4-METHOXY-N-METHYL-1,8-NAPHTHALIMIDE

CAS NO. 3271-05-4

Prepared by Technical Resources Internation Inc,
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- **BASIS OF NOMINATION TO THE CSWG**

  A class study review of fluorescent brightening agents indicated that 4-methoxy-N-methyl-1,8-naphthalimide has a moderate production level for use in several industry sectors and in a variety of substrates. For example, for whitening synthetic fibers made of acetate, polyamide, polyacrylonitrile, polyolefin, and polyester. This chemical is presented to the CSWG as a candidate for nomination for testing by the National Toxicology Program (NTP) because of:

  -potential for occupational exposures based on a moderate annual production level

  -potential for general population environmental exposures based on industrial wastewater and drinking water pollution

  -lack of genetic and chronic toxicity test data

  -suspicion of carcinogenicity based on naphthalimide-type structure.

- **SELECTION STATUS**

  ACTION BY CSWG: 12/3/96

  Studies requested:

  - Chemical disposition studies

  Priority: Moderate

  Rationale/Remarks:

  - Potential for human exposure

  - Need to determine whether the chemical is absorbed before considering for carcinogenicity

  - Structural interest

- **INPUT FROM GOVERNMENT AGENCIES/INDUSTRY**

  Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided information on the annual production range of 4-methoxy-N-methyl-1,8-naphthalimide.

CHEMICAL IDENTIFICATION

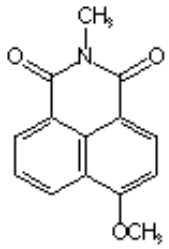
CAS Registry Number: 3271-05-4

Chemical Abstracts Service Name: 1H-Benz[de]isoquinoline-1,3(2H)-dione, 6- methoxy-2-methyl (9CI); 4-methoxy-N-methyl-1,8-naphthalimide (8CI)

Synonyms and Trade Names: Mikawhite AT/ATN; Viophos PA; MMNI; C.I. Fluorescent Brightener 162; C.I. 56190; FB 162

Structural Class: Substituted naphthyl imide

Structure, Molecular Formula and Molecular Weight:



$C_{14}H_{11}NO_3$ Mol. wt.: 241.26

Chemical and Physical Properties:

Description: Yellowish needles (from methanol) (Adam *et al.*, 1993)

Melting Point: 197-201°C (Adam *et al.*, 1993)

Solubility: Insoluble in water; soluble in methanol and ethanol

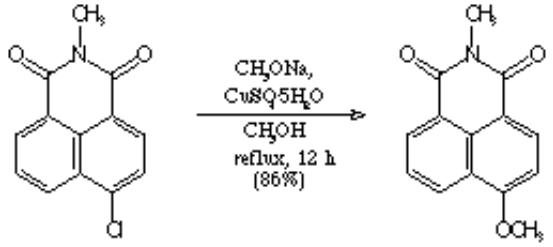
(Chiaki μ Fujimoto, 1965; Adam *et al.*, 1993)

Stability: Stable to chlorite (Anon., 1971)

Technical Products and Impurities: No information was found on commercial products, their purity levels or impurities.

EXPOSURE INFORMATION

- **Production and Producers 4-Methoxy-N-methylnaphthalimide (FB 162) is conveniently prepared by heating 4-chloro- or 4-sulfo-substituted N-methylnaphthalimide with methanol (Naik *μ* Puro, 1995). Thus, Adam and coworkers (1993) obtained the starting material, 4-chloro-N-methyl-1, 8-naphthalimide, from commercially available 4-chloro-1,8-naphthalic anhydride and methoxylated it in the presence of cupric ion as catalyst, producing FB 162 with a yield of 86%. The reaction is shown schematically as follows:**



