(1) Sprague-Dawley rats (15/sex/dose) were administered tetramethyl thiuram disulfide at 0, 30, 125 and 500 ppm (approximately 0, 1.5, 6.25 or 25 mg/kg-bw/day, respectively) for 90 days. No toxicity was observed at 1.5 mg/kg-bw/day. At 6.25 mg/kg-bw/day, adverse effects on body weight and food consumption were observed. At 25 mg/kg-bw/day, body weight and food consumption were depressed. Functional Observation Battery (FOB) was affected slightly but no changes in motor activity or neuropathology were observed.

(2) (<http://www.epa.gov/ncea/iris/subst/0267.htm>) Rats (24/dose) were administered tetramethyl thiuram disulfide at 0, 100, 300, 1000 or 2500 ppm (approximately 0, 5, 15, 50 or 125 mg/kg-bw/day, respectively) in the diet for two years. Observations and tests for effects included body weight, mortality, clinical signs, neurological examination and microscopic examination of the tissues. Weakness, ataxia, varying degrees of hind limb paralysis and calcified masses in the basal ganglia and in the cerebellum were noted at 300 ppm (15 mg/kg-bw/day) and above.

**Conclusion:** Acute oral toxicity of the thiuram category members in rats, and acute dermal toxicity in rabbits is low. Acute inhalation toxicity of CASRN 137-26-8 in rats is moderate. Repeated-dose subchronic toxicity studies of CASRN 97-74-5 in rats via oral routes showed reduced body weight gain and effects on hematological parameters, phospholipids, liver and kidney at 26 mg/kg/day, the lowest dose; the NOAEL for systemic toxicity was not established. Repeated-dose subchronic toxicity studies of CASRN 97-74-5 to rats via inhalation showed reduced body weight gain and effects on liver and kidney at 0.4 mg/L/day, the only dose tested; the NOAEL for systemic toxicity was not established. Repeated-dose chronic toxicity/two-year bioassays of CASRN 137-26-8 in rats via oral routes showed reduced body weight gain and liver effects at 7.5 mg/kg/day; the NOAEL for systemic toxicity was 1.5 mg/kg/day. Repeated-dose chronic toxicity/two-year bioassays of CASRN 137-26-8 in mice via oral routes showed reduced body weight gain and histopathological effects in various organ tissues at 25 mg/kg/day; the NOAEL for systemic toxicity was 2.5 mg/kg/day. Repeated-dose chronic toxicity/two-year bioassays of CASRN 97-77-8 via oral routes showed no systemic toxicity at the highest dose tested in rats (30 mg/kg/day), male mice (300 mg/kg/day) and female mice (75 mg/kg/day). A two-generation oral reproductive toxicity study with CASRN 137-26-8 showed reduced body weight and food consumption at 3.8 mg/kg/day (F0 males) and 5.1 mg/kg/day (F0 females); the NOAEL for systemic toxicity for male and female rats was 1.5 mg/kg/day and 2.3 mg/kg/day, respectively. The study showed no reproductive or developmental (pre- and post-natal) toxicity at the highest doses tested in male rats (8.9 mg/kg/day) and female rats (14 mg/kg/day). In an oral prenatal developmental toxicity study of CASRN 137-26-8 in rats at higher dose levels, no maternal toxicity was observed at 30 mg/kg/day but there was developmental toxicity at 30 mg/kg/day as demonstrated by decreased fetal weights; the NOAEL for developmental toxicity was 15 mg/kg/day. In an oral prenatal developmental toxicity study of CASRN 137-26-8 in rabbits, no maternal or developmental toxicity was observed at 5 mg/kg/day (highest dose tested). In oral prenatal developmental toxicity studies of CASRN 97-77-8 in rats, no maternal or developmental toxicity was observed at 250 mg/kg/day (only dose tested). In oral prenatal developmental toxicity studies of CASRN 97-77-8 in mice, no maternal or developmental

toxicity was observed at 4900 mg/kg/day (only dose tested). CASRN 137-26-8 and 97-77-8 induced gene mutation *in vitro* and induced chromosomal aberrations when tested *in vitro* but not *in vivo*. The category members are irritating to rabbit eyes. CASRN 97-74-5 is also a skin irritant in rabbits. CASRN 97-74-5 and 137-26-8 are skin sensitizers in humans and guinea-pigs, respectively. The category members are not carcinogenic in rats and mice. Studies in rats exhibited some evidence of neurotoxicity for CASRN 137-26-8.

