

**STILBENE INTERMEDIATES CATEGORY**

RECEIVED  
OPPT CBIC

06 JAN -9 AM 10:44

**HPV Challenge Program**

**201-16114A**

**TEST PLAN AND CATEGORY JUSTIFICATION**

**Submitted to the U.S. Environmental Protection Agency  
Under the High Production Volume (HPV) Chemicals Challenge Program**

**By**

**The ETAD Fluorescent Whitening Agent Task Force**

**December 16, 2005**

## TABLE OF CONTENTS

<b>1.</b>	<b>INTRODUCTION.....</b>	<b>3</b>
<b>2.</b>	<b>IDENTIFICATION OF CATEGORY MEMBERS .....</b>	<b>3</b>
<b>3.</b>	<b>JUSTIFICATION FOR STILBENE INTERMEDIATECATEGORY .....</b>	<b>4</b>
<b>4.</b>	<b>CRITERIA FOR DETERMINING ADEQUACY OF DATA .....</b>	<b>7</b>
<b>5.</b>	<b>DISCUSSION OF AVAILABLE TEST INFORMATION .....</b>	<b>7</b>
	<b>5.1 PHYSICAL CHEMICAL PROPERTIES FOR CATEGORY MEMBERS.....</b>	<b>9</b>
	5.1.1 Melting Point .....	9
	5.1.2 Boiling Point.....	9
	5.1.3 Vapor Pressure.....	10
	5.1.4 Partition Coefficient.....	10
	5.1.5 Water Solubility.....	10
	5.1.6 Summary/Test Plan for Physical Properties .....	10
	<b>5.2 ENVIRONMENTAL FATE DATA FOR CATEGORY MEMBERS .....</b>	<b>11</b>
	5.2.1 Photodegradation .....	11
	5.2.2 Stability in Water (Hydrolysis).....	11
	5.2.3 Environmental Transport .....	11
	5.2.4 Biodegradation.....	12
	5.2.5 Summary/Test Plan for Environmental Fate Parameters.....	13
	<b>5.3 AQUATIC TOXICITY DATA.....</b>	<b>13</b>
	5.3.1 Acute Fish Toxicity.....	13
	5.3.2 Acute Toxicity to Aquatic Invertebrates.....	14
	5.3.3 Acute Toxicity to Aquatic Plants.....	14
	5.3.4 Acute Toxicity to Bacteria.....	14
	5.3.5 Chronic Toxicity to Aquatic Species.....	14
	5.3.6 Test Plan for Aquatic Toxicity.....	15
	<b>5.4 MAMMALIAN TOXICITY .....</b>	<b>15</b>
	5.4.1 Acute Oral Toxicity .....	15
	5.4.2 Acute Inhalation Toxicity .....	16
	5.4.3 Acute Dermal Toxicity .....	16
	5.4.4 Irritation/Sensitization.....	16
	5.4.5 Repeated-Dose Toxicity.....	17
	5.4.6 Genetic Toxicity: Gene Mutations and Chromosome Aberrations.....	18
	5.4.7 Carcinogenicity.....	19
	5.4.8 Reproductive Toxicity .....	20
	5.4.9 Developmental Toxicity.....	20
	5.4.10 Other Effects.....	20
	5.4.11 Test Plan for Mammalian Toxicity.....	21
<b>6.</b>	<b>SUMMARY .....</b>	<b>22</b>
<b>7.</b>	<b>REFERENCES.....</b>	<b>23</b>
<b>8.</b>	<b>APPENDIX .....</b>	<b>29</b>

## 1. Introduction

The Fluorescent Whitening Agent Task Force of ETAD has committed to sponsor a category of 3 intermediates for stilbene-based fluorescent whitening agents and dyes in the US EPA High Production Volume Chemical Program. The members of this Task Force are:

Ciba Corporation

Clariant Corporation

LANXESS Deutschland GmbH, successor of Bayer Chemicals AG and parts of Bayer AG

## 2. Identification of Category Members

The members of the Stilbene Intermediates Category are listed in Table 1. The molecular structures of category members are shown in Figure 1. The category consists of 3 sponsored stilbenes and one surrogate with supporting data. CAS Nos. 81-11-8 and 7336-20-1 are the same except that the former is the free sulfonic acid and the latter is the disodium salt. The surrogate (CAS No. 78447-91-3) has the same molecular structure as CAS No. 3709-43-1, except that CAS No. 3709-43-1 is the disodium salt, and CAS No. 78447-91-3 is the dipotassium salt.

The members of the category (CAS Nos. 81-11-8, 7336-20-1 and 3709-43-1), plus the surrogate (CAS No. 78447-91-3) are intermediates that are used to manufacture fluorescent whitening agents and dyes.

