Test Plan

1H-Isoindole-1,3-(2H)-dione, 2-(cyclohexylthio)-

CAS Registry Number 17796-82-6

Rubber and Plastic Additives Panel
American Chemistry Council
December 2003

List of Member Companies in the Rubber and Plastic Additives Panel

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

Executive Summary

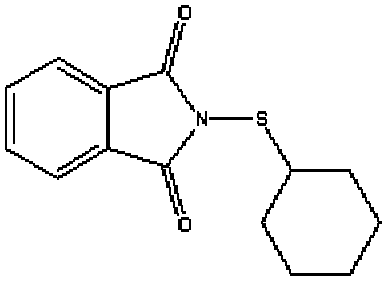
The member companies of the American Chemistry Council's Rubber and Plastic Additives (RAPA) Panel hereby submit for review and public comment their test plan for 1H-Isoindole-1,3-(2H)-dione, 2-(cyclohexylthio)-, [CAS no. 17796-82-6, commonly abbreviated as CTP for N-(cyclohexylthio)phthalimide] under the HPV Chemical Challenge Program.

CTP is used as a pre-vulcanization inhibitor for synthetic and natural rubber. There are no other known commercial uses. Exposure to production workers is considered minimal. CTP is an idustrial chemical, with no known sales to consumers, thus exposure to children and the general public is essentially nil.

Existing data for this compound indicate that it is of low concern for mammalian toxicity but toxic to fish and moderately toxic to other aquatic organisms. CTP is incorporated into polymers, and is thus low concern for environmental release, environmental persistence and bioaccumulation. Extensive mutagenicity and repeat dose testing, as well as a tumor initiation-promotion study, indicate CTP does not present a chronic health hazard to humans. CTP is of moderate concern for skin irritation and allergic skin reaction.

The RAPA Panel concludes that there are sufficient data on CTP to meet the requirements of the HPV Chemical Challenge Program and no additional testing is recommended.

Chemical Structure:



Aquatic Toxicology: CTP is highly toxic to fish and moderately toxic to algae, midge and *Daphnia magna.* The 96-hr LC_{50} for rainbow trout is 0.40 mg/l and 1.20 mg/l for bluegill sunfish. A chronic 14-day study using fathead minnows produced an LC_{50} value of 0.39 mg/l. The 48-hr EC_{50} for *Daphnia magna* is 32.0 mg/l and 130 mg/l for midge. The 96-hr EC50 for the green algae *Selenastrum capricornutum* is 21.0 mg/l. The octanol/water partition coefficient is 3.76, and the bioconcentration factor is 130.

CTP is readily biodegradable. Testing in activated sludge showed 99+% biodegradation after 190 hours. Degradation via hydrolysis is 99.7% after seven days at pH 7.0 and 25C; the primary breakdown product is the carboxylic acid (ring-opened half-acid) derivative N-(Cyclohexylthio)phthalamide. Laboratory results have been confirmed by field tests on manufacturing plant effluent.

Acceptable data are available on toxicity to algae, toxicity to aquatic invertebrates, toxicity to fish and biodegradability. The data warrant handling the product as an environmentally hazardous, but not persistent, substance; no additional ecotoxicity testing is proposed.

Acute Toxicity: The acute oral and dermal LD_{50}s for CTP are >2600 mg/kg and >5010 mg/kg, respectively. There is chronic but not acute data on the inhalation LC_{50}. Since acceptable acute data are available on two routes of exposure, no additional acute toxicity testing is proposed.

Primary Irritation: CTP was slightly irritating (score 5.5/110.0) to the eyes of white rabbits, and practically non-irritating (score 0.0/8.0) to the shaved skin of white rabbits in two Draize studies.

Immunotoxicity: CTP was evaluated in a repeat insult patch test using 55 human volunteers. Under the conditions of this test, CTP was considered to be a primary and cumulative skin irritant, as well as a sensitizing agent. In another repeat insult patch test on human volunteers, CTP (2%), as a component of compounded rubber stock, produced only mild cumulative irritation and no sensitization in 53 test subjects.

Mutagenicity: Five *in vitro* and two *in vivo* genetic toxicity studies have been conducted on CTP and results were uniformly negative.

In an Ames assay, CTP was not mutagenic in all five tested strains of Salmonella, both with and without metabolic activation. A mitotic recombination assay using the yeast *Saccharomyces cerevisiae*, strain D4, was also negative. CTP did not induce unscheduled DNA synthesis in an *in vitro* rat liver hepatocyte assay. Negative results were obtained in the L5178Y mouse lymphoma and the CHO/HGPRT forward mutation assays.

CTP did not produce chromosomal aberrations in the *in vivo* mammalian bone marrow chromosome aberration assay, nor did it produce unscheduled DNA synthesis or S-phase DNA replication in hepatocytes taken from rats dosed at up to 1000 mg/kg in the *in vivo* UDS assay.

Repeated Dose Toxicity: No adverse effects were observed in a four-week subchronic dust inhalation study with rats exposed to CTP at concentrations up to 536 mg/m3 for six hours per day and five days per week.

In a 90-day inhalation study, male and female rats were exposed to CTP dust for six hours per day at levels of 0, 15, 50 or 150 mg/m3. High-dose animals of both sexes and mid-dose females had decreased body weights. Elevations in kidney weights were noted in high-dose males. Males also showed dose-related increases in the incidence of kidney lesions which were characterized by eosinophilic droplets in the proximal tubule, degeneration and regeneration of tubular epithelium, and granular casts occluding and causing dilation of renal tubules. Scattered granulomas of the lung were noted in both controls and treated animals; these were seen most frequently in high-dose males. The no-effect level was considered to be 15 mg/m3 for females. A no-effect level for males could not be established.

In a four-week dietary study using rats dosed at 0, 50, 150, 300, 600 or 1500 ppm, body weights, clinical signs of toxicity, food consumption and gross necropsy observations were recorded. With the exception of reduced body weights at the two highest dose levels, no treatment-related effects were observed.

In another dietary study, CTP was fed to male rats for 23 months and to female rats for 24 months. Doses were 0, 50, 150 or 500 mg/kg/day. Treated males exhibited decreased body weights in comparison to controls. High-dose females and, to a lesser extent, mid-dose females had elevations in gamma glutamyl transpeptidase, a serum enzyme which could be indicative of liver damage. High-dose males and females showed lowered hematocrit and hemoglobin values. Decreased red blood cell counts were also seen in this group of males. Increases in absolute liver weight were observed in all treatment groups; males also showed elevated levels of protein in the urine. Fatty infiltration of the liver and bile duct hyperplasia were noted in high-dose males and females as well as in mid-dose females. Males at all dose levels exhibited significant elevations in kidney weight/body weight ratios. High-dose females had significant increases in relative kidney weights. Absolute kidney weights were elevated in 150 and 500 mg/kg/day males. Microscopic examination of the kidneys revealed

glomerulonephritis. Although this lesion was present in all groups, the incidence was greatest in mid- and high-dose males and in high-dose females. The most notable finding in this study was a dose-related increase in benign liver adenomas in mid- and high-dose female rats. These lesions were accompanied by fatty infiltration, bile duct proliferation, necrosis, and increased liver weights. Due to the lack of progression from benign to malignant lesions, the lack of proliferative lesions in males or at other sites, and the uniformly negative genetic *in vitro and in vivo* toxicology findings, and the results of a tumor initiation-promotion study (see below), the benign liver tumors were not considered to pose a significant human health risk. Furthermore, information collected by manufacturers indicates no evidence of liver tumors has been seen in workers engaged for 25+ years in the manufacture of CTP.

These data are acceptable to characterize the subchronic and chronic toxicity of CTP in the Program and no additional subchronic or chronic toxicity testing is proposed for this compound.

Reproductive and Developmental Toxicity: CTP was not considered teratogenic when evaluated in a teratology study using pregnant rabbits dosed with 0, 10, 30 or 100 mg/kg/day on days 7-19 of gestation. No maternally toxic, embryotoxic, fetotoxic or teratogenic effects were observed on low- and mid-dose animals. Maternal weight loss, decreased fetal weight, and delayed fetal development, as evidenced by certain ossification variations, were observed in the high-dose animals.

CTP was evaluated in a one-generation reproduction study on rats (F0 generation) given 0, 50, 150 or 500 ppm of the test compound in their diet from gestation onward through lactation. F1 offspring were separated from siblings seven days after weaning and randomly selected to continue as future parents. F1 rats were raised to maturity and mated to produce the F2a and F2b litters. No treatment-related effects were observed in the F0 parents at any dose level. Mean body weights were lower in the first generation high-dose animals. High-dose females also exhibited a lower body weight gain during gestation. A lower mean number of live pups and an increase in the mean number of dead pups at birth were observed for the F2a litters at 500 ppm. Pup body weights, sex ratio and necropsy findings were comparable between the control and treated groups. No consistent reproductive effects were noted in this study.

Tumor Initiation-Promotion Study: CTP exhibited tumor promotional activity in female rat livers when administered at a dose of 10,000 ppm in the diet for 9 months. This effect was demonstrated by the observation of an increase in the number and the size of focal nodules as compared to controls. No tumor initiating activity was noted in this study.

Conclusion: The physical, chemical, environmental and toxicological properties of 1H-Isoindole-1,3-(2H)-dione, 2-(cyclohexylthio)-, or CTP, have been considerably studied and documented. A detailed hazard and risk analysis can be made with the data available; additional studies would not significantly change what is already known about this product. Therefore, the RAPA Panel concludes that there are sufficient data on this compound to meet the requirements of the HPV Chemcial Challenge Program and recommend no additional testing.

Background Information: Manufacturing and Commercial Applications

Manufacturing

CTP was discovered in the 1960s and commercialized in the 1970s. As a prevulcanization inhibitor, CTP achieves its purpose with increased efficiency and reduced human health hazards. The manufacturing process is rather complex and involves five distinct chemical reactions which all take place in a high-boiling hydrocarbon solvent. Butanol and potassium hydroxide are reacted to form potassium butoxide. Phthalic anhydride and ammonia are reacted to form phthalimide. Potassium butoxide and phthalimide are reacted to form potassium phthalimide. Cyclohexyl mercaptan and chlorine are reacted to form cyclohexylsulfenyl chloride, which is reacted with the potassium phthalimide to form the product, CTP. The complexity of the chemistry and the cost of the equipment required tend to limit the number and type of manufacturers to those with rather sophisticated operations.

Commercial Applications

CTP is used as a pre-vulcanization inhibitor for synthetic and natural rubber. There are no other known commercial uses. It is generally used in conjunction with sulfenamide and thiazole accelerators to control processing safety with little or no resultant changes in cure characteristics or physical properties. Use of CTP gives significant improvements in green rubber stock storage stability to minimize waste. CTP usage to control scorch safety enables rubber processing equipment (calendars and extruders) to be operated at higher temperatures and through-put to increase productivity. CTP is used in the manufacture of large rubber articles such as tires, tubes, hoses, belts and other mechanical rubber products. The typical range of usage in compounded rubber is 0.1 to 0.4 parts of CTP per hundred parts of rubber (phr). It is NOT necessary, and therefore not used, in thin rubber or latex applications such as gloves, baby bottle nipples or pacifiers.

Worker/Consumer Exposure

CTP is used for the manufacturer of industrial rubber products; sophisticated industrial users handle this material. Most large industrial users have mechanized materials handling systems, so exposure is minimal. The greatest potential for skin and inhalation exposure is at the bagging/packing station at the manufacturing site and, to a lesser degree, during mixing and weighing activities at the customer site. Manufacturers of CTP sell this compound in product forms designed to minimize worker exposure to dust. These product forms include oil-treated dedusted powders, pellets formed by compression, wax pellets, CTP/clay pellets, and polymer-bound masterbatches.

Consumer exposure to CTP is essentially nil. During the rubber vulcanization process, the cyclohexylthio portion of the CTP molecule becomes polymer bound, releasing free phthalimide. In cases where an excess of CTP has been used in the rubber compounding process (loadings greater than 0.6 phr), free phthalimide can migrate (bloom) onto the surface of the rubber article. CTP is not used in rubber gloves, food containers or other food-contact applications, children's toys, pacifiers, baby bottle nipples, elastic, adhesives or medical device applications.

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Physical-Chemical				
Melting Point	**Boiling Point**	**Vapor Pressure**	**Partition Coefficient**	**Water Solubility**
A	A	A	A	A

Environmental Fate			
Photodegradation	**Stability in Water**	**Transport/ Distribution**	**Biodegradation**
Calc	A	Calc	A

Ecotoxicity		
Acute Toxicity to Fish	**Acute Toxicity to Aquatic Plants (e.g., Algae)**	**Acute Toxicity to Aquatic Invertebrates (e.g., Daphnia)**
A	A	A

Mammalian Toxicity					
Acute Toxicity	**Bacterial Genetic Toxicity *In Vitro***	**Mammalian Genetic Toxicity *In Vivo***	**Repeat Dose Toxicity**	**Reproductive Toxicity**	**Developmental Toxicity**
A	A	A	A	A	A

Legend	
Symbol	**Description**
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
SAR	Structure-Activity Relationship