7-(2H-NAPHTHO[1,2-d]TRIAZOL-2-YL)-3-PHENYLCOUMARIN
CAS NO. 3333-62-8

BASIS OF NOMINATION TO THE CSWG

A class study review of fluorescent brightening agents indicated that 7-(2H-naphtho[1,2-d]triazol-2-yl)-3-phenylcoumarin has a moderately high 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 moderately high annual production range and estimate of potential worker exposures in the National Occupational Exposure Survey (NOES)
- lack of genetic and chronic toxicity test data
- suspicion of carcinogenicity based on coumarin-type structure.

SELECTION STATUS

ACTION BY CSWG: 12/3/96

Studies requested:

- Chemical disposition studies

Priority: Moderate

Rationale/Remarks:

- Potential for human exposure
- Relatively high production
- Need to determine whether the chemical is absorbed before considering for carcinogenicity
- Structural interest

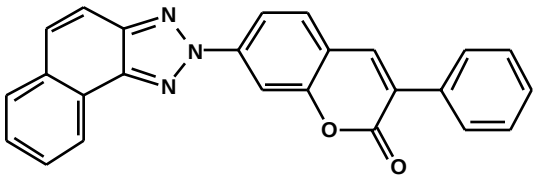
INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided information on the annual production range of 7-(2H-naphtho[1,2-d]triazol-2-yl)-3-phenylcoumarin (FB 236). Dr. Daniel Benz, Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA), provided information on FB 236 from FDA's Priority-Based Assessment of Food Additives (PAFA) database.

CHEMICAL IDENTIFICATION

CAS Registry Number:	3333-62-8
Chemical Abstracts Service Name:	2H-1-Benzopyran-2-one, 7-(2H-naphtho[1,2-d] triazol-2-yl)-3-phenyl-; coumarin, 7-(2H-naphtho[1,2-d]triazol-2-yl)-3-phenyl- (7CI, 8CI)
Synonyms and Trade Names:	Leucophor EGA; Leucopure/Leukopur EGM; Hakkol 8542/CHP-B/PSR; C.I. Fluorescent Brightener 236; C.I. 55135; FB 236
Structural Class:	Triazole substituted coumarin (lactone)

Structure, Molecular Formula and Molecular Weight:



$C_{25}H_{15}N_3O_2$ Mol. wt.: 389.42

Chemical and Physical Properties:

Description:	Green-yellow powder (Clariant Corporation, 1996)
Melting Point:	252%C (STN, 1996a)
Specific Gravity:	1.34 (Clariant Corporation, 1996)
Solubility:	Soluble in hot organic solvents; soluble in dichloromethane; insoluble in water (Anon., 1971;
Ballard &	Betowski, 1986; Clariant Corporation, 1996)
Stability:	Stable to acids and alkalis (Anon. 1971)
Reactivity:	Incompatible with strong oxidizing agents (Clariant Corporation, 1996).

Technical Products and Impurities: Clariant Corporation supplies FB 236 under the trade name, Leucopure EGM powder. The purity is not stated in the Material Safety Data Sheet (MSDS), and no impurities or hazardous components are listed (Clariant Corporation, 1996).

EXPOSURE INFORMATION

Production and Producers: 7-(2H-Naphtho[1,2-d]triazol-2-yl)-3-phenylcoumarin (FB 236) is manufactured by the reaction of diazotized 7-amino-3-phenylcoumarin with 2-aminonaphthalene and subsequent cyclization (Ballard & Betowski, 1986).

FB 236 is listed in the EPA's TSCA Inventory (STN International, 1996b). United States production of FB 236 in 1993 was reported to be in the range of 10 thousand-1 million pounds based on non-confidential data received by the EPA (Walker, 1996). No other quantitative information on annual production was found in the available literature. The development and commercialization of amino coumarin-type brighteners was carried out in the late 1960s and early 1970s by Bayer A.-G., Ciba Geigy A.-G., Hickson & Welch Ltd., Sandoz Ltd., and Showa Chemical Industries Ltd. (Dialog Information Services, 1996; STN International, 1996c). Sandoz Colors & Chemicals of East Hamilton, NJ, was listed in the EPA's TSCA Plant & Production (TSCAPP) database as both a producer and importer of FB 236; but no production or import volume data were included (CIS, 1996). According to the Colour Index, Sandoz Colors and Chemicals, Hanover, NJ, subsidiary of Sandoz, Ltd., Basel, Switzerland, and a consortium of Japanese dye and pigment manufacturers produce or supply FB 236 (Anon., 1989). Sandoz Colors and Chemicals, Charlotte, NC, Chem Service, Inc., West Chester, PA, and Quantum Chemical Corp., Cincinnati, OH, have been cited in recent technical publications as sources of FB 236 (Ballard & Betowski, 1986; Yinon *et al*., 1989; Lee *et al.*, 1996). [N.B. Sandoz Colors and Chemicals of Charlotte, NC, is now known as Clariant Corporation. A customer service representative at Chem Service, Inc., stated that they do not currently supply this chemical.]