**Table 4. Summary of Health Effects Data**

<b>Endpoints</b>	<b>Tetramethyl thiuram monosulfide (TMTM) (97-74-5)</b>	<b>Tetraethyl thiuram disulfide (TETD) (97-77-8)</b>	<b>Tetramethyl thiuram disulfide (TMTD) (137-26-8)</b>
<b>Acute Oral Toxicity</b> <b>LD<sub>50</sub> (mg/kg-bw)</b>	<b>1320</b>	<b>4573 (f)</b> <b>&gt;5200 (m)</b>	<b>1080-1800</b>
<b>Acute Dermal Toxicity</b> <b>LD<sub>50</sub> (mg/kg-bw)</b> <b>rabbit</b>	<b>&gt;2000</b>	<b>&gt; 2000</b>	<b>&gt;7940</b>
<b>Acute Inhalation Toxicity</b> <b>LC<sub>50</sub> (mg/L)</b>	No Data 4.42 (RA)	No Data 4.42 (RA)	<b>4.42</b>
<b>Repeated-Dose Toxicity</b> <b>NOAEL/LOAEL</b> <b>Oral (mg/kg-bw/day)</b>	<b>NOAEL = Not established</b> <b>LOAEL = 26 (rat)</b> <b>(28 days)</b>	<b>NOAEL = 30 (rat);</b> <b>mouse: 300(m),75 (f)</b> <b>(2-yr.) (hdt)</b>	<b>NOAEL = 2.5 (rat)</b> <b>LOAEL = 25 (rat)</b> <b>(90 days)</b> <b>NOAEL = 1.5 (rat)</b> <b>LOAEL = 7.5 (rat)</b> <b>(2 yr.)</b> <b>NOAEL = 2.5 (mouse)</b> <b>LOAEL = 25 (mouse)</b> <b>(2 yr.)</b>
<b>Repeated-Dose Toxicity</b> <b>NOAEL/LOAEL</b> <b>Inhalation (mg/L/day)</b>	<b>NOAEL = Not established</b> <b>LOAEL = 0.4</b> <b>(15 days)</b>	No Data NOAEL = Not established LOAEL = 0.4 (RA)	No Data NOAEL = Not established LOAEL = 0.4 (RA)
<b>Reproductive Toxicity</b> <b>NOAEL/LOAEL</b> <b>Oral (mg/kg-bw/day)</b> <b>Systemic toxicity</b> <b>Systemic toxicity</b> <b>Reproductive toxicity</b> <b>Reproductive toxicity</b>	No Data NOAEL=1.5(m) 2.3(f) LOAEL=3.8(m) 5.1(f)  NOAEL=8.9(m) 14(f) (RA)	No Data NOAEL=1.5(m) 2.3(f) LOAEL=3.8(m) 5.1(f)  NOAEL=8.9(m) 14(f) (RA)	<b>NOAEL=1.5(m)/2.3(f)</b> <b>LOAEL=3.8(m)/5.1(f)</b>  <b>NOAEL=8.9(m)/14(f)</b> (hdt)
<b>Developmental Toxicity</b> <b>NOAEL/LOAEL</b> <b>Oral (mg/kg-bw/day)</b> <b>Maternal toxicity</b> <b>Developmental Toxicity</b>	No Data NOAEL =15 (rat), 5 (rabbit) LOAEL = 30 (rat), NOAEL = 15 (rat) = 5 (rabbit)	<b>NOAEL = 250(rat),</b> <b>4900(mouse),</b> <b>NOAEL = 250(rat),</b> <b>4900 (mouse)</b>	<b>NOAEL = 15(rat),</b> <b>5 (rabbit)</b> <b>LOAEL = 30(rat),</b> <b>NOAEL = 15 (rat)</b> <b>= 5 (rabbit)</b>

<b>Table 4. Summary of Health Effects Data</b>			
<b>Endpoints</b>	<b>Tetramethyl thiuram monosulfide (TMTM) (97-74-5)</b>	<b>Tetraethyl thiuram disulfide (TETD) (97-77-8)</b>	<b>Tetramethyl thiuram disulfide (TMTD) (137-26-8)</b>
	(RA)		
<b>Genetic Toxicity – Gene Mutation</b> <i>In vitro</i>	<b>Negative</b>	<b>Positive</b>	<b>Positive</b>
<b>Genetic Toxicity – Chromosomal Aberrations</b> <i>In vitro</i>	No Data Positive (RA)	<b>Positive</b>	<b>Positive</b>
<b>Genetic Toxicity – Chromosomal Aberrations</b> <i>In vivo</i>	<b>Negative</b>	No Data Negative (RA)	No Data Negative (RA)
<b>Genetic Toxicity – Other Effects</b> <b>Sister Chromatid Exchange (<i>in vitro</i>)</b> <b>DNA Repair Assay (<i>in vitro</i>)</b> <b>Unscheduled DNA synthesis</b> <b>Mouse micronucleus assay (<i>in vivo</i>)</b>	– – – –	<b>Negative</b> – – <b>Negative</b>	– <b>Negative</b> <b>Negative</b> <b>Negative</b>
<b>Irritation (skin)</b>	<b>Irritating</b>	<b>No</b>	<b>Irritating</b>
<b>Irritation (eye)</b>	<b>Irritating</b>	<b>Irritating</b>	<b>Irritating</b>
<b>Sensitization</b>	<b>Positive</b>	–	<b>Positive</b>
<b>Neurotoxicity Oral (mg/kg-bw/day)</b>	–	–	<b>NOAEL~5</b> <b>LOAEL~15</b>
<b>Carcinogenicity</b>	<b>Negative</b>	<b>Negative</b>	<b>Negative</b>