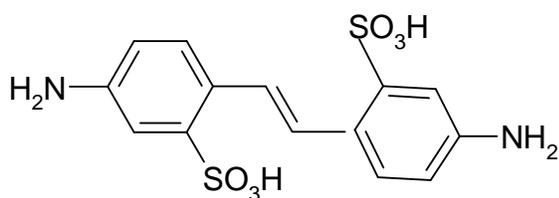
**Table 1. Identification of Category Members**

<b>CAS No.</b>	<b>Chemical Name</b>	<b>Common or Trade Name</b>
<b>81-11-8*</b>	4,4'-diaminostilbene-2,2'-disulphonic acid	Amsonic Acid
<b>7336-20-1</b>	disodium 4,4'-diaminostilbene-2,2'-disulphonate	
<b>3709-43-1</b>	disodium 4,4'-dinitrostilbene-2,2'-disulphonate	
78447-91-3	2,2'-Stilbendisulfonic acid-4,4'-dinitro, dipotassium salt	(surrogate for CAS No. 3709-43-1)

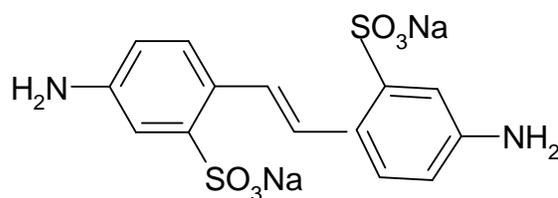
Bolded entries represent category members, non-bolded designate the surrogate with supporting data.

\* Reviewed at SIAM 4

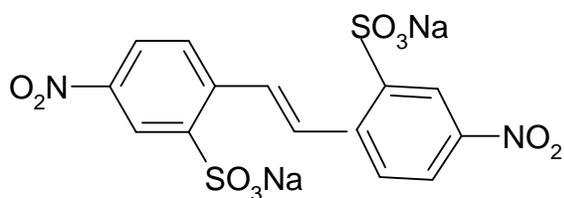
Figure 1. Chemical Structures of Category Members and Surrogates



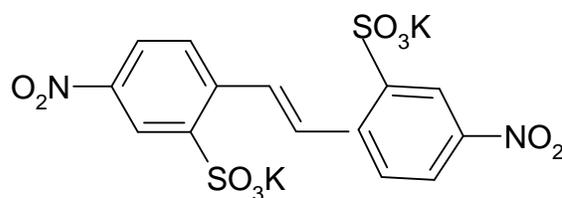
CAS No. 81-11-8



CAS No. 7336-20-1



CAS No. 3709-43-1



CAS No. 78447-91-3  
(surrogate)

### 3. Justification for Stilbene Intermediates Category

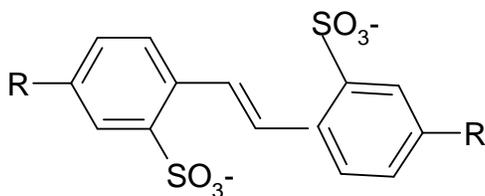
The merits for the category approach for the 3 sponsored chemical substances are summarized as follows:

- The substances possess similar chemical structures and functionality
- The substances display similar physical chemistry and environmental fate properties
- Existing data for the substances indicate that they exert similar effects with respect to aquatic and mammalian toxicology
- The use, release and exposure profiles for the substances are similar

The attributes summarized above are discussed in more detail below:

a. Category members possess similar molecular structures and functionality.

The three members of the category and the surrogate 78447-91-3 all possess the following stilbene backbone molecular structure, shown below:



for CAS Nos. 81-11-8 and 7336-20-1, R = NH<sub>2</sub>

for CAS Nos. 3709-43-1 and 78447-91-3, R = NO<sub>2</sub>

All category members possess two sulfonate groups. The only difference between the category members is in the substitution at the para positions on the benzene rings designated by the “R Group.” Two of the members possess amino (-NH<sub>2</sub>) groups as the R groups, and the other category member and surrogate possess nitro (-NO<sub>2</sub>) groups as the R groups. CAS Nos. 81-11-8 and 7336-20-1 are identical substances, (where the R group is an amino function). The former is the free base and the latter is the disodium salt. The surrogate (CAS No. 78447-91-3) has the same molecular structure as CAS No. 3709-43-1 (where in both cases the R is a nitro function), except that CAS No. 3709-43-1 is the disodium salt, and CAS No. 78447-91-3 is the dipotassium salt.

b. Category members display similar physical chemical and environmental fate properties.

