AR201-13348A

Thiuram Category Justification and Testing Rationale

CAS Registry Numbers **97-77-8 and 137-26-8**

Rubber and Plastic Additives Panel
American Chemistry Council
December 2001

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council includes the following member companies: Bayer Corporation, Ciba Specialty Chemicals Corporation, Crompton Corporation, Flexsys America L.P., The Goodyear Tire & Rubber Company, The Lubrizol Corporation, Noveon, R.T. Vanderbilt Company, Inc., and UOP, LLC.

Summary

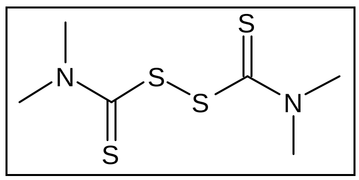
The member companies of the American Chemistry Council's Rubber and Plastic Additives Panel (RAPA) hereby submit for review and public comment their test plan for the thiurams under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program.

The thiurams are used as primary accelerators in natural and synthetic rubbers. Their use in rubber products requires negligible water solubility, high organic/oil solubility, relatively low melting point and low vapor pressure. Existing data for members of this category indicate that they are of low concern for mammalian toxicity but toxic to aquatic organisms. The thiurams are biodegradable, so there is little concern for ecological persistence or bioaccumulation. They are of moderate concern for skin irritation and allergic skin reaction. We conclude that there are sufficient data on the members of this category to meet the requirements of the EPA High Production Volume Chemical Testing Program and no additional testing is recommended.

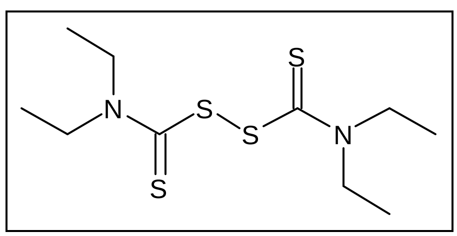
Thiuram category

As defined by EPA under the HPV Program, a chemical category is "a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducing additional testing.

Based on EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program,"[1] in which use of chemical categories is encouraged, the following chemicals constitute a chemical category:



tetramethyl thiuram disulfide
thiram
thioperoxydicarbonic diamide, tetramethyl-
137-26-8



tetraethyl thiuram disulfide
thioperoxydicarbonic diamide, tetraethyl-
97-77-8

Figure 1. Chemical structures

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[1] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm

Structural Similarity. The materials in this category share the basic thiuram 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 to form the thiuram disulfide.

Activity Similarity: The thiurams are fast-curing primary accelerators for natural and synthetic rubbers, speeding the formation of the sulfur crosslinks and donating sulfur to the rubber to form those cross-links. They are also secondary accelerators for thiazole and sulfenamide accelerators.

Both of these thiurams are used in agriculture as fungicides. Tetraethyl thiuram disulfide is also a prescription drug used in the treatment of alcoholism; its brand name is Antabuse (generic name disulfiram).

Common Precursors: The thiurams are manufactured from a secondary amine (dimethylamine or diethylamine) and carbon disulfide to form a dithiocarbamate; two of these dithiocarbamate molecules are attached to each other using an oxidizer such as hydrogen peroxide.

Common Breakdown Products: Both tetramethyl and tetraethyl thiuram disulfide degrade to their respective dithiocarbamates when exposed to heat or alkaline conditions.

Table 1. Physico-chemical Properties

Chemical **CAS#**	**tetramethyl thiuram disulfide** **137-26-8**	**tetraethyl thiuram disulfide** **97-77-8**
molecular weight	240.4	296.66
Melting Point	145 - 155° C (decomposes)	64° C
Boiling Point	129°C @ 20 mm Hg (decomposes)	117° C @ 17 mm Hg
Relative Density	1.3 – 1.4 g/cm3 @25℃	1.3 g/cm3
Vapour Pressure	2.3x10(-5)hPa @25℃	no data
Partition Coefficient (log Pow)	1.73	3.88
Water Solubility	30 mg/l @ 20℃	4.1 mg/l @ 25℃

Similarity of Physicochemical Properties. The similarity of the physicochemical properties of these materials parallels their structural similarity. Both are room-temperature solids with low vapor pressures, negligible water solubility, Log P values below 5, and subject to rapid hydrolysis.

Fate and Transport Characteristics. The thiurams decompose in water, especially under alkaline conditions. The presence or absence of light does not significantly alter the degradation rate, so additional photodegradation data collection studies are not proposed. These materials have been shown not to partition to water or air if released into the environment due to their low water solubility and low vapor pressure. Calculated Bioconcentration Factors and Log P values indicate that these materials are not Persistent Organic Pollutants (POPS). Additional computer-modeled environmental partitioning data is not proposed for the members of this category.

Toxicological Similarity*.* Existing published and unpublished test data for the thiurams demonstrate the similarity of the two compounds.

