PB81-148819

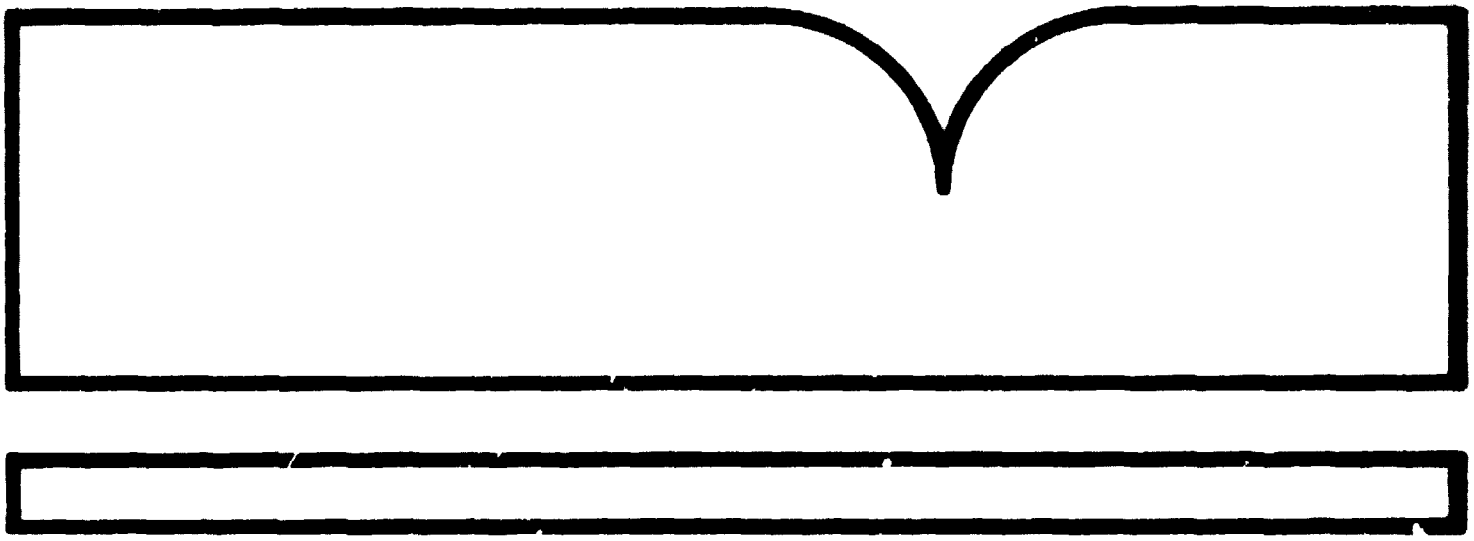
Information Profiles on Potential Occupational Hazards. Volume II. Chemical Classes Fluorescent Whitening Agent (FWA'S)

Syracuse Research Corp., NY

Prepared for

National Inst. for Occupational Safety and Health, Rockville, MD

Dec 79



CUMENTATION PAGE

PB81-148818

4. Title and Subtitle
Potential Occupational Hazards, Volume II, Chemical Classes
Fluorescent Whitening Agents (FWA's)

5. Report Date
December 1979

6. NA

7. Author(s)
Anonymous

8. Performing Organization Rept. No.
NA

9. Performing Organization Name and Address
Center for Chemical Hazard Assessment
Syracuse Research Corporation
Syracuse, New York

10. Project/Task/Work Unit No.
NA

11. Contract(C) or Grant(G) No.
(C) 210-78-0019
(G)

12. Sponsoring Organization Name and Address
National Institute for Occupational Safety and Health
Rockville, Maryland

13. Type of Report & Period Covered
Contract Final Report

14. NA

15. Supplementary Notes
NA

16. Abstract (Limit: 200 words)

ABSTRACT: This information profile on fluorescent whitening agents (FWA's) is part of a group of 46 such profiles that provide information about chemicals or industrial processes considered to be potential occupational hazards. Each profile contains summary data on known and suspected health effects, the extent of worker exposure and the industrial importance of either a single chemical, class of chemicals, or a particular industrial process. The report was developed for use by occupational safety and health professionals in industry, and labor and other areas, to provide them with a synopsis of information on each subject and to identify potential hazards in their workplaces.

17. Document Analysis a. Descriptors

Toxicology
Physiological-efficts
Chemical-properties
Occupations
Industrial-processes
Work-environment
Safety-research

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement
Available to the public

19. Security Class (This Report)
NA

20. Security Class (This Page)

21. No. of Pages

22. Price

00098769

INFORMATION PROFILES ON POTENTIAL OCCUPATIONAL HAZARDS

VOLUME II. CHEMICAL CLASSES

Center for Chemical Hazard Assessment
Syracuse Research Corporation
Merrill Lane
Syracuse, New York 13210

Final Report
Contract No. 210-78-0019 (20)

December 1979

Prepared for:

National Institute for Occupational Safety and Health
5600 Fishers Lane
Rockville, Maryland 20857

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INTRODUCTION

An information profile is a working paper used by the National Institute for Occupational Safety and Health (NIOSH) to assist in establishing Institute priorities. It is an initial step in determining the need to develop comprehensive documents or to initiate research. Each profile summarizes data on known and suspected health effects, the extent of worker exposure, physical and chemical properties, and the industrial importance of individual chemicals and classes of chemicals. The profile may also be used by industry, labor, and the occupational health community as a synopsis of information on each subject and to identify possible health hazards associated with their workplaces.

Although detailed literature searches are conducted using computerized and manual searching techniques to identify pertinent and recent information, not all the literature obtained is incorporated in the report due to the summary nature of the profiles. Further, literature published after 1978 may not be included in these profiles because it was generally unavailable at the time the search was completed.

FLUORESCENT WHITENING AGENTS (FWA's)

SUMMARY

FWA's are a group of compounds that absorb radiant energy in the ultraviolet region and re-emit it as visible light. These compounds are used as brighteners in laundering products, clothing, synthetic fibers, plastics, and paper. Based on current projections, the production of these materials is not expected to increase significantly above current levels of about 30 million pounds per year.