Since category members are all metal-organic salts or an internal salt (in the case of CAS No. 81-11-8), they exhibit high melting points, do not boil without decomposing and do not exert vapor pressure, except vapor pressure attributed to volatile impurities or additives, such as water. In addition, category members possess low or negative partition coefficients and are stable to hydrolysis. As a result of the stilbene portion of the molecule, these stilbene intermediates have an UV absorption maximum between 340 to 360 nm in water, which makes them subject to photodegradation in the hydrosphere. Finally, category members biodegrade only slowly.

c. Existing data for the substances indicate that they exert similar effects with respect to aquatic and mammalian toxicology.

Available studies suggest that the category members are of low toxicity to fish, annelids and bacteria and are of low to moderate toxicity to aquatic invertebrates and algae. With respect to mammals, the category members are of low acute or repeated dose oral toxicity, are not mutagenic or clastogenic, and are not reproductive or developmental toxicants. They are generally not irritating or sensitizing to skin and are slightly to moderately irritating to eyes.

d. Category members possess similar use, release and exposure profiles.

As stated above, the category members are the intermediates used to manufacture fluorescent whitening agents and dyes. CAS Nos. 3709-43-1 and 78447-91-3 are intermediates used to manufacture CAS Nos. 81-11-8 and 7336-20-1 via catalytic reduction of the nitro groups to the amine groups. CAS Nos. 81-11-8 and 7336-20-1 are then chemically converted on to dyes and fluorescent brightening agents. According to the SIDS Initial Assessment Report (SIAR) for CAS No. 81-11-8, which was reviewed at SIAM 4 (with Japan as the country sponsor), this category member is used to manufacture pigments and fluorescent brighteners in closed systems in Japan.

The sponsors of this category are not aware of any uses of these category members other than as industrial intermediates. As industrial intermediates, these materials are in general manufactured and converted to dyes and brighteners using closed systems. CAS Nos. 81-11-8 and 7336-20-1 may be sold to other companies who convert these substances on to dyes and brighteners. Therefore, these are not site limited intermediates. Exposures to category members are largely limited to an industrial setting, and minimized by being manufactured and chemically converted to final products using closed systems. Some environmental releases may be possible, but have not been quantified. Spills of CAS Nos. 81-11-8 and 7335-20-1 could occur during transport from the manufacturing sites to companies where the substances are converted to dyes and brighteners.

Examples of fluorescent brighteners made from CAS No. 81-11-8 and 7335-20-1 are given in Appendix A of the test plan. The brighteners in Appendix A are being sponsored as a separate category designated the Fluorescent Whitening Agent Category.

#### **4. Criteria for Determining Adequacy of Data**

All available studies for CAS Nos. 81-11-8, 7336-20-1, 3709-43-1 and 78447-91-3 were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate. The dossier for CAS No. 81-11-8 that was presented at SIAM 4 is not up to current standards and is not included in this submission. A new dossier has been created which contains data from the dossier presented at SIAM 4 and new information that was not available at SIAM 4. Information obtained from the dossier presented at SIAM 4 is clearly marked.

#### **5. Discussion of Available Test Information**

The test plan matrix (as shown in Table 2 on the next page) was constructed after a careful evaluation of all existing data (see below). This matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the sets of robust summaries.

**Table 2. Plan Matrix for Stilbene Intermediates Category**

<b>CAS No.</b>	<b>81-11-8</b>	<b>7336-20-1</b>	<b>3709-43-1</b>	<b>78447-91-3</b>
<b>ENDPOINT</b>				
<b>PHYSICAL CHEMISTRY</b>				
Melting point	Y	Y	M, C	M (NR)
Boiling point	NA	NA	NA	NA
Vapor Pressure	Y	NA	NA	NA
Water Solubility	Y	Y	C	Y
Kow	Y	M	M	M (NR)
<b>ENVIRONMENTAL FATE</b>				
Photodegradation	NR	Y	NR	NR
Stability in Water	Y	S	S	S (NR)
Biodegradation	Y	Y	Y	Y
Transport between Environmental Compartments (Fugacity)	M	M	M	M (NR)
<b>ECOTOXICITY</b>				
Acute Toxicity to Fish	Y	Y	C	Y
Acute Toxicity to Aquatic Invertebrates	Y	Y	C	NR
Toxicity to Aquatic Plants	Y	Y	C	NR
Toxicity to Bacteria (NR)	Y	NR	NR	Y
Toxicity to Terrestrial Organisms (NR)	NR	NR	NR	NR
Chronic Toxicity to Fish (NR)	NR	NR	NR	NR
Chronic Toxicity to Invertebrates (NR)	Y	NR	NR	NR
<b>TOXICOLOGICAL DATA</b>				
Acute Toxicity	Y	Y	C	Y
Repeated Dose Toxicity	C	Y	C	NR
Genetic Toxicity-Mutation	Y	Y	C	Y
Genetic Toxicity-Chromosomal Aberrations	Y	Y	C	NR
Carcinogenicity (NR)	C	Y	C	NR
Toxicity to Reproduction	Y	C	C	NR
Developmental Toxicity	Y	C	C	NR
<b>OTHER TOXICITY DATA</b>				
Irritation (NR)	Y	Y	Y	Y
Sensitization (NR)	N	NR	NR	NR
Human Experience (NR)	Y	NR	NR	NR