FB 162 is listed in the EPA's TSCA Inventory (STN International, 1996a). United States production of FB 162 in 1993 was reported to be in the range of 1,000-100,000 pounds based on non-confidential data received by the EPA (Walker, 1995). No other quantitative information on annual production was found in the available literature. FB 162 was not listed in recent issues of chemical industry directories or catalogs. The original development of this and related naphthalimide fluorescent brighteners was carried out in Japan by Kasai and coworkers in the late 1960s and early 1970s (Barton *μ* Davidson, 1974). Chemical manufacturers involved in further development of the naphthalimide brighteners in the early 1970s and to whom patents were assigned for preparation and/or processing included: BASF; Hickson *μ* Welch, Ltd.; Mitsubishi Chemical Industries, Ltd.; Nippon Kayaku Co., Ltd.; Sandoz, Ltd.; Sumitomo Chemical Co., Ltd.; and Ugine Kuhlmann (Barton *μ* Davidson, 1974; Dialog Information Services, 1996; STN International, 1996b). Mitsubishi Chemical Industries, Ltd., and Nippon Kayaku Co., Ltd., were listed as manufacturers of FB 162 in the *Colour Index* (Anon., 1989).

- **<u>Use Pattern</u>: FB 162 is a substituted naphthalimide-type fluorescent whitening agent (also known as a fluorescent or optical brightener). It is most useful in the textile industry for whitening of synthetic fibers, such as acetate, polyamide, polyacrylonitrile, polyolefins and polyester (Zweidler *μ* Hefti, 1978; Otake *et al.*, 1987). According to Naik and Puro (1995), FB 162 gives a chlorite-resistant fluorescent brightening effect in the thermosol dyeing process on cellulose acetate, polyacrylonitrile, polyolefins, polyoxymethylene and polyester fibers. Besides being stable to chlorite, it is useful in the pH range of 3-11, imparting a neutral white effect with excellent fastness to light, washing, perspiration and heat (Anon., 1971). FB 162 has been included by two chemical companies, Hoechst A.-G. and Nippon Kayaku Co. Ltd., as a component in mixtures of substituted naphthalimide brighteners combined for their synergistically improved whitening effect on synthetic fibers (STN International, 1996b). In a recent patent Sony Corp. described the use of FB 162 as a coating component in the dye-receiving layer of thermal transfer recording paper (Ito *et al.*, 1996).**

- **<u>Human Exposure</u>: There is potential for occupational, environmental or consumer exposure to FB 162 by ingestion or dermal contact.**

***Occupational exposure*: No data were found on occupational exposures to FB 162. However, because of its use in various applications in the textile and plastics industries, there is potential for worker exposures.**

***Environmental exposure*: Many people were exposed to FB 162 by consuming polluted drinking water from a river source, according to Otake *et al.*, 1987. The river was contaminated by a textile factory's disposal of wastewater which contained FB 162 at a level of 0.01 ppm in water treated by the activated-sludge method and released from the factory's treatment plant.**

***Consumer exposure*: Suzuki and coworkers (1983) identified FB 162 as a chemical used in the household [details of mode of use not explained]. No information was found on potential dermal exposures to any residual FB 162 resulting from its use in clothing and other human contact materials.**

Environmental Occurrence: FB 162 has not been reported to occur naturally. FB 162 has been identified as a water pollutant with very low biodegradability, according to Otake and coworkers (1987). They reported that large amounts of FB 162 remained in activated sludge-treated wastewater from the textile industry. Miyajima and coworkers (1981) reported the results of biological treatment of wastewater containing FB 162 as follows: ~90% of FB 162 was removed under anaerobic conditions, but none was removed under aerobic conditions. The sludge acclimation period which was required was approximately 5 days.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupation exposure to or workplace maximum allowable levels of FB 162. The American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) for this compound.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to FB 162 and cancer risk in humans were identified in the available literature.

Animal Data: No 2-year carcinogenicity studies of FB 162 in animals were identified in the available literature. Toxicity information identified was limited to acute and subacute/subchronic studies.

Acute: The following acute toxicities of FB 162 in animals have been reported:

oral rat LD_{50}>20,000 mg/kg (Suzuki *et al*., 1983)

ip mouse LD_{50}7,700 mg/kg (Otake *et al*., 1987)

Subacute: The oral toxicity of FB 162 was assessed in male Sprague-Dawley rats (6 per group) following gavage administration of 10 or 100 mg/day for 21 days. Histopathological alterations were consistently noted in the liver and kidneys of high-dose rats. Changes in the liver included lipid accumulation, focal necrosis, vacuolated hepatocytes, and proliferation of smooth endoplasmic reticulum (SER). In the kidneys, vacuolation of the tubular cells and numerous hyalin droplets were noted. Blood analysis revealed a dose-related increase in total serum protein (Otake *et al*., 1987).

Subchronic: In a 90-day study, the liver, kidneys, and pancreas were target sites for the toxicity of FB 162 in Sprague-Dawley rats. Male and female rats (4 per group) were fed 67, 670, 6,700, or 30,000 ppm FB 162 in the diet for 90 days. In the liver, enlargement of hepatocytes, Mallory's bodies, and swelling of the mitochondria with disappearance of matrix were noted in the 30,000 ppm groups. Proliferation of SER in the hepatocytes occurred in rats fed 670, 6,700, and 30,000 ppm FB 162. In the kidneys, numerous hyalin droplets were seen in the tubular cells of both males and females fed 30,000 ppm FB 162. Vacuolated exocrine pancreatic cells were noted in the high-dose female rats. Nonspecific thymic atrophy was noted in animals treated with 6,700 and 30,000 ppm FB 162, and enhancement of immune responses was observed in treated male rats. Elevated levels of total serum proteins and serum cholesterol were seen in rats of the 6,700 and 30,000 ppm dose groups (Otake *et al*., 1987).

Short-Term Tests: FB 162 was not mutagenic when tested with and without S-9 activation at 20-100 µg/plate in DMSO in the *Salmonella typhimurium* assay with strains TA98 or TA100. However, irrespective of S9 metabolic activation or ß-glucuronidase treatment, urine samples obtained from rats treated with 30,000 ppm FB 162 were slightly mutagenic, with a 50% increase in the number of revertant colonies in strain TA100, compared with urine samples from untreated rats. In their discussion, the authors noted that FB 162 is not soluble in DMSO or water which may have contributed to the negative *in vitro* assay results (Otake *et al*., 1987).

At 480 µg/ml in water, FB 162 was not genotoxic when tested with and without S-9 in the *Salmonella typhimurium umu* test with strain TA1535/pSK1002 (Nakamura *et al*., 1993). As noted above, the negative result in the modified *Salmonella*/microsome assay system might have resulted from the lack of water solubility of the test chemical.

Metabolism: Administration of 6,700 ppm FB 162 in the diet of Sprague-Dawley rats for 7 consecutive days resulted in the accumulation of FB 162 in adipose tissue, liver, and large intestine. Small amounts of FB 162 were detected in the small intestine, kidneys, spleen, thymus, and serum. Two major metabolites, the C-

hydroxide and a conjugate, were found in the urine and tissues of FB 162-treated rats. However, the chemical structures of the conjugate and other metabolites were unknown. FB 162 and its metabolites rapidly cleared from the body. Urine was the most important route of metabolic clearance, and metabolites were not detected in the feces (Otake *et al.*, 1987).

Other Biological Effects: FB 162 was one of four representative, commercially available fluorescent brightening agents tested in the yeast, *Saccharomyces cerevisiae* by Sugihara (1989). He reported that FB 162 (10, 20, 40, 80 mg/L) showed no significant effect on growth or activity of enzymes related to the election transport system.

Structure Activity Relationships: Four compounds, structurally similar to FB 162, were screened for relevant information associating these related chemicals with a carcinogenic or mutagenic effect. No information was found on carcinogenicity or mutagenicity for these four structurally related compounds: N-methylnaphthalimide [2382-08-3], 1,8-naphthalimide [81-83-4], 4-methoxynaphthalimide [33429-98-0], and naphthalic anhydride [81-84-5].

However, some naphthalimide derivatives have been reported to have pharmacologic or other biologic activity, such as antitumorigenicity or enzyme effects. In an *in vitro* study of various compounds, including 1,8-naphthalimide, on the activity of poly (ADP-ribose) synthetase purified from bovine thymus, 1,8-naphthalimide was found to be a very strong inhibitor of the enzyme (Banasik *et al.*, 1992). The NCI investigated a large number of benzo(de)isoquinoline-1,3-diones, including N-butyl-1,8-naphthalimide (NSC 27337), for antitumor activity against P388 lymphocytic leukemia and L1210 lymphoid leukemia; N-butyl-1,8-naphthalimide was not selected for preclinical toxicology studies (Paull *et al.*, 1984)

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