The FWA's appear to have moderate to low acute toxicity, with oral LD_{50}'s in experimental mammals of over 5000 mg/kg. The sublethal acute effects of these compounds have not been extensively studied. Most are only moderately irritating and do not appear to be sensitizing.

Many of these compounds have been tested for chronic effects and the results of these tests do not suggest a high potential hazard to man from repeated exposures. The tested compounds do not appear to be mutagenic, carcinogenic, or teratogenic to experimental mammals and, at the concentrations tested, do not appear to induce other specific pathological damage.

These compounds have not been shown to cause dermal irritation or sensitization in humans. No reports of occupational problems or other adverse human effects have been encountered in the literature.

1. Synonyms

2. Registry of Toxic Effects of Chemical Substances (RTECS) Number

3. Chemical Abstracts Service (CAS) Number

4. Molecular Formula

5. Chemical Structure

6. Physical and Chemical Properties

The above information for the fluorescent whitening agents included in this profile is presented in Table 1. Because of the complex structures and nomenclature of FWA's, the system of abbrevations proposed by Gloxhuber and Bloching (1978) will be used in this report. These abbreviations are presented in Table 2.

7. Producer and User Data

Production and Trends

In 1977, 33.254 million pounds of fluorescent brightening agents were manufactured in the U.S. (USITC, 1977). This production figure is a decrease of 5-10 million from those of the preceding three years. At this time, the production of fluorescent brighteners is not expected to significantly increase beyond production levels of 1974-1976.

The only production breakdown available for the individual fluorescent brighteners in 1977 is listed below (USITC, 1977):

Fluorescent brightening agent	28	1.042	million pounds
Fluorescent brightening agent	61	0.115	million pounds

In 1969, 0.254 million pounds of fluorescent brightening agent 9 were produced (USITC, 1969).

Imports of fluorescent brightening agents totalled 0.938 million pounds in 1977 (USITC, 1977), or about 2.8 percent of domestic production.

The following fluorescent brightening agents that have color index number assignments are among those commercially produced in 1977 (USITC, 1977): Fluorescent brightening agent 9, 22, 24, 25, 28, 46, 49, 52, 59, 61, 68, 71, 75, 126, 128, 134, 148, 159, 191, 200.

Uses

In recent years, optical brighteners (fluorescent brighteners) have become one of the more important components of laundering products manufactured in the United States. Millions of pounds are used yearly for this purpose.

Table 1. Fluorescent Brightening Agents: Physical and Chemical Properties

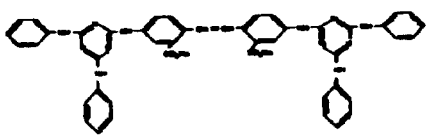
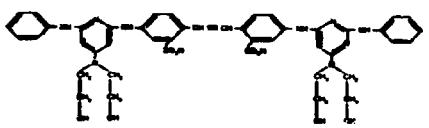
	4,4'-Bis[(4,6-dianilino-S-triazin-2-yl)amino]-2,2'-Stilbenedisulfonic acid, disodium salt	4,4'-Bis[[4-anilino-6-[bis(2-hydroxyethyl)amino]-S-triazin-2-yl]amino]-2,2'-Stilbenedisulfonic acid
Synonyms	Fluorescent Brightening Agent 9 Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-[[4,6-bis(phenylamino)-1,3,5-triazin-2-yl]amino]-disodium salt Commercial Names: Blancophor HZP, Tintophen CX (Gaf Corp.); Blancophor HZP (Farbenfabriken Bayer A.G., Germany); Calcofluor White MR (American Cyanamid Co.); Leukophor DNH (Sandoz Colors and Chemicals); Rylux PP (Chemopol, Czech.); Tinopal TAS, TASD (Ciba-Geigy Corp.); Whitex SB (Sumitomo Chemical Co., Ltd., Japan)	Fluorescent Brightening Agent 28 Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-[[4-[bis(2-hydroxyethyl)amino]-6-phenylamino)-1,3,5-triazin-2-yl]amino]- Commercial Names: Blancol CFB new (L.B. Holliday and Co., Ltd., England); Blancophor FB, Tintophen FB (GAF Corp.); Calcofluor White PMS, PMM, ST (American Cyanamid Co.); Hiltamine Arctic White CWD (Hilton-Davis Division of Sterling Drug Co.); Paper White BN, BP, Pontamine White BT, BTS (I.E. du Pont de Mours and Co., Inc.); Tinopal 4BM, 4BMA, 4 BMT (Ciba-Geigy Corp.)
Cas Number	133-66-4	4404-43-7
RTECS Number		
Molecular Formula	$C_{44}H_{36}N_{12}O_6S_2 \cdot 2Na$	$C_{40}H_{44}N_{12}O_{12}S_2$
Chemical Structure		
Physical and Chemical Properties		
Molecular Weight		
Physical State		Yellow powder or clear solution
Boiling Point, °C		
Melting Point, °C		
Vapor Pressure		
Evaporation Rate		
Solubility		Soluble in water
Specific Gravity		
Stability		Stable

Table 1. Fluorescent Brightening Agents: Physical and Chemical Properties (Cont'd)