Category members are depicted in boldface type. Y = endpoint filled by experimental data; C = endpoint filled by category approach; NA = not applicable; S = endpoint filled by general analysis of chemical structure; M = endpoint filled by modeling; NR = not required

## 5.1 Physical Chemical Properties for Category members

The physical chemical properties for category members are summarized in Table 3.

**Table 3. Chemical/Physical Property Data for Stilbene Intermediates Category**

Chemical CAS No.	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (hPa) @ 20°C	Water Sol. (g/l) @20°C	Log Kow
<b>81-11-8</b>	> 300 <sup>a</sup>	No data	< 1.3 (25°C) <sup>b</sup>	0.032 at 25 <sup>b</sup>	-1.7 <sup>c</sup>
<b>7336-20-1</b>	> 300 <sup>d</sup> 349.84 <sup>f</sup>	No data	No data	> 100 <sup>e</sup> (21°C)	-3.99 <sup>f</sup>
<b>3709-43-1</b>	349.84 <sup>f</sup>	No data	No data	No data	-2.52 <sup>f</sup>
78447-91-3	> 200 <sup>g</sup> 349.84 <sup>f</sup>	No data	No data	4.34 <sup>h</sup>	0.2 <sup>i</sup> -2.52 <sup>f</sup>

Bolded type represents category members; regular type represents the surrogate with supporting data.  
<sup>a</sup>Huang- Minlon, 1948; <sup>b</sup>MITI, 1994; <sup>c</sup>Bayer AG, 1991a, calculated; <sup>d</sup>Ciba Geigy AG, 1986; <sup>e</sup>Ciba Geigy AG, 2005; <sup>f</sup>estimated using EPIWIN; <sup>g</sup>Bayer AG, no year listed; cited in an IUCLID document for CAS No. 78447-91-3; <sup>h</sup>Bayer AG, 1989a; <sup>i</sup>Bayer AG, 1991b

### 5.1.1 Melting Point

Measured melting point data are available for two of the category members. Category members have consistently high melting points, as would be expected for organic molecules that exist primarily as ionic salts. The estimated melting points are generally consistent with the measured melting points.

### 5.1.2 Boiling Point

None of the category members will exhibit a boiling point range, because they are either organo sodium salts or an inner salt. Organic salts exist in ionic form instead of unionized molecular form and will decompose on heating to temperatures above the melting point without boiling. As shown in Table 3, melting of category members generally does not occur below 300°C (with the exception of CAS No. 78447-91-3, which begins to decompose above 200°C), and decomposition (not boiling) would then be expected above these temperatures.

### **5.1.3 Vapor Pressure**

Since all category members exist as ionized organic salts, and therefore do not exist as molecules that can volatilize, vapor pressure determination is not relevant or needed. A measured vapor pressure of 1.3 hPa is reported for CAS Nos. 81-11-8, but it is likely that this appreciable vapor pressure is attributable to the presence of water or other volatile impurities. As salts, category members themselves will not exert appreciable vapor pressure. No testing is needed or planned.

### **5.1.4 Partition Coefficient**

Partition coefficient data are available for all category members as shown in Table 3. The partition coefficients were estimated using EPIWIN Kowwin or a similar model. The values are low or negative (ranging from 0.2 to -3.99), which are consistent with the low Log Pows that would be anticipated for organic salts.

### **5.1.5 Water Solubility**

Water solubility data are available for CAS Nos. 81-11-8, 7336-20-1 and 78447-91-3. The values range from < 1 g/l for the acid (CAS No. 81-11-8), to > 100 g/l for the corresponding salt (CAS No. 7336-20-1). The value for CAS No. 78447-91-3 (4.34 g/l) will be predictive of that for CAS No. 3709-43-1, since the former is the potassium salt and the latter is the sodium salt of the same molecule.