Measured data in bold text; RA = Read Across; (f) = female; (m) = male; hdt = highest dose tested.

#### **4 Hazards to the Environment**

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read across (RA) to untested members of the category.

##### ***Acute Toxicity to Fish***

###### ***Tetramethyl thiuram monosulfide (CASRN 97-74-5)***

(1) Rainbow trout (*Salmo gairdneri*) were exposed to tetramethyl thiuram monosulfide at nominal concentrations (not stated) under static closed system conditions for 96 hours. Acetone was used as the solvent and solvent control. All concentrations were observed once every 24 hours for mortality and abnormal effects.

**96-h LC<sub>50</sub> = 2.3 mg/L**

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to tetramethyl thiuram monosulfide at nominal concentrations (not stated) under static closed system conditions for 96 hours. Acetone was used as the solvent and solvent control. All concentrations were observed once every 24 hours for mortality and abnormal effects.

**96-h LC<sub>50</sub> = 2.6 mg/L**

###### ***Tetraethyl thiuram disulfide (CASRN 97-77-8)***

(1) Bluegill sunfish (*Lepomis macrochirus*) were exposed to tetraethyl thiuram disulfide at nominal concentrations of 0, 0.010, 0.018, 0.032, 0.056 and 0.10 mg/L under static conditions for 96 hours. Acetone was used as the solvent and solvent control. All concentrations were observed once every 24 hours for mortality and abnormal effects.

**96-h LC<sub>50</sub> = 0.067 mg/L**

(2) Rainbow trout (*Salmo gairdneri*) were exposed to tetraethyl thiuram disulfide at nominal concentrations of 0, 0.056, 0.10, 0.18, 0.32 and 0.56 mg/L under static conditions for 96 hours. Acetone was used as the solvent and solvent control. All concentrations were observed once every 24 hours for mortality and abnormal effects.

**96-h LC<sub>50</sub> = 0.22 mg/L**

(3) Guppies (*Poecilia reticulata*) were exposed to tetraethyl thiuram disulfide at nominal concentrations (not stated) in two separate experiments under semi-static conditions for 96 hours. Test media were renewed at 48 hours.

**96-h LC<sub>50</sub> = 0.187 - 0.32 mg/L**

###### ***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) Fathead minnow (*Pimephales promelas*) were exposed to tetramethyl thiuram disulfide at nominal concentrations of 0, 0.1, 0.18, 0.32, 0.56 and 1.0 mg/L under static conditions for 96 hours. Acetone was used as the solvent and solvent control. All concentrations were observed once every 24 hours for mortality and abnormal effects.

**96-h LC<sub>50</sub> = 0.27 mg/L**

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to tetramethyl thiuram disulfide at nominal concentrations of 0, 0.056, 0.1, 0.18, 0.32 and 0.56 mg/L under static conditions for 96 hours. Acetone was used as the solvent and solvent control. All concentrations were observed once every 24 hours for mortality and abnormal effects.

**96-h LC<sub>50</sub> = 0.13 mg/L**

(3) Rainbow trout (*Salmo gairdneri*) were exposed to tetramethyl thiuram disulfide at nominal concentrations of 0, 0.032, 0.056, 0.10, 0.18 and 0.32 mg/L under static conditions for 96 hours. Acetone was used as the solvent and solvent control. All concentrations were observed once every 24 hours for mortality and abnormal effects.

**96-h LC<sub>50</sub> = 0.13 mg/L**

### *Acute Toxicity to Aquatic Invertebrates*

#### *Tetramethyl thiuram monosulfide (CASRN 97-74-5)*

*Daphnia magna* were exposed to tetramethyl thiuram monosulfide at nominal concentrations (not stated) under static, closed system conditions for 48 hours. Acetone was used as the solvent for the test solutions, and the experiment included both a control and a solvent control. *Daphnia* in all concentrations were observed once every 24 hours for mortality and abnormal effects. All concentrations of the test substance demonstrated abnormal effects.