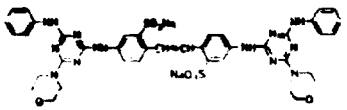
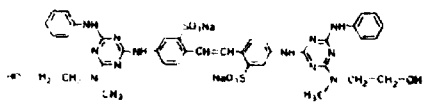
	Fluorescent Brightener 61	4,4'-Bis[(4-anilino-6-morpholino-S-triazin-2-yl)amino]-2,2'-stilbenedisulfonic acid, disodium salt	4,4'-Bis[[[4-anilino-6-(2-hydroxyethyl)(methyl)amino]-S-triazin-2-yl]amino]-2,2'-stilbenedisulfonic acid, disodium salt
Synonyms		Fluorescent Brightening Agent 260	
	Aminocoumarin derivative	Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-[[4-(4-morpholinyl)-6-(phenylamino)-1,3,5-triazin-2-yl]amino]-disodium salt	Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-[[4-[(2-hydroxyethyl)methylamino]-6-(phenylamino)-1,3,5-triazin-2-yl-amino]-, disodium salt
	Commercial Names: Blancophor AW, FFG; Tintophen AW, FFG (GAF Corp.); Calcofluor White RW, RWP, SD (American Cyanamid Co.); Uvitex WGS (Ciba-Geigy Corp.)	Commercial Name: Tinopal AMS (Ciba-Geigy Corp.)	Commercial Name: Tinopal 5BM (Ciba-Geigy Corp.)
CAS Number	12224-04-3	16090-02-1	
RTECS Number			
Molecular Formula		$C_{40}H_{40}N_{12}O_8S_2 \cdot 2Na$	
Chemical Structure			
Physical and Chemical Properties			
Molecular Weight			
Physical State			
Boiling Point, °C			
Melting Point, °C			
Vapor Pressure			
Evaporation Rate			
Solubility			
Specific Gravity			
Stability			

Table 1. Fluorescent Brightening Agents: Physical and Chemical Properties (Cont'd)

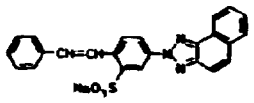
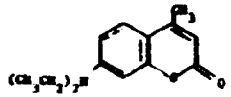
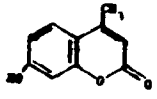
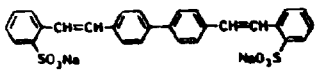
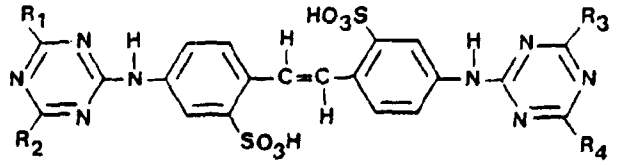
	4-(2H-Naphtho[1,2-d]triazol-2-yl)-2-Stilbenedisulfonic acid, sodium salt	7-(Diethylamino)-4-methylcoumarin	7-Hydroxy-4-methylcoumarin	2,2'-(4,4'-Biphenylenedivinylene)dibenzenesulfonic acid, disodium salt
Synonyms	Fluorescent Brightening Agent 46			
	Benzenesulfonic acid, 5-(2H-naphtho[1,2-d]triazol-2-yl)-2-(2-phenylethenyl)-, sodium salt	2H-1-Benzopyran-2-one, 7-(diethylamino)-4-methyl	2H-1-Benzopyran-2-one, 7-hydroxy-4-methyl Hymecromone 8-methylumbelliferone Resocyanin	4,4'-Bis(2-sulfostyryl)biphenyl, disodium salt
	Commercial Name: Tinopal RBS (Ciba-Geigy Corp.)	Commercial Name: Advabrite MDAC (Cincinnati Milacron Chemicals, Inc.)	Commercial Name: Advabrite BMV (Cincinnati Milacron Chemicals, Inc.)	
CAS Number	6416-68-8	91-44-1	90-33-5	
RTECS Number		GN 6370000		
Molecular Formula	$C_{24}H_{17}N_3O_3S.Na$	$C_{14}H_{17}NO_2$	$C_{10}H_8O_3$	$C_{28}H_{20}O_6S_2.2Na$
Chemical Structure				
Physical and Chemical Properties				
Molecular Weight				
Physical State		White to light tan powder	Light tan powder	
Boiling Point, °C				
Melting Point, °C		68-73	184-194	
Vapor Pressure				
Evaporation Rate				
Solubility				
Specific Gravity				
Stability		Excellent heat stability and outdoor durability	Outdoor durability	

Table 2. Symbols for FWA's (Gloxhuber and Blocking, 1978)

symbol: DASC



DASC	Chemical name
1	Disodium 4,4'-bis[(4-anilino-6-morpholino-1,3,5-triazin-2-yl)amino]-stilbene-2,2'-disulfonate
2	Disodium 4,4'-bis{[4-anilino-6-(N-methyl-N-2-hydroxyethyl)-amino-1,3,5-trizain-2-yl]amino}stilbene-2,2'-disulfonate
3	Disodium 4,4' bis[(4,6-dianilino-1,3,5-triazin-2-yl)amino]-stilbene-2,2'-disulfonate
4	Disodium 4,4'-bis[(4-phenoxy-6-methoxy-1,3,5-triazin-2-yl)-amino]-stilbene-2,2'-disulfonate
5	Tetrasodium 4,4'-bis{[4-(3-sulfoanilino)-6-bis(2-hydroxy-ethyl)-amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
6	Disodium 4,4'-bis{[4-(4-methoxyanilino)-6-morpholino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
7	Disodium 4,4'-bis[(4,6-disubst.-1,3,5-triazin-2-yl)amino]-stilbene-2,2'-disulfonate
8	Disodium 4,4'-bis{[4-anilino-6-bis(2-hydroxyethyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
9	Disodium 4,4'-bis[(4-anilino-6-methoxy-1,3,5-triazin-2-yl)-amino]stilbene-2,2'-disulfonate
10	Disodium 4,4'-bis[(4-anilino-6-ethylamino-1,3,5-triazin-2-yl)amino]stilbene-2,2'-disulfonate
11	Disodium 4,4'-bis{[4-anilino-6-(2-hydroxypropyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
12	Disodium 4,4'-bis{[4-anilino-6-(2-hydroxyethyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate

Table 2. Symbols for FWA's (Gloxhuber and Blocking, 1978) (Cont'd)