> **Aquatic Toxicology***.* The thiurams are toxic to algae, water fleas and fish. The 96-hour EC_{50} for algal growth inhibition is approximately 1 mg/l (1 ppm). The 48-hr EC_{50} for *Daphnia* is less than 0.3 ppm; the 96-hr LC_{50} for fish (bluegill) is approximately 0.1 ppm. Since acceptable data are available on both compounds, no additional ecotoxicity testing is proposed.
>
> **Acute Toxicity:** Acute oral and dermal toxicity data are available for both compounds. The acute oral LD_{50} for TMTD is 1080 mg/kg; for TETD, approximately 1300 mg/kg. The acute dermal LD_{50} for TMTD is >2000 mg/kg; for TETD, 2050 mg/kg. The acute inhalation LC_{50} for TMTD is 4.4 mg/l. Acceptable data on two routes of exposure are available for both compounds. Given their structural and biological similarity we believe that the inhalation toxicity of TETD would closely resemble that of TMTD. Since acceptable data are available on both compounds, no additional acute toxicity testing is proposed for these materials.
>
> **Mutagenicity:** Bacterial reverse mutation assays, *in vitro* and *in vivo* chromosome aberration studies, and other *in vitro* and *in vivo* genetic toxicity studies have been conducted on both TMTD and TETD. Positive and negative results have been observed in essentially all *in vitro* studies conducted on both compounds; further studies will not resolve this issue. The results of in vivo mutagenicity studies are uniformly negative. We conclude that the thiurams are weakly mutagenic when tested using *in vitro* methods and non-mutagenic using *in vivo* methods. Since acceptable data are available on both compounds, no additional mutagenicity testing is proposed for these materials.
>
> **Repeated Dose Toxicity:** Several 90-day subchronic toxicity studies and a 2-year carcinogenicity study have been conducted on TMTD. A 90-day study and a 2-year carcinogenicity study have been conducted on TETD. These data are acceptable to characterize the subchronic and chronic toxicity of these compounds. In addition, TETD has been used as a human drug for several decades with few adverse effects reported. Since acceptable data are available on both compounds, no additional subchronic or chronic toxicity testing is proposed for these materials.

Reproductive and Developmental Toxicity: Developmental toxicity data are available for both materials; reproductive toxicity data are available for TMTD. The results of these studies show that neither compound is a selective or specific developmental or reproductive toxin. Since acceptable developmental toxicity data are available on both compounds and acceptable reproductive toxicity data are available on TMTD, no additional reproductive or developmental testing is proposed for these materials.

Conclusion: The physical, chemical and toxicological properties of the thiurams are similar and follow a regular pattern. Therefore, the EPA's definition of a chemical category has been met.

Test Plan: TMTD and TETD meet the EPA definition of a chemical category. Acceptable data on at least one member of the chemical category exist for acute toxicity, repeated dose toxicity, ecotoxicity, mutagenicity, reproductive toxicity and developmental toxicity. In the case of TETD, human data are also available due to its use as a prescription drug. A thorough and defensible hazard analysis and risk assessment can be made with the data available; additional animal studies would not significantly change what is already known about these two products.

We conclude that there are sufficient data on this category to meet the requirements of the EPA High Production Volume Challenge Program, and recommend no additional testing.

Table 2. Test Plan for the Thiuram Category

Test	tetramethyl thiuram disulfide **137-26-8**	tetraethyl thiuram disulfide **97-77-8**
Hydrolysis	A	C
Biodegradability	A	C
Photodegradation	A	C
Acute Fish Toxicity	A	A
Acute Invertebrate Toxicity	A	A
Alga Toxicity	A	A
Acute Toxicity	A	A
Mutagenicity – gene mutation	A	A
Mutagenicity – chromosome aberration	A	A
Repeated Dose	A	A
Reproductive Toxicity	A	C
Developmental Toxicity	A	A

Key for symbols in table:

A = Adequate data available

C = Use of Category Approach

Background Information: Manufacturing and Commercial Applications

Manufacturing

The thiuram rubber accelerators have been manufactured world wide for over 60 years. They are manufactured by batch rather than continuous process. Thiurams are manufactured by combining a secondary amine with carbon disulfide in alkaline aqueous solution, forming a dithiocarbamate salt. The salt is then oxidized, usually with hydrogen peroxide; two molecules of dithiocarbamate joining to form one molecule of thiuram.

Commercial Applications

The largest commercial use of the thiurams is as general purpose cure rate accelerators for natural and synthetic rubber vulcanization. Thiram accelerators are typically used at 0.5 to 2 parts accelerator per every 100 parts of rubber (phr).

Shipping/Distribution

Thiuram-based compounds are shipped extensively throughout the world from manufacturing plants located in North America, South America, Europe, and Asia.

Worker/Consumer Exposure

The vast majority of thiurams is used by the rubber industry, and most thiurams are sold to large industrial users as ingredients for their rubber compounding processes.

The rubber and plastics additives industry has a long safety record and only sophisticated industrial users handle these materials. These materials are available as pellets or powders; they are frequently treated with other materials to minimize dust generation. Most large industrial users also have mechanized materials handling systems, so exposure is minimal. The greatest potential for skin and inhalation exposure is at the packing station at the manufacturing site and, to a somewhat lesser degree during weighing activities at the customer site. Nuisance dust is the primary source of worker exposure.

Consumer exposure is minimal. Small amounts are used in rubber processing, and the materials themselves decompose or become bound in the rubber matrix during vulcanization. The most likely route of consumer exposure is skin contact from rubber or latex articles. Skin irritation, or possibly an allergic skin reaction may occur, but only in sensitive individuals subjected to prolonged and repeated exposure, especially under moist conditions.

TETD and TMTD are Regulated for Use in food-contact applications by the Food and Drug Administration:

> 21 CFR 177.2600 (Rubber Articles intended for Repeated Use): As accelerator, not to exceed 1.5% by weight of rubber product
>
> 21 CFR 175.105 (Adhesives): no limitations

TMTD (thiram) is an EPA-approved fungicide (40 CFR 180.132):

> Sec. 180.132 Thiram; tolerances for residues.
>
> Tolerances for residues of the fungicide thiram (tetramethyl thiuram disulfide) in or on raw agricultural commodities are established as follows:
> 7 parts per million in or on apples, celery, peaches, strawberries, tomatoes.
> 7 parts per million in or on bananas, (from preharvest and postharvest application) of which not more than 1 part per million shall be in the pulp after peel is removed and discarded.
> 0.5 part per million in or on onions (dry bulb).

TMTD is a restricted-use pesticide; it can be purchased and applied only by licensed professionals. It is not sold to the general public.