**48-h EC<sub>50</sub> = 1.6 mg/L**

#### *Tetraethyl thiuram disulfide (CASRN 97-77-8)*

*Daphnia magna* were exposed to tetraethyl thiuram disulfide at nominal concentrations of 0, 0.032, 0.056, 0.1, 0.18, 0.32 and 0.56 mg/L under static conditions for 48 hours. Acetone was used as the solvent and solvent control.

**48-h EC<sub>50</sub> = 0.24 mg/L**

#### *Tetramethyl thiuram disulfide (CASRN 137-26-8)*

(1) *Daphnia magna* were exposed to tetramethyl thiuram disulfide at nominal concentrations of 0, 0.032, 0.056, 0.1, 0.18, 0.32 and 0.56 mg/L under static conditions for 48 hours. Acetone was used as the solvent and the solvent control.

**48-h EC<sub>50</sub> = 0.24 mg/L**

(2) *Daphnia magna* were exposed to tetramethyl thiuram disulfide at nominal concentrations (not stated) under static conditions for 48 hours.

**48-h EC<sub>50</sub> = 0.21 mg/L**

### *Toxicity to Aquatic Plants*

#### *Tetramethyl thiuram monosulfide (CASRN 97-74-5)*

Green algae (*Chlorella pyrenoidosa*) were exposed to tetramethyl thiuram monosulfide at nominal concentrations (not stated) in a closed system for 96 hours.

**96-h EC<sub>50</sub> = 1.0 mg/L**

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

(1) Green algae (*Chlorella pyrenoidosa*) were exposed to tetramethyl thiuram disulfide at nominal concentrations (not stated) for 96 hours in a growth rate endpoint study. No details of the test conditions were provided.

**96-h EC<sub>50</sub> = 1.0 mg/L**

(2) Green algae (*Scenedesmus acutus*) were exposed to tetramethyl thiuram disulfide at nominal concentrations (not stated) under static conditions for 72 hours. Ethyl alcohol was used as co-solvent. At 72 hours, tetramethyl thiuram disulfide was lethal to algae at 10 mg/L. After 5 days, there was a decrease of 57.2% in growth at 0.5 mg/L tetramethyl thiuram disulfide. EPA calculated the 72-hour EC<sub>50</sub> value from the available data.

**120-h EC<sub>50</sub> = 0.5 mg/L**

**72-h EC<sub>50</sub> = 1.3 mg/L**

(3) Green algae (*Pseudokirchneriella subcapitata*) were exposed to tetramethyl thiuram disulfide at measured concentrations for 120 hours using EPA/FIFRA u 122-2/123-2 method.

**120-h EC<sub>50</sub> = 0.076 mg/L**

***Chronic Toxicity to Aquatic Invertebrates***

***Tetramethyl thiuram disulfide (CASRN 137-26-8)***

*Daphnia magna* were exposed to tetramethyl thiuram disulfide at nominal concentrations (not stated) for 21 days in a not assignable study (reliability rating of 4).

**21-day EC<sub>50</sub> = 0.008 mg/L**

**Conclusion:** For the acute hazard of thiuram category chemicals, based on CASRN 137-26-8, the measured 96-hour LC<sub>50</sub> values to fish range from 0.13 to 0.27 mg/L, the measured 48-hour EC<sub>50</sub> values to aquatic invertebrates range from 0.21 to 0.24 mg/L, and the measured 96-hour EC<sub>50</sub> to aquatic plants is 1.0 mg/L.

<b>Table 5. Summary of Environmental Effects – Aquatic Toxicity Data</b>			
<b>Endpoints</b>	<b>Tetramethyl thiuram monosulfide (TMTM) (CASRN 97-74-5)</b>	<b>Tetraethyl thiuram disulfide (TETD) (CASRN 97-77-8)</b>	<b>Tetramethyl thiuram disulfide (TMTD) (CASRN 137-26-8)</b>
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	<b>2.3–2.6 (m)</b>	<b>0.067 – 0.32 (m)</b>	<b>0.13 – 0.27 (m)</b>
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	<b>1.6 (m)</b>	<b>0.24 (m)</b>	<b>0.21 – 0.24 (m)</b>
<b>Aquatic Plants 96-h EC<sub>50</sub> (mg/L) (growth and biomass)</b>	<b>Biomass = 1.0 (m)</b>	No data RA 1.0	<b>Growth = 1.0 (m) Growth (120-h) = 0.076– 0.5 (m) Growth (72-h) = 1.3 (m)</b>
<b>Chronic Toxicity to Aquatic Invertebrates 21-day EC<sub>50</sub> (mg/L)</b>	No data RA 0.008	No data RA 0.008	<b>0.008 (m)</b>

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e., derived from modeling); (RA) = Read across