Use Pattern: FB 236 is a substituted coumarin-type fluorescent whitening agent (also known as a fluorescent or optical brightener). According to Dien (1978) coumarins have been in use as fluorescent brighteners for some time. Naik and Puro (1995) reported that derivatives of 3-phenyl-7-aminocoumarin are industrially important for use in both animal textile materials and synthetic fibers; some typical substrates for which they are used include wool, nylon, polyamides, cellulose acetates, plastics, and other synthetic fibers. The 3-phenyl-7-(azol-2-yl)coumarins, including FB 236, are especially useful in the textile industry for secondary acetate, polyester, and polyacrylonitrile fibers and in the synthetic fibers and plastics industry in polyester, poly(vinyl chloride) and polystyrene products, including photographic film layers, electrophotographic toners, and UV detecting resin compositions (Zweidler & Hefti, 1978; STN International 1996c). According to the Colour Index, FB 236 exerts blue fluorescence when applied

to polyester by mass coloration (Anon., 1971). Some specific applications using FB 236 reported in the available literature are summarized as follows:

•UV stabilizing additive (at 0.01-5%) in a laser beam printable polymeric sheathing material for electrical conductive conduits (Lee *et al*., 1996).

•polymer additive (at 0.03-0.04%) for improved brightening in PET and PVC (Di Pasquale *et al*., 1996) .

brightener incorporated into polyester matrix for photographic paper (Marien *et al.*, 1994).

•anti-yellowing brightener for PVC plastisols used as sealants in automobile manufacture (Brito Marqina & Garcia Ferreira, 1993).

•whitening agent for acrylic fibers useful in wearing apparel and interior design materials (Takemoto *et al*., 1989).

•optical brightener at 85 ppm in impact-resistant polystyrene to prevent yellow discoloration (Koski *et al.*, 1983).

•fluorescent whitener (at 0.005-1.0%) for improved whiteness and washfastness of polyester fibers for underwear (Anon., 1982).

Human Exposure: There is potential for occupational exposures to FB 236 by inhalation, ingestion or dermal contact. Clariant Corporation recommends the use of respiratory protection in circumstances where exposure levels exceed regulatory limits for nuisance dust (Clariant Corporation, 1996).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 9,719 workers, including 5,892 female employees, were potentially exposed to FB 236 in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

Environmental Occurrence: FB 236 is not known to occur naturally. However, this fluorescent brightener has been identified as a water pollutant. It is one of 16 commercial dyes representing different chemical classes studied at the US EPA Environmental Monitoring Systems Laboratory in Las Vegas, NV, to improve sensitivity of analytical detection methods applied to waste discharges from dye manufacturing and

use industries into the aquatic environment (Ballard & Betowski, 1986; Yinon *et al.*, 1989).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupation exposure to or workplace maximum allowable levels of FB 236. The American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) for this compound.

FB 236 has been approved by the Food and Drug Administration (FDA) as an indirect food additive (optical brightener) for use in olefin polymers for food packaging materials intended for food contact in 21 CFR 121.2501, 21 CFR 177.1520 & 2800, and 21 CFR 178.3297 (Benz, 1996). The FDA regulations were amended, according to Federal Register (1991), to extend approval for use of this fluorescent brightener as a colorant for polymers for packaging materials intended for food contact.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to FB 236 and cancer risk in humans were identified in the available literature.

Animal Data: No 2-year carcinogenicity studies of FB 236 were identified in the available literature.

In an acute toxicity test in animals, FB 236 was found to be virtually non-toxic with a rat oral LD_{50} >5000 mg/kg. FB 236 was non-irritating to the skin and eyes of rabbits and was without sensitizing action (Clariant Corporation, 1996). Additional subacute and subchronic studies were identified in the FDA's PAFA database; data are to be provided in response to an information retrieval request (Benz, 1996).

Short-Term Tests: No *in vitro* or *in vivo* studies evaluating FB 236 for mutagenic effects were found in the available literature. FB 236 has been selected as a candidate for testing in the Ames/*Salmonella typhimurium* and mouse lymphoma assays by the NCI/DCB short-term test program (STTP).

Metabolism: No studies on the metabolism of FB 236 were identified in the available literature. However, a 1971 human metabolism study was identified in the FDA's

PAFA database; data are to be provided in response to an information retrieval request (Benz, 1996).

Structure Activity Relationships: Six compounds structurally similar to FB 236 were screened for relevant information associating these related compounds with a mutagenic or carcinogenic effect. A summary of information found in the available literature for five of these compounds is presented in Table 1. No information was found on carcinogenicity or mutagenicity for 3-phenyl-7-aminocoumarin [4108-61-6].

Carcinogenicity/Tumor Inhibition: Information on carcinogenicity was identified for three of the structurally related compounds: coumarin, 6-methylcoumarin, and esculetin. Coumarin was the only compound with studies reporting positive indications of carcinogenic activity. The main target tissues were the kidney and bile duct in rats and alveolar/bronchiolar tissue in mice.

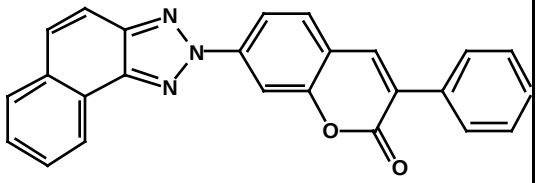
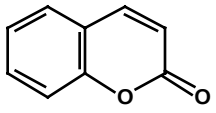
In studies on the suppression of carcinogen-induced tumors, coumarin and esculetin demonstrated some inhibitory capability and warfarin was shown to suppress metastasis. Umbelliferone was negative in the single inhibition study identified.

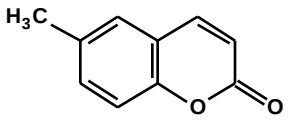
Mutagenicity/Antimutagenicity: Mutagenicity data were available for three of the compounds. Coumarin was mutagenic in *S. typhimurium* and it induced sister chromatid exchanges (SCEs) and chromosomal aberrations (CAs) in Chinese hamster ovary (CHO) cells. 6-Methylcoumarin demonstrated marginal mutagenic activity for *S. typhimurium* in one study; however, other reports were negative. Umbelliferone was not mutagenic in *S. typhimurium*, but positive results were reported for *Klebsiella pneumoniae.*

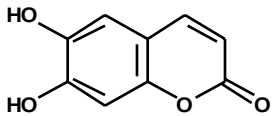
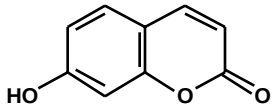
All five compounds were shown to be antimutagens in bacteria with a level of activity ranging from weak to significant.

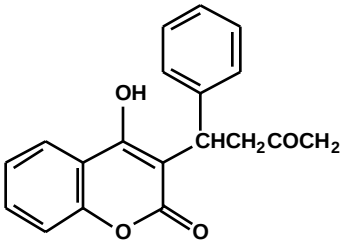
Teratogenicity: Wafarin is teratogenic in humans.

Table 1. Summary of Information on FB 236 and Structurally Related Compounds

Chemical Name	Carcinogenicity/Inhibition Data	Mutagenicity/ Antimutagenicity Data
FB 236 [3333-62-8] 	NDF	NDF
Coumarin [91-64-5] 	IARC group 3 chemical (agents not classifiable as to their carcinogenicity to humans)(IARC, 1987) 2-year gavage study results in F344 rats (25, 50, 100 mg/kg bw) and B6C3F$_1$ mice (50, 100, 200 mg/kg bw) showed: - some evidence of carcinogenic activity in male rats based on increased incidences of renal tubule adenomas - equivocal evidence in female rats based on marginally increased incidence of renal tubule adenomas - some evidence in male mice based on increased incidence of alveolar/bronchiolar adenomas - clear evidence in female mice based on increased incidences of alveolar/bronchiolar adenomas, carcinomas and hepatocellular adenomas (NTP, 1993) negative for tumors in Osborne-Mendel rats of both sexes following 1000, 2500, 5000 mg/kg/diet for 2 years; bile duct proliferation, cholangiofibrosis, and focal necrosis seen at highest doses (Hagan *et al.*,	positive in *S. typhimurium* TA100 with S9, negative without S9; negative in TA98, TA1535, TA1537 with and without S9 (NTP, 1993) positive without S9 for induction of sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells (NTP, 1993) positive for induction of chromosomal aberrations (CAs) in CHO cells with S9 (NTP, 1993) negative for sex-linked recessive lethal mutations in *Drosophila melanogaster* (NTP, 1993) no increase of micronucleated erythrocytes of B6C3F$_1$, mice following 13-wk administration by gavage (NTP, 1993) negative for unscheduled DNA synthesis (UDS) in rat tracheal epithelium cells (Ide *et al.*, 1981) clear antimutagenic activity on mutagenicity induced by 4-nitroquinoline 1-oxide (4-NQO) or UV irradiation in *E. coli* (Ohta *et al.*, 1983)

	1967 as cited in IARC, 1975) induced bile duct carcinomas in albino rats of both sexes following 5000 mg/kg diet for 2 yr; bile duct carcinomas also occurred in both sexes in a subsidiary experiment with 3500 mg/kg diet (Bär & Griepentrog, 1967; Griepentrog, 1973, as cited in IARC, 1975)	
Coumarin (continued)	no evidence of biliary hyperplasia or fibrosis seen in male baboons fed 2.5, 7.5, 22.5, 67.5 mg/kg/d for 16-24 mo; however, marked dilatation of the endoplasmic reticulum seen in high-dose group (Evans *et al*., 1978) negative for hepatocarcinogenicity in female hamsters fed 0.1 or 0.5% in diet for up to 2 yr (Ueno & Hirono, 1981) inhibited benzo[a]pyrene-induced forestomach tumors in female ICR mice (Wattenberg *et al.*, 1979). inhibited DMBA-induced mammary tumors in Sprague-Dawley female rats (Wattenberg *et al*., 1979; Feuer & Kellen, 1974)	weak antimutagenic activity on 2-amino-3-methyl-imidazo[4,5-f]quinoline (IQ)-induced mutagenicity in *S. typhimurium* TA98 (Edenharder *et al.*, 1995)
6-Methylcoumarin [92-48-8] 	negative for tumors in Osborne-Mendel rats following 500 to 15,000 ppm in diet for up to 2 years (Hagan *et al*., 1967 as cited in Opdyke, 1976) no effect on 1 male and 1 female dog following 50 mg/kg/d for 2 yr (Hagan *et al*., 1967 as cited in Opdyke, 1976)	negative in *S. typhimurium* TA98, TA100, TA1535 and TA1537 with and without S9 (Haworth *et al.*, 1983) marginal mutagenic activity in *S. typhimurium* TA100 with S9 (Wild *et al*., 1983) negative for sex-linked recessive mutations in *Drosophila melanogaster* (Wild *et al*., 1983)

	no significant inhibition of benzo[a]pyrene-induced forestomach tumors in female ICR mice (Wattenberg *et al*., 1979)	negative in the micronucleus test in female NMRI mice (Wild *et al*., 1983) moderate antimutagenic activity on IQ-induced mutagenicity in *S. typhimurium* TA98 (Edenharder *et al*., 1995)
Esculetin [305-01-1] 	no significant induction of bladder tumors in stock mice following implant (dose not stated) in cholesterol pellets (Boyland *et al*., 1964) significant inhibition of DMBA-induced mammary carcinoma in Sprague-Dawley rats (Kitagawa & Noguchi, 1994) no effect on multiplicity of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumors in A/J mice (Boukharta *et al*., 1992)	moderate antimutagenic activity on IQ-induced mutagenicity in *S. typhimurium* TA98 (Edenharder *et al*., 1995)
Umbelliferone [93-35-6] 	no significant inhibition of DMBA-induced mammary tumors in Sprague-Dawley rats; no significant inhibition of benzo[a]pyrene-induced forestomach tumors in ICR mice (Wattenberg *et al*., 1979)	negative in *S. typhimurium* TA100, TA98, TA1537 with and without S9 (Voogd *et al*., 1980 positive in *Klebsiella pneumoniae* (Voogd *et al*., 1980) clear antimutagenic activity on mutagenicity induced by 4-NQO or UV irradiation in *E. coli* (Ohta *et al*., 1983) moderate antimutagenic activity on IQ-induced mutagenicity in *S. typhimurium* TA98 (Edenharder *et al*., 1995)
Warfarin [81-81-2]	adjuvant therapy with anticoagulant coumarin derivatives including warfarin and warfarin sodium (coumadin) found to have a pronounced effect on the death rate of cancer patients; experiments with	weak antimutagenic activity on IQ-induced mutagenicity in *S. typhimurium* TA98 (Edenharder *et al*., 1995)

	mice indicated that survival was enhanced through prevention of metastasis (Grigg, 1978) significantly reduced spontaneous metastasis to the lungs of sc implanted rat mammary carcinoma (Mtln3) in female F344 rats (McCulloch & George, 1989) [administration of warfarin during pregnancy is a cause of birth defects and abortion; nasal hypoplasia and stippled epiphyseal calcification may result from use during first trimester; central nervous system abnormalities reported following second and third trimester exposure (Majerus *et al*., 1990)]	

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