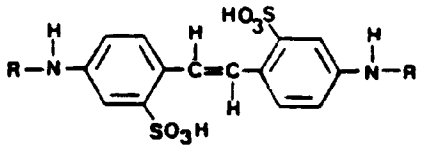
DASC	Chemical name
13	Disodium 4,4'-bis{[4-anilino-6-(2-methoxyethyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
14	Disodium 4,4'-bis[(4-anilino-6-hydroxy-1,3,5-triazin-2-yl)-amino]stilbene-2,2'-disulfonate
15	Tetrasodium 4,4'-bis{[4-(4-sulfoanilino)-6-bis(2-hydroxyethyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
16	Disodium 4,4'-bis[(4-anilino-6-methylamino-1,3,5-triazin-2-yl)amino]stilbene-2,2'-disulfonate
17	Disodium 4,4'-bis{[4-amino-6-(2-hydroxyethyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
18	Disodium 4-(4,6-dianilino-1,3,5-triazin-2-yl)-4'-(4''-anilino-6''-diethanolamino-1'',3'',5''-triazin-2''-yl)-diaminostilbene-2,2'-disulfonate
19	Disodium 4,4'-bis{[4-methylamino-6-bis(2-hydroxyethyl)-amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
20	Disodium 4-(4-amino-6-anilono-1,3,5-triazin-2-yl)-4'-{4''-[(4'''-acetyl-amino-2'''-sulfophenylamino-carbonyl) phenylamino]-6''-amino-1'',3'',5''-triazin-2''-yl}diaminostilbene-2,2'-disulfonate
21	Tetrasodium 4,4'-bis{[4-(3-sulfonanilino)-6-(2-hydroxyethyl)-amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
22	4,4'-bis{[4-(4-sulfoanilino)-6-bis(2-hydroxypropyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonic acid
23	Tetrasodium 4,4'-bis{[4-(4-sulfoanilino)-6-morpholino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
24	Hexasodium 4,4'-bis{[4-(2,5-disulfoanilino)-6-diethylamino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
25	Hexasodium 4,4'-bis{[4-(2,5-disulfoanilino)-6-morpholino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
26	4,4'-bis{[4-bis(2-hydroxyethyl)amino-6-methoxy-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonic acid
27	Disodium 4,4'-bis{[4-bis(2-hydroxyethyl)amino-6-methoxy-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate

Table 2. Symbols for FWA's (Gloxhuber and Blocning, 1976) (Cont'd)

DASC	Chemical name
28	Disodium 4,4'-bis{[4-chloro-6-bis(2-hydroxyethyl)amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate
29	4,4'-bis{[4-(2-methoxyethoxy)-6-(N-methyl-N-2-sulfoethyl)-amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonic acid
30	Disodium 4,4'-bis{[4,6-di-(9-hydroxy-4,7-dioxa-1-nonyl)-amino-1,3,5-triazin-2-yl]amino}stilbene-2,2'-disulfonate

4,4'-Diamino-stilbene-2,2'-disulfonic acid derivatives

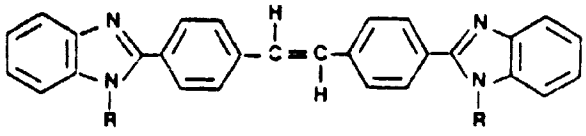
symbol: DAS



DAS	Chemical name
1	Disodium 4,4'-bis(4,6-dimethoxy-benzamido)stilbene-2,2'-disulfonate
2	Disodium 4,4'-bis(anilino-carbonylamino)stilbene-2,2'-disulfonate

4,4'-Bis[(N-substituted)benzimidazol-2-yl]stilbene derivatives

symbol: BIS



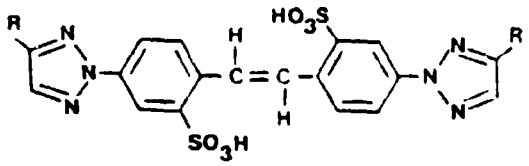
BIS	Chemical name
1	4,4'-Bis[N-(2,9-dihydroxy-4,7-dioxanonyl)benzimidazol-2-yl]stilbene

Table 2. Symbols for FWA's (Gloxhuber and Blocking, 1978) (Cont'd)

BIS	Chemical name
2	4-(Benzimidazol-2-yl)-4'-[N-(2,9-dihydroxy-4,7-dioxanonyl)-benzimidazol-2-yl]stilbene

4,4'-Bis(4-substituted-1,2,3-triazol-2-yl)stilbene-2,2'-disulfonic acid derivatives

symbol: TS



TS	Chemical name
1	4,4'-Bis(1,2,3,-triazol-2-yl)stilbene-2,2'-disulfonic acid
2	Disodium 4,4'-bis(4-phenyl-1,2,3-triazol-2-yl)stilbene-2,2'-disulfonate
3	Dipotassium 4,4'-bis(4-phenyl-1,2,3-triazol-2-yl)stilbene-2,2'-disulfonate
4	Tetrasodium 4,4'-bis[4-(4-sulfophenyl)-1,2,3-triazol-2-yl]-stilbene-2,2'-disulfonate

2-(4-Styryl-3-sulfophenyl)2H-naphtho[1,2-d]-triazole derivatives and 4,4'-Bis(2H-naphtho[1,2-d]-triazol-2-yl)stilbene-2,2'-disulfonic acid derivatives

symbol: NTS

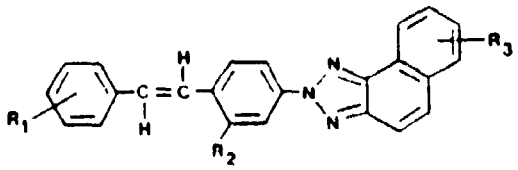
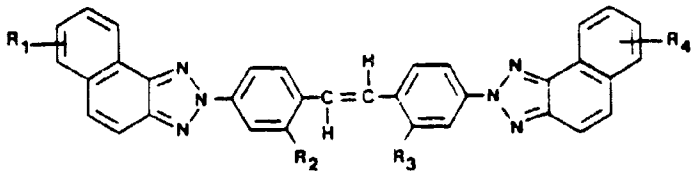
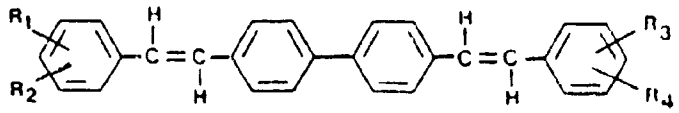