### **5.1.6 Summary/Test Plan for Physical Properties**

Adequate measured information is available for physical properties. The high melting points are consistent with molecular structure and functionality (all category members are organic salts). As metal organic salts or inner salts, category members exist in ionic form and not as discrete molecules. Therefore, these materials do not boil without first undergoing decomposition at or above their melting points. Nor do they exert significant vapor pressure, other than that attributable to volatile impurities or additives that may be present, such as water. Sufficient estimated data are available for category members with respect to partition coefficient to predict

that Log Pow values will be low or negative (consistent with the presence of multiple sulfonic acid salt functions). The water solubility value for CAS No. 78447-91-3 is predictive of that for CAS No. 3709-43-1. No further testing is therefore planned for physical properties.

## **5.2 Environmental Fate Data for Category Members**

### **5.2.1 Photodegradation**

None of the category members volatilize to any degree, since they are all ionized organic salts. Therefore, they will not be found in any significant concentration in the atmosphere other than in particle form. For this reason, atmospheric photodegradation is not an appreciable or important degradative pathway, and testing for atmospheric photodegradation would not serve a useful purpose.

However, since the category members have the ability to absorb part of the terrestrial UV-sunlight ( $\lambda = 300 - 400$  nm) and transform it into visible, blue fluorescence light (Kramer, 1996), they are potentially photodegradable substances. A half-life of  $1.78 \times 10^{-2}$  years and a rate constant of  $6.19 \times 10^{-11}$  mol/l/sec in water were estimated by MITI (1994) for CAS No. 81-11-8 (according to the method of Lyman et al. [1981]) for the direct photodegradation of the material in water due to the absorption of UV light. The available data indicate that stilbenes have a strong potential to undergo photodegradation in the hydrosphere.

### **5.2.2 Stability in Water (Hydrolysis)**

CAS No. 81-11-8 has been found to be stable in water at pH 4, 7 and 9 in an OECD Guideline 111 study (MITI, 1994), which was reviewed at SIAM 4. The available measured data are consistent with predicted stability to hydrolysis based on molecular structure. The category members do not possess functional groups (esters, carbamates, etc.) that are normally expected to be susceptible to abiotic hydrolysis. Based on measured data and known lack of functionality susceptible to hydrolysis, sufficient information exists to address the hydrolysis endpoint.

### **5.2.3 Environmental Transport**

Because the category members are salts, they cannot volatilize to the atmosphere, but would enter the atmosphere only in particulate form and in very limited amounts, where they would be removed by wet or dry deposition. The appreciable water solubilities of category members and their low or negative partition coefficients, suggest a limited potential to bioaccumulate, and a strong tendency to partition to the hydrosphere, as well as soil.

The EPIWIN Level III Fugacity program has been run for the category members using measured values for melting point water solubility, and partition coefficient (when available). As expected, the model results predict that the stilbene intermediates will partition predominately to water and soil and negligibly to the atmosphere and biota (Table 4).

**Table 4. Level III Fugacity Modeling for Category Members**

CAS No.	Fugacity Mass Percent				Half-lives (Hours)			
	Air %	Water %	Soil %	Biota %	Air	Water	Soil	Biota
<b>81-11-8</b>	0	57.8	42.1	0.107	1.18	900	900	3600
<b>7336-20-1</b>	0	57.9	42.0	0.107	1.18	900	900	3600
<b>3709-43-1</b>	0	59.1	40.8	0.112	1.47	1440	1440	5760

Emission rates inputted to the model are 1000 kg/hr to water and to soil, and 0 kg/hr to air

#### 5.2.4 Biodegradation

As shown in Table 5 below, all studies that have been conducted on the category members indicate that most members are not readily biodegradable.

**Table 5. Biodegradation Rates for Stilbene Intermediates Category**

Category Member	Biodegradation Rate
<b>81-11-8</b>	5% after 28 days (OECD 302B) <sup>a</sup> 0% (BOD), 1-4% (HPLC), (OECD 301C) <sup>b</sup>
<b>7336-20-1</b>	< 15 % after 56 days (OECD 302B) <sup>c</sup>
<b>3709-43-1</b>	4.3% after 31 days [(OECD 2) A-12] <sup>d</sup>
78447-91-3	0.7% after 29 days (modified OECD Screening Test) <sup>e</sup>

Bolded type represents category members; regular type represents the surrogate with supporting data.

<sup>a</sup> Bayer AG, 1989b; <sup>b</sup> MITI (1994), reviewed at SIAM 4; <sup>c</sup> ETAD, 1992; <sup>d</sup> Ciba-Geigy, 1986;

<sup>e</sup> Ciba-Geigy, 1989a

### 5.2.5 Summary/Test Plan for Environmental Fate Parameters

Since the category members do not volatilize, atmospheric photodegradation is not an important degradative pathway, and conducting atmospheric photodegradation studies would not be useful. Available data indicate that these materials undergo photodegradation in the hydrosphere as well as slow biodegradation. Studies performed with all members of the category indicate that these materials are not readily biodegradable.

