Revised Test Plan for

IRGANOX 259

1,6-Hexamethylene bis (3,5-di-(tert)-butyl-4-hydroxyhydrocinnamate)

CAS No. 35074-77-2

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EXECUTIVE SUMMARY

A. Introduction

An important objective of EPA's High Production Volume (HPV) chemical challenge program is the gathering and public release of basic hazard information on those chemicals manufactured at high volumes in the United States. Ciba Specialty Chemicals has agreed to participate in this program and hereby submit for review and public comment our available data and test plan for Irganox 259.

B. General Substance Information

Chemical Name:1,6-Hexamethylene bis (3,5-di-(tert)-butyl-4-hydroxyhydrocinnamate)

Appearance: White to off-white crystalline powder.

Typical Commercial Purity: >98%

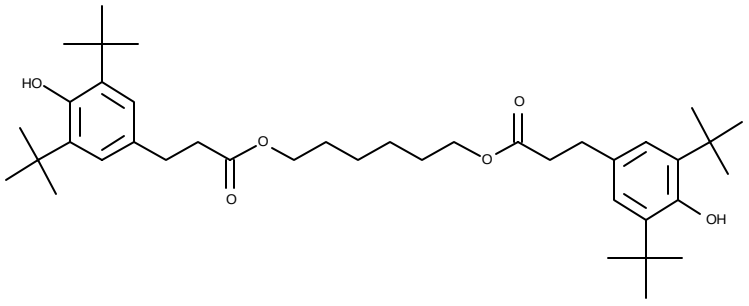
Chemical abstract Service Registry Number: CAS # 35074-77-2

Common Name / Trade Name: Irganox 259

Chemical Formula: C40H62O6

Molecular weight: 639.0

Structure:



C. General Use Information

1,6-Hexamethylene bis (3,5-di-(tert)-butyl-4-hydroxyhydrocinnamate), commercially known as Irganox 259, is a sterically hindered phenolic antioxidant. Irganox 259 is a stabilizer for organic substrates such as plastics, synthetic fibers, and elastomers.

This product has been cleared by the FDA for use in polymers, resins or adhesives intended for food contact applications [21 CFR (Code of Federal Regulations) § 178.2010]. Irganox 259 also has FDA clearance for lubricants with incidental food contact.

Sales of Irganox 259 are to industrial users only. The polymer industry has a record of safe use of additives such as Irganox 259 and worker exposures are considered minimal. Industrial Hygiene programs and Responsible Care® practices are the norm throughout the industry and it is the experience of Ciba Specialty Chemicals that its customers handle such products in a careful and conscientious manner. Ciba distributes Material Safety Data Sheets (MSDS) that present detailed hazard data and provide directions for safe handling. Ciba has established an Internal Exposure Limit for airborne exposure for Irganox 259 of 10 mg/m^3 for particulate matter; this information is also communicated on the MSDS. After Irganox 259 is incorporated in the polymer matrix it is relatively immobile and release-exposure to humans or the environment is considered minimal.

Environmental Endpoints

Existing ecotoxicology data for this chemical indicate that there is low concern for acute toxicity to fish, aquatic plants and aquatic invertebrates. The solubility of the compound is very low and residues that enter aquatic systems will likely become bound to sediment. The material is not readily biodegradable, however, environmental exposures are expected to be negligible.

A hydrolysis study has not been conducted. The very low water solubility of the compound makes such testing impractical or impossible. The low water solubility of the material also makes it unlikely that hydrolysis would be a significant route of environmental degradation (fugacity modeling indicates 99% of material will be in soil and sediment and 1% in water). The EPIWIN Hydrowin program using surrogate fragments also estimated slow hydrolysis (59 days at pH 7, 1.6 years at pH 8). Steric hindrance is another factor to be considered. The bulky tertiary groups attached to the phenyl group renders it sterically hindered for further reaction. It is concluded that, with low solubility, slow hydrolysis rate and steric hindrance, the compound will be relatively stable in water. No testing is proposed for this endpoint.

Toxicology Endpoints

Available mammalian acute toxicity data indicates very low toxicity by oral, dermal or inhalation exposure.

The requirement for reproductive and developmental toxicity data is fulfilled by consideration of the available developmental study and the analysis of male and female reproductive organs in several repeat-dose toxicity studies. This information demon-strates that Irganox 259 is not teratogenic and does not impact reproductive organs, even at high exposure levels.