Table 2. Symbols for FWA's (Gloxhuber and Blocking, 1978) (Cont'd)



NTS	Chemical name
1	Sodium 2-(4-styryl-3-sulfophenyl)-2H-naphtho [1,2-d]-triazole
2	Disodium 2-(4-styryl-3-sulfophenyl)-7-sulfo-2H-naphtho-[1,2-d]-triazole
3	Disodium 4,4'-bis(6-sulfo-2H-naphtho[1,2-d]-triazol-2-yl)-stilbene
4	Trisodium 4-(1,2,4-triazol-1-yl)-4'-(7-sulfo-2H-naphtho-[1,2-d]-triazol-2-yl)stilbene-2,2'-disulfonate

4,4'-Bis(styryl)biphenyl derivatives, (Distyryl-biphenyl derivatives)
symbol: DSBP

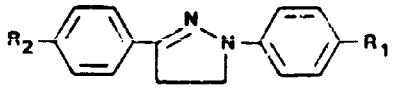


DSBP	Chemical name
1	Disodium 4,4'-bis(2-sulfostyryl)biphenyl
2	4,4'-Bis(styryl)biphenyl-derivative
3	4,4'-Bis(2-sulfostyryl)biphenyl
4	Disodium 4,4'-Bis(4-chloro-3-sulfostyryl)biphenyl

Table 2. Symbols for FWA's (Gloxhuber and Blocking, 1978) (Cont'd)

1,3-Diphenyl-2-pyrazoline derivatives

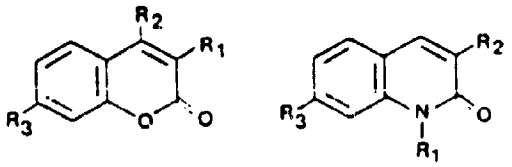
symbol: PYZ



PYZ	Chemical name
1	Mixture of
1a	1-(3-Chlorophenyl)-3-phenyl-2-pyrazoline and
1b	1-(3-Chlorophenyl)-3-(4-chlorophenyl)-2-pyrazoline
2	1-[4-(N-Methyl)-carbonamido-phenyl]-3-phenyl-2-pyrazoline
3	1-(4-Sulfonamidophenyl)-3-(4-chlorophenyl)-2-pyrazoline
4	1-(4-Carboethoxyphenyl)-3-(4-chlorophenyl)-2-pyrazoline
5	1-(4-Carbomethoxyphenyl)-3-(4-chlorophenyl)-2-pyrazoline
6	1,3-Diphenyl-2-pyrazoline derivative
7	Sodium 1-(4-sulfophenyl)-3-phenyl-2-pyrazoline
8	Sodium 1-(4-sulfophenyl)-3-(4-chlorophenyl)-5-phenyl-2-pyrazoline
9	1-(4-Methylsulfonylphenyl)-3-(4-chlorophenyl)-2-pyrazoline

Coumarin and quinolone derivatives

symbols: COUM and QUIN



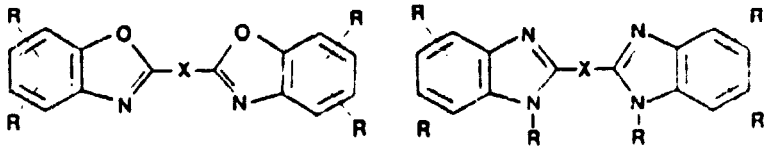
Derivative	Chemical name
COUM	
1	3-Benzyl-4-methyl-coumarin

Table 2. Symbols for FWA's (Gloxhuber and Blocking, 1978) (Cont'd)

Derivative	Chemical name
COUM	
2	4-Methyl-7-(N,N-disubst.)alkylaminocoumarin
3	4-Methyl-7-dimethylaminocoumarin
4	3-Phenyl-7-(N-ethoxycarbonyl)amino-3,4 H-coumarin
5	4-Methyl-7-diethylaminocoumarin
6	3-Phenyl-7-(3-methylpyrazol-1-yl)coumarin
7	3-Phenyl-7-(4-methyl-5-phenyl-1,2,3-triazol-2-yl)coumarin
8	3-(4-Chloropyrazol-1-yl)-7-(4-methyl-5-phenyl-1,2,3-triazol-2-yl)coumarin
QUIN	
1	1-Ethyl-3-phenyl-7-dimethylamino-2-quinolone
2	1-Subst.-3-phenyl-7-dimethylamino-2-quinolone

Combinations of benzoxazol-2-yl and/or benzimidazol-2-yl derivatives with conjugated systems

symbols: BO and BI



Derivative	Chemical name
BO	
1	2,5-Bis(benzoxazol-2-yl)thiophene
2	2,5-Bis(5-tert.butylbenzoxazol-2-yl)thiophene
3	2-(4-Phenyl-stilbene-4'-yl)-5-tert.-butylbenzoxazole
4	1,2-Bis(5-methylbenzoxazol-2-yl)ethylene
5	Sodium 3,3'-dimethyl-5,5'-dimethoxy-oxacyanine-p-toluol-sulfonate

Table 2. Symbols for FWA's (Gloxhuber and Blocking, 1978) 'Cont'd)

Derivative	Chemical name
BI	
1	1-(Benzimidazol-2-yl)-2-(N-hydroxyethylbenzimidazol-2-yl)ethylene
2	1-(Benzimidazol-2-yl)-2-(benzoxazol-2-yl)ethylene

Other fluorescent whitening agents (FWA)

FWA	Chemical name
I	1,2-Bis(6-methyl-3H-indol-2-yl)ethylene
II	Disodium 3,7-bis(2,4-dimethoxybenzamido)-2,8-dibenzothiophenedisulfonate-5,5-dioxide
III	2-Styryl-naphtho[2,1-d]-oxazole

Virtually all clothing contains brighteners; they are used extensively for the mass whitening of synthetic polymer fibers, during which the optical brightener is added to the spinning solution or melt. They are also used in the finishing of textiles, including "wash-wear" cottons, where they are applied to the fabric along with a finishing agent. In paper manufacture, the brighteners can be applied to the pulp in the dipping process or during the coating operation. Most of the vast numbers of articles that are manufactured from plastics contain brighteners, including wrappers and containers for foodstuffs (Sweeney, 1974).