Level III fugacity modeling suggests that category members, when released to the environment, will partition predominately to soil and water, and negligibly to the atmosphere. Further environmental fate testing is not planned.

### 5.3 Aquatic Toxicity Data

Aquatic toxicity data for the category members are summarized in Table 6.

**Table 6. Aquatic Toxicity of Stilbene Intermediates Category**

Chemical	Fish Acute Toxicity LC <sub>50</sub> (mg/l) <sup>a</sup>	Invertebrate Acute Toxicity EC <sub>50</sub> (mg/l) <sup>b</sup>	Algae Acute Toxicity EC <sub>50</sub> (mg/l) <sup>c</sup>
<b>81-11-8</b>	>1000 (1) 200 (LC0) (2)	130 (1) 210 (24 hr) (1)	76 (1)
<b>7336-20-1</b>	≥ 500 (3)	300 to 500 (4)	> 100 (3)
<b>3709-43-1</b>	> 1000 (5) <sup>d</sup>	No data	No data
78447-91-3	> 3395 (6)	No data	No data

Bolded type represents category members; regular type represents the surrogate with supporting data.

<sup>a</sup> 96 hours unless listed otherwise; <sup>b</sup> *Daphnia magna* (48 hrs) unless stated otherwise; <sup>c</sup> 96 hours unless stated otherwise; <sup>d</sup> Study given a reliability rating of 4 (not assignable due to insufficient documentation); (1) EA, 1994; (2) Bayer AG (date unknown); (3) ETAD, 1992; (4) Bayer AG, 1986; (5) Ciba-Geigy, 1986; (6) Fraunhofer-Institut, 1989

#### 5.3.1 Acute Fish Toxicity

An OECD Test Guideline 203 study was conducted with CAS No. 81-11-8 in *Oryzias latipes* (Japanese Rice Fish) (EA, 1994). The 96-hour LC50 value was > 1000 mg/l (highest concentration tested). The 48-hour LC0 for CAS No. 81-11-8 in a non-GLP study with *Leuciscus idus* (golden orfe) was 200 mg/l. Both of these studies were included in the SIDS dossier accepted at SIAM 4.

OECD Test Guideline 203 studies conducted in *Brachydanio rerio* (zebrafish) indicate a 96-hour LC0 value of  $\geq 500$  mg/l for CAS No. 7336-20-1 (ETAD, 1992) and  $\geq 3395$  mg/l for a formulation containing 64.4% CAS No. 78447-91-3 (Fraunhofer-Institut, 1989). A study conducted in *Brachydanio rerio* that was given a reliability rating of 4 (not assignable) due to insufficient information indicates a 96-hour LC50 value of  $> 1000$  mg/l for a formulation containing 60% CAS No. 3709-43-1 and 35% water (Ciba-Geigy, 1986).

### **5.3.2 Acute Toxicity to Aquatic Invertebrates**

The 24-hour EC50 value for CAS No. 81-11-8 in an OECD Test Guideline 202 study conducted in *Daphnia magna* is 210 mg/l (EA, 1994), which was reviewed at SIAM 4. The 48-hour EC50 value for immobility, determined in the 21-day OECD Test Guideline 202 study described under 5.3.5 below, is 130 mg/l CAS No. 81-11-8 (EA, 1994). A 48-hour EC50 value between 300 and 500 mg/l was determined for CAS No. 7336-20-1 in an OECD Test Guideline 202 study in *Daphnia magna* (ETAD, 1992).

### **5.3.3 Acute Toxicity to Aquatic Plants**

Results of an OECD Test Guideline 210 study reviewed at SIAM 4 indicate that the 72-hour EC50 value for CAS No. 81-11-8 in *Selenastrum capricornutum* is 76 mg/l (EA, 1994). An OECD Test Guideline 201 study listed a 72-hour EC50 value of  $> 100$  mg/l CAS No. 7336-20-1 for either *Scenedesmus subspicatus*, *Selenastrum capricornutum* or *Ankistodesmus bibraianus* (actual species used was not listed) (ETAD, 1992).

### **5.3.4 Acute Toxicity to Bacteria**

The 24-hour EC0 values reported by Bayer for CAS Nos. 81-11-8 at SIAM 4 and 7336-20-1 in *Pseudomonas fluorescens* bacteria are 1000 mg/l.

The 3-hour EC50 values for inhibition of respiration of activated sludge by CAS Nos. 7336-20-1 and 78447-91-3 are  $> 100$  and  $> 10000$  mg/l, respectively (Ciba-Geigy AG, 1986; Ciba-Geigy, 1989b).