Irganox 259 was not mutagenic in an Ames assay and not clastogenic in an *in vivo* rodent dominant lethal test. In the review of the original submission, the agency has indicated a need for additional genotoxicity testing. Ciba believes the available genetic toxicity tests, supplemented with the toxicity findings on other structurally-related phenolic antioxidants,[1] and when considered within the context of the testing presented here where mutagenic and clastogenic effects *would be manifest* (i.e., the available chronic and developmental tests), provide adequate evidence that the substance is not mutagenic. Testing requirements for these endpoints are considered fulfilled.

Several subchronic tests are available covering rodents and dogs that show the compound, though generally well tolerated, has effects on liver and thyroid at high doses; a 2-year chronic study in rats indicates the material is not carcinogenic. All toxicology endpoints are considered fulfilled.

Conclusions

The available data are sufficient to meet the requirements of the HPV challenge program and no additional testing is proposed.

[1] Irganox 259 is structurally related to several hindered phenol antioxidants also involved in the HPV program, notably CAS 2082-79-3 and CAS 6683-19-8, which are also sponsored by Ciba Specialty Chemicals Corporation. For additional supporting data relating to hindered phenol antioxidants, information presented for the HPV Hindered Phenol Category, sponsored by the American Chemistry Council, should also be reviewed. These data support a low concern for mutagenic or clastogenic effects, reproductive, developmental or chronic toxicity and a low potential for adverse environmental effects.

SUMMARY TABLE

CAS No. 35074-77-2			
PHYSICAL/CHEMICAL ELEMENTS	**DATE**	**RESULTS**	**FULFILLS REQUIREMENT**
Melting Point	1989	104-108 ^{o}C	Yes
Boiling Point	2001	654.41 ^{o}C	Yes
Vapor Pressure	2001	1.75 x 10^{-17} mm Hg	Yes
Partition Coefficient	2001	Log Kow > 11.74 (estimated)	Yes
Water Solubility	2001	3.3 x 10^{-7} mg/ L (estimated)	Yes
ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS			
Photodegradation	2001	For reaction with hydroxyl radicals, predicted rate constant = 47.0 x 10^{-12} cm^3/molecule-sec predicted half-life = 2.73 h	Yes
Stability in Water	2001	Low solubility makes testing of stability in water impractical. EPIWIN model estimated slow hydrolysis based on surrogate fragments.	Waiver
Fugacity	2001	Predicted distribution using Level III fugacity model Air 0.0118 % Water 1.1 % Soil 41 % Sediment 57.9 % Persistence = 677 h	Yes
Biodegradation	1989	Not biodegradable 10 mg/L: 1% in 28 days 20 mg/L: 1% in 28 days	Yes
ECOTOXICITY ELEMENTS			
Acute Toxicity to Fish	1988	LC_{50} (96 h) > 100 mg/L	Yes
Toxicity to Aquatic Plants	1992	EC_{50} (0-72 h) > 100 mg/L	Yes
Acute Toxicity to Aquatic Invertebrates	1988	EC_{50} (24 h) > 100 mg/L	Yes

SUMMARY TABLE (CONTINUED)

CAS No. 35074-77-2 HEALTH ELEMENTS	DATE	RESULTS	FULFILLS REQUIREMENT
Acute Toxicity	1978	Mice: LD_{50} (Oral) > 7,750 mg/kg	Yes
	1970	Rabbits: LD50 > 10,000 mg/kg	
	1973	Rat: LD_{50} (Inhalation) > 1700 mg/ m^3	
Genetic Toxicity ▪ In Vitro (Ames)	1978	Ames Test – Salmonella typhimurium: No increase in mutations with or without metabolic activation (at doses of 0.2, 2.0, 20, 200 and 2000 ì g/ plate)	Yes
▪ In Vivo (Dominant Lethal Assay)	1978	No dominant lethal effect.	Yes
Repeated Dose Toxicity			
A. Subchronic Toxicity i) 90-Day dietary toxicity study in rats	1971	NOEL < 1000 ppm Thyroid	Yes
ii) 90-Day dietary toxicity study in rats	1970	NOEL < 2000 ppm Thyroid and Liver	
iii) 90-Day dietary toxicity study in rats	1975	NOEL = 400 ppm Thyroid and Liver	
iv) 90-Day dietary toxicity study in dogs	1976	NOEL = 1500 ppm Liver	
B. Chronic dietary toxicity study in rats	1982	NOEL = 150 ppm (food consumption) NOAEL = 450 ppm (Not carcinogenic)	
Reproduction and Developmental Toxicity *A. Developmental Toxicity*	1978	NOEL = 150 mg/kg be No teratogenic effect.	Yes
B. Reproductive Toxicity	1971-1982	No effect on reproductive organs in subchronic and chronic tests.	Yes