Approximately 70 percent of the total sales of fluorescent brighteners is used in soaps and detergents (Anon., 1974).

Producers and Distributors

The following companies produce and distribute fluorescent brightening agents (SRI, 1978; USITC, 1977):

American Cyanamid	
Ciba-Geigy Corp.	GAF Corp.
Cincinnati Milacron Chem.	Mobay (Verona Chem.)
Crompton & Knowles Corp.	Morton-Norwich Prod.
Day-Glo Color Corp.	Sandoz Color & Chem.
DuPont	Sterling Drug (Hilton-Davis Chem.)

The following companies also distribute fluorescent brighteners (OPD, 1978; Chem. Week, 1978):

BASF Wyandotte
Eastman Chem.
J.F. Henry Chem.
Suburban Chem.

Manufacturing Process

The following is a general description of the manufacturing process that can be applied to the manufacture of most fluorescent brightening agents. A batch reactor that contains a reaction medium of water, or less frequently, an organic solvent is used. Chemical intermediates are introduced into the reactor for synthesis; varying time and temperature conditions are imposed. Depending upon the complexity of the fluorescent agent being prepared, as many as seven or eight chemical syntheses steps may be required within the reactor. At the conclusion of syntheses steps, the fluorescent agent will normally be in solution; it is precipitated from solution by a process called "salting-out" in which sodium carbonate, chloride, or acetate is added to the reactor bath to initiate precipitation. The precipitate is washed with water or alcohol to remove impurities and then dried, if required, by ovens or spray driers. The final commercial product is then prepared; it may be in the form of a solution or a dry product. The dry product is normally a mixture of the fluorescent agent with surfactants, non-dusting agents, sodium sulfate, and various inert ingredients.

Fluorescent brightening agent 9 is prepared by treating 4,4'-diamino-2,2'-stilbenedisulfonic acid, in an aqueous sodium carbonate solution, with cyanuric chloride, in a $(CH_3)_2CO$ medium. The reaction product is then reacted with aniline (Nishi, 1951).

Fluorescent brightening agent 28, Tinopal AMS, and Tinopal 5BM are also prepared from 4,4'-diamino-2,2'-stilbenedisulfonic acid and the appropriate intermediates.

7-Hydroxy-4-methylcoumarin is obtained by the condensation of resorcinol with acetoacetic ester, $CH_3COCH_2COOC_2H_5$, in the presence of acid catalysts such as sulfuric acid or phosphorus pentoxide (Raff, 1953).

8. Biological Effects of Exposure

a) Acute Effects

Acute toxicity data for the fluorescent whitening agents are presented in Table 3. 7-Hydroxy-4-methylcoumarin produced ataxia and tranquilization in both mice and rats administered oral, intraperitoneal, and intravenous doses (EPA, 1975). Intravenous injections of 251 mg/kg produced respiratory arrest and 292 mg/kg produced cessation of the cardiac QRS complex.

Fluorescent brightener 28 gave a general fluorescence to the skin, mucosa, intestinal tract, and muscles of laboratory animals given intravenous and oral doses. An affinity for the spleen, fatty tissue, nervous system, pancreas, and glandular system was demonstrated (EPA, 1975).

4-Methyl-7-diethylamino coumarin was administered orally and intravenously to rabbits (EPA, 1975). It was determined that this compound was eliminated in the urine and bile. An affinity for the nervous system was exhibited upon tissue analysis.

7-Hydroxy-4-methylcoumarin and its tissue distribution were studied in Sprague-Dawley rats given 50 mg/kg (1 percent suspension in 0.5 percent carboxymethylcellulose solution) via stomach tube (EPA, 1975). The cumulative amounts of total and free methylhydroxycoumarin were measured in plasma, urine, and tissue. This compound is metabolized via a sulfate conjugation; thus, sulfatase hydrolysis was used to determine total (conjugated plus free) methylhydroxycoumarin. The cumulative amounts of free methylhydroxycoumarin detected in the urine were 2.96 percent, 30.4 percent, and 3.12 percent of the total dose after 24, 48, and 72 hours, respectively. The values were 85.7 percent, 87.0 percent, and 94.6 percent after sulfatase hydrolysis. The largest amounts of both total and free methylhydroxycoumarin were measured in the kidneys, liver, and plasma; however, the distribution of the total versus the free form was predominant in the brain, indicating easier passage of this form through the blood brain barrier.

Primary skin and eye irritation of several fluorescent whitening agents was tested using rabbits (Thomann and Krüger, 1975). The following compounds were held in contact with shaved skin for 24 hours or introduced to

Table 3. Fluorescent Whitening Agents: Acute Toxicity Data

Species	Route	Dose	Result	Reference
4,4´-Bis[4-anilino-6-[bis(2-hydroxyethyl)amino]-s-triazin-2yl]amino]-2,2´-stilbenedisulfonic acid and disodium salt (technical grade)				
rat	oral	14530 mg/kg	LD_{50}	Thomann & Krüger, 1975
(35% active ingredient)				
rat	oral	14530 mg/kg	LD_{50}	" "
rabbit	skin	>2000 mg/kg	LD_{50}	" "
7-(Diethylamino)-4-methylcoumarin (technical grade)				
rat	oral	5000 mg/kg	LD_{50}	" "
mouse	ip	180 mg/kg	LD_{50}	NIOSH, 1978
7-Hydroxy-4-methylcoumarin				
rat	oral	6200 mg/kg	LD_{50}	EPA, 1975
rat	ip	750 mg/kg	LD_{50}	"
mouse	oral	7500 mg/kg	LD_{50}	"
mouse	ip	325 mg/kg	LD_{50}	"
mouse	iv	250 mg/kg	LD_{50}	"
4,4´-Bis[(4-anilino-6-morpholino-s-triazin-2-yl)amino]2,2´-stilbenedisulfonic acid, disodium salt (technical grade)				
rat	oral	>10250 mg/kg	LD_{50}	Thomann and Krüger, 1975
rabbit	skin	>10000 mg/kg	LD_{50}	" "

Table 3. Fluorescent Whitening Agents: Acute Toxicity Data (Cont'd)

Species	Route	Dose	Result	Reference
4,4'-Bis[[[4-anilino-6-(2-hydroxyethyl)(methyl)amino]-s-triazin-2-yl]amino]-2,2'-stilbenedisulfonic acid, sodium salt (60% active ingredient)				
rat	oral	>10250 mg/kg	LD_{50}	Thomann and Krüger, 1975
rabbit	skin	> 200 mg/kg	LD_{50}	Thomann and Krüger, 1975
2,2'(4,4'-biphenylylendivinylene)dibenzenesulfonic acid, disodium salt (technical grade)				
rat	oral	5580 mg/kg	LD_{50}	Thomann and Krüger, 1975
rat	skin	> 1000 mg/kg	LD_{50}	Thomann and Krüger, 1975
rabbit	skin	> 2500 mg/kg	LD_{50}	Thomann and Krüger, 1975
4,(2H-naphtho[1,2-d]triazol-2-yl)-2-stilbenedisulfonic acid, sodium salt				
rat	oral	> 21.5 gm/kg	LD_{50}	Snyder et al., 1963
mouse	oral (in water)	> 10 gm/kg	LD_{50}	Snyder et al., 1963
mouse	oral (in olive oil)	> 5 gm/kg	LD_{50}	Snyder et al., 1963
4,4'-Bis[(4,6-dianilino-s-triazin-2-yl)amino]-2,2'-stilbenedisulfonic acid, disodium salt				
rat	oral	> 10 gm/kg	LD_{50}	Snyder et al., 1963
guinea pig	oral	> 7 gm/kg	LD_{50}	Snyder et al., 1963

the conjunctival sac and their effects on the rabbits were observed for 3-8 days: FBA 46, FBA 28, Tinopal AMS, 7-(Diethylamino)-4-methylcoumarin and 2,2'-(4,4'-biphenylylenedivinylene)dibenzene sulfonic acid, disodium salt. The only significant reactions observed were slight skin irritation from FBA 46 and 2,2'-(4,4'-biphenylylenedivinylene)dibenzenesulfonic acid, disodium salt; moderate eye irritation from FBA 28; and extreme eye irritation from 2,2'-(4,4'-biphenylylenedivinylene)dibenzenesulfonic acid, disodium salt.

The absorption of a fluorescent whitening agent into the skin of hairless mice was monitored using dipotassium 4,4'-bis(4-phenyl-1,2,3-triazol-2-yl)stilbene-2,2'-disulfonate (Laukhaus and Löser, 1975). The mice were painted with a 0.1 or 0.01 percent aqueous solution over an area of 6-8 sq cm. Tissue samples were studied using the microscopic phase-contract fluorescence method 10 minutes, 1, 8, 14 and 48 hours, and 7 and 21 days after application of the FWA. No evidence of penetration into the dermis or subcutaneous tissue by this type of FWA, bis(phenyl-triazolyl)stilbene-disulfonate, was detected.

b) Subchronic Effects

A subchronic feeding study involving rats found no adverse affects from dose levels of 200 mg/kg or 40 mg/kg/day of 7-hydroxy-4-methylcoumarin administered over a three month period (EPA, 1975). Growth, food intake, mortality, blood and urine analysis, and organ histology were all normal.

Snyder and coworkers (1963) applied a 7.5 percent solution of a detergent containing 1 percent of a fluorescent whitening agent to the clipped skin of rabbits at a dose of 1.5 mg/kg/day for a period of 13 weeks. Neither 4,4'-bis[[4-anilino-6-[bis(2-hydroxyethyl)amino]-s-triazin-2-yl]amino]-2,2'-stilbenedisulfonic acid nor 4-2H-naptho[1,2-d]triazol-2-yl)-2-stilbenedisulfonic acid, sodium salt produced any adverse effects based on analysis of weight gains, blood chemistry values, and examination of internal organs.

c) Chronic Effects

i. Carcinogenicity

Gloxhuber and Bloching (1978) have summarized the available information on the carcinogenicity of FWA's that have been tested both alone and in combination with ultraviolet (UV) light.

No evidence for carcinogenicity has been obtained from studies using FWA's alone. In two-year exposure studies involving simultaneous oral dosing and subcutaneous applications of DASC 2 and DASC 17, no increased tumor incidence was observed in mice (Neukomm and DeTrey, 1961). Similarly, skin painting studies in mice using DAS 1, DASC 3, DASC 8, BI 1, and NTS 1 yielded no positive indication of carcinogenicity. Negative results were also obtained in chronic oral and subcutaneous exposures of mice to PYZ 5 (Snyder et al., 1963). Chronic oral administration of NTS 1, DASC 1, DASC 2, and DSBP 1 in rats and dogs also resulted in no significant tumor increase (Keplinger et al., 1975).

In tests involving exposures to both FWA's and UV light, only one study has suggested a positive carcinogenic response. In this study, mice were given dermal applications of COUMI, DAS 1, and DASC 3 with simultaneous exposure to UV light at wave lengths that are not present in sunlight (215-270 nm). In mice exposed to all three chemicals in combination with UV light and in mice exposed to UV light alone, squamous cell carcinomas developed. Mice exposed to the FWA's alone did not develop tumors (Bingham and Falk, 1970). A similar study by Forbes and Urbach (1975a) using DASC 3 was unable to confirm these results. Studies using UV-A and UV-B light, NST 1, DASC 1, DASC 2, and DSBP 1 yielded no evidence of photocarcinogenicity (Forbes and Urbach, 1975b and c).

ii. Teratogenicity

Embryo toxicity of four FWA's (NTS 1, DASC 1, DASC 2, and DSBP 1) in New Zealand white rabbits was studied by Keplinger and coworkers (1974). The rabbits were administered one of two dose levels, 10 or 30 mg/kg/day, from the 6th to the 18th day of pregnancy. No teratogenic effects were observed. Gross abnormalities occurred no more frequently than in controls; the slight increases in resorptions from treatments on days 7, 8 and 9 may have been due to maternal toxicity rather than specific fetal toxicity.

Keplinger et al. (1975) conducted further studies with the same four compounds, this time covering three successive generations of albino rats. The animals were fed diets containing 40, 200, or 1000 ppm of each compound. Body weights, weight gains, and survival of the parental generation were normal. No gross pathological changes or histopathological changes could be correlated with treatment. Reproductive performance (defined as mating index, fertility index, incidence of pregnancy, incidence of parturition) and survival data for progeny (defined as live birth index, 24 hour survival index, 5 day survival index, lactation index) did not differ with treatment. All pups were free of malformations; no significant changes in pathology or histology of the progeny were found. Some random decreases in the number of progeny of rats that received a FWA were noted, but the authors felt that these decreases were not related to ingestion of the FWA since no dose-related effect or consistent pattern of occurrence was observed.

7-Hydroxy-4-methylcoumarin did not cause any teratogenic effects when administered orally to laboratory animals before mating or from the 6th to 15th days of gestation. The following dosage schedule was employed: rats received 15 to 1200 mg/kg/day and rabbits received 50 to 800 mg/kg/day during gestation; mice were given 50-800 mg/kg/day, beginning 15 days before mating (EPA, 1975).

iii. Mutagenicity

Using the dominant lethal assay in mice, Lorke (1973) found no positive results for T51 at a dose of 5000 mg/kg. Lorke and Machemer (1975) administered single oral doses of 5000 mg/kg each of TS 3, DASC 1, DASC 16, and PYZ 3. Oral doses of 1000 mg/kg of trimethyl phosphate (TMPO) and intraperitoneal injections of 100 mg/kg of methyl methanesulfonate (MMS), two known

mutagens, were used as positive controls. Each of the treated male mice was mated with three untreated females per week for 8 weeks. The females were sacrificed on the 14th day of gestation; the number of fertile matings, implantations, resorptions, live fetuses, and corpora lutea were counted. The animals did not exhibit any toxic symptoms from either of the compounds nor did any of the above parameters differ significantly from those of the untreated controls. Both positive controls produced dominant lethal mutations in the early weeks of mating.

Keplinger and coworkers (1974) administered two dose levels of each of four FWA's: NTS 1, DASC 1, DASC 2 (at 5 and 10 mg/kg) and DSBP 1 (at 25 and 50 mg/kg) to mice in the dominant lethal assay. Ethyl methanesulfonate (EMS) was the positive control. None of the FWA's caused a dominant lethal effect at any of the dosage levels investigated. Fertilization, the number of implantations, resorptions, viable embryos, and pre implantation losses did not differ from untreated controls.

Müller and coworkers (1975) also found no evidence for mutagenicity based on cytogenic assays in hamsters after exposures to NTS 1, DASC 1, DASC 2, and DSBP 1.

iv. Other Effects

Keplinger and coworkers (1975) conducted two-year chronic feeding studies with albino rats and beagle dogs with NTS I (rats only), DASC 1, DASC 2, and DSBP 1. The rats were divided into groups receiving 0, 40, 200, and 1000 ppm of each compound, while the dogs were administered dietary levels of 0, 80, 400, and 2000 ppm. Body weights, food consumption, hematological values, blood chemistry, urine analysis, and histological samples were normal for rats at all dose levels. Treated animals exhibited no significant increases in either the number or type of tumors or the time for neoplasm development recorded during the two-year study period. The results of the study involving dogs were normal (tumor incidence was not monitored).

d) Human Effects

A summary of sensitization patch tests conducted on human subjects revealed a lack of sensitization and no photosensitizing effect upon exposure to a series of optical brighteners (EPA, 1975). Within the group of chemicals studied were several derivatives of 4,4'-diamino-2,2'-stilbenedisulfonic acid. Some reaction was noted when ultraviolet light or abrasive action was applied in conjunction with the optical brighteners. Transient hyperemia and erythema were the most serious symptoms observed.

Keplinger and coworkers (1974) applied each of the following optical brighteners -- fluorescent brightener 46, Tinopal AMS, Tinopal 5BM, and 2,2'-(4,4'-biphenylylenedivinylene)dibenzenesulfonic acid, disodium salt -- to the skin of 50 volunteers, three times per week (10 times total). Ten to 14 days later, the compounds were applied again. None of the subjects were irritated or sensitized upon examination 24-48 hours later. Fluorescent brightener 61 has been labeled by a major producer as a skin and eye irritant (EPA, 1975).

The absence of dermal irritation in humans was confirmed by Gloxhuber and Bloching (1978) in a summary of studies. No irritation was produced from contact with 0.5 and 1.0 percent solutions of FBA 28 for 24 and 48 hours, 1 percent solutions of Tinopal 5BM, or 2 percent solutions of FBA 260. FBA 260, FBA 9, FBA 28, and Tinopal 5BM did not reveal sensitizing properties when applied in repeated patch tests.

Gloxhuber and coworkers (1975) conducted handwashing tests with detergents containing 0.05-0.25 percent of one of the following types of FWA's: quinoline derivative (3-phenyl-7-dimethylamino-2-quinolone), bis(styryl)biphenyl derivative (4,4'-bis(styryl)biphenyl), pyrazoline derivative (1,3-diphenyl-2-pyrazoline) and stilbenedisulfonic acid derivative (4,4'-bis[(4,6-disubst.-1,3,5-triazin-2-yl)amino]-stilbene-2,2'-disulfonic acid). Only slight amounts, 0.06 mg to 0.17 mg, were detected on the hands after washing, and, after 24 hours, no FWA's were found.

9. Threshold Limit Values, OSHA Standards, NIOSH Recommended Standards

No exposure limits have been proposed.

10. Other Standards

No data were encountered.

11. Occupational Exposures

No data were available.

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