### **5.3.5 Chronic Toxicity to Aquatic Species**

The chronic toxicity of CAS No. 81-11-8 to *Daphnia magna* has been tested according to OECD Test Guideline 202. Forty daphnids were exposed in an open system to each of 5 nominal concentrations ranging from 21-210 mg/l. Immobility and reproduction rate were monitored for a period of 21 days. The 21 day EC50 value (with 95% confidence limits) for immobility was 44 mg/l (63-86 mg/l). The 21 day EC50 value (with 95% confidence limits) for reproduction was 92 mg/l (85-98 mg/l) (EA, 1994). This study was reviewed at SIAM 4.

### 5.3.6 Test Plan for Aquatic Toxicity

Adequate acute fish toxicity tests have been performed for all materials in the category. All 96 hr LC50 values are  $\geq 500$  mg/l. Invertebrate toxicity testing has been performed on all category members except CAS No. 3709-43-1. All EC50 values in *Daphnia magna* for the tested category members are  $> 100$  mg/l. Algae toxicity tests that have been performed on CAS Nos. 81-11-8 and 7336-20-1 indicate LC50 values  $\geq 76$  mg/l. Additional studies indicate that the test materials are of low toxicity to bacteria. Based on similarities in structure, it is expected that the EC50 values for CAS No. 3709-43-1 for *Daphnia* and algae will be similar to those of CAS Nos. 81-11-8 and 7336-20-1. No additional testing is necessary.

## 5.4 Mammalian Toxicity

Acute mammalian toxicity studies that have been performed are summarized in Table 7.

**Table 7. Acute Mammalian Toxicity of the Stilbene Intermediates Category**

Chemical	Acute Rat Oral LD <sub>50</sub> (mg/kg)	Acute Rat Inhalation LD <sub>50</sub> (mg/l)	Acute Rat Dermal LD <sub>50</sub> (mg/kg)
<b>81-11-8</b>	>3000 (LC0) (1) 47000 (guinea pig) (2)	No data	No data
<b>7336-20-1</b>	> 5000 (3)	No data	No data
<b>3709-43-1</b>	> 16000 (4)	No data	No data
78447-91-3	> 2000 (5)	No data	No data

Bolded type represents category members; regular type represents the surrogate with supporting data. (1) Smith and Quinn (1992); (2) Zaitseva and Kulikov, 1980; (3) Loeser, 1979; (4) reference unknown. Data cited in an IUCLID document for CAS No. 3709-43-1. Assigned a reliability rating of 4 (not assignable); (5) Bayer AG, 1989c

### 5.4.1 Acute Oral Toxicity

The oral LD50 values reported for CAS No. 81-11-8 at SIAM 4 were 3000 mg/kg in the rat and 47000 mg/kg in the guinea pig. The oral LD50 value reported for the related material CAS No. 7336-20-1 is > 5000 mg/kg in the male rat. A rat oral LD50 value of > 16000 mg/kg CAS No. 3709-43-1 was reported in IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000. The primary reference was not stated and was not able to be located. Therefore, the study was assigned a reliability rating of 4 (not assignable). In a guideline, GLP study, the related material CAS No. 78447-91-3 had an oral LD50 value in the rat of > 2000 mg/kg bw.

#### 5.4.2 Acute Inhalation Toxicity

No studies were located.

#### 5.4.3 Acute Dermal Toxicity

No studies were located.

#### 5.4.4 Irritation/Sensitization

Results of irritation /sensitization tests performed with the category members are shown in Table 8.

**Table 8. Irritation/Sensitization of Stilbene Intermediates Category**

Chemical	Skin Irritation (not required)	Eye Irritation (not required)	Sensitization (not required)
<b>81-11-8</b>	Not irritating	None to moderate	No data
<b>7336-20-1</b>	Not irritating	None to moderate	No data
<b>3709-43-1</b>	Not irritating	Not irritating	No data
78447-91-3	Not irritating	Not irritating	No data

Bolded type represents category members; regular type represents the surrogate with supporting data.

#### *Irritation*

OECD Test Guideline 404 and 405 studies performed in rabbits indicate that CAS Nos. 81-11-8, 7336-20-1, 78447-91-3 and a formulated product containing 60% CAS No. 3709-43-1 and 35% water are not irritating to skin or eyes (Krotlinger, 1993a,b; Ciba-Geigy Limited, 1986a,b; Bayer

AG 1989d). Additional studies that were not available for review but are cited in European IUCLID documents indicate moderate eye toxicity for CAS No. 81-11-8 and 7336-20-1 (RTECS, no date listed).

#### *Sensitization*

No studies were located.

### **5.4.5 Repeated-Dose Toxicity**

Repeated dose toxicity studies that have been performed with the category members are summarized in Table 9 below.

The repeated dose toxicity of CAS No. 7336-20-1 has been tested in rats and mice by the NTP (USDHHS, 1992). This study was used to fill the repeated dose toxicity endpoint for CAS No. 81-11-8 at SIAM 4. Dietary doses administered to rats and mice in a 13 week study were 6250, 12500, 25000, 50000 and 100000 ppm. The 13-week NOAELs in the rat and mouse were 25000 (approximately 1529 and 1715 mg/kg/day for males and females, respectively) and 12500 ppm (approximately 1738 and 2081 mg/kg/day for males and females, respectively). Mean body weight gain was decreased in male rats and female mice receiving 50,000 or 100000 ppm, in male mice receiving doses  $\geq$  25000 ppm, and in female rats receiving 100000 ppm. Clinical findings in rats given 50000 or 100000 ppm and mice given 100000 ppm included diarrhea, emaciation, and hyperemia of the perineum. Histopathologic lesions in rats ingesting 100000 ppm were bone marrow hypercellularity and chronic inflammation of the anus and rectum. Similar changes in the anus and /or rectum were observed in mice ingesting concentrations  $\geq$  50000 ppm. Male mice receiving 100000 ppm had atrophy of the thymus and females receiving this dose exhibited atrophy of the uterus and ovaries.

In 2 year studies, 12500 and 25000 ppm CAS No. 7336-20-1 were tested in rats and 6250 and 12500 ppm 7336-20-1 were tested in mice. These studies were also reviewed for CAS No. 81-11-8 at SIAM 4. In the 2 year study, the NOAELs in the rat and mouse were 12500 and 6250 ppm, respectively (approximately 765 and 1400 mg/kg/day, respectively). At study termination,

**Table 9. Repeated Dose Toxicity for Stilbene Intermediates Category**

Category Member	Species/ Exposure	Dose <sup>a</sup>	Gross Changes	Histopathological Changes
<b>81-11-8</b>	Data for 7336-20-1 used at SIAM 4			
<b>7336-20-1</b> (USDHHS, 1992)	F344 rat, oral feed, 2 years, 12500 and 25000 ppm	12500 <sup>b</sup> 25000 <sup>c</sup>	None ↓ bw, males	None related to treatment
(USDHHS, 1992)	F344 rat, oral feed, 13 weeks, 6250, 12500, 25000, 50000, 100000 ppm	6250 12500 25000 <sup>b</sup> 50000 <sup>c</sup>  100000	None None None ↓ bw, diarrhea, emaciation, red anus ↓ bw, food, emaciation, red anus, diarrhea	None None None None  Inflammation in rectum and anus, hypercellularity of bone marrow
(USDHHS, 1992)	B6C3F1 mouse, oral feed, 2 years, 6250 and 12500 ppm	6250 <sup>b</sup> 12500 <sup>c</sup>	None ↓ bw (females)	None None
(USDHHS, 1992)	B6C3F1 mouse, oral feed, 13 weeks, 6250, 12500, 25000, 50000, 100000 ppm	6250 12500 <sup>b</sup> 25000 <sup>c</sup>  50000  100000	None None ↓ bw (males)  ↓ bw, changes in organ weights Increased mortality (males), ↓ bw, ↑ feed, diarrhea, emaciation, lethargy, tremors	None None Inflammation in rectum and anus Inflammation in rectum and anus Inflammation in rectum and anus, atrophy of thymus (males), uterus and ovaries
<b>3709-43-1</b>	No data			
78447-91-3	No data			

Bolded type represents category members; regular type represents the surrogate with supporting data.

<sup>a</sup> Dose is in ppm unless listed otherwise; <sup>b</sup> NOAEL; <sup>c</sup> LOAEL

mean body weights were marginally decreased for male rats receiving 25000 ppm and female mice receiving 12500 ppm. Feed consumption and survival were not affected by treatment and no abnormal clinical findings were noted in treated animals. There was no effect of treatment on the incidences of neoplasms in rats and mice.

#### 5.4.6 Genetic Toxicity: Gene Mutations and Chromosome Aberrations

Genetic toxicity tests that have been performed with the category members are listed in Table 10.

**Table 10. Genotoxicity of Stilbene Intermediates Category**

Category Member	Ames Test (w/wout activation)	Cytogenicity (CHO cells)
<b>81-11-8</b>	Negative (1)	Negative (2)
<b>7336-20-1</b>	Negative (3)	Negative (3)
<b>3709-43-1</b>	No data	No data
78447-91-3	Negative (4) Ambig (E. coli) (5)	No data

Bolded type represents category members; regular type represents the surrogate with supporting data.

(1) Zeiger et al. 1987; (2) Loveday et al., 1990; (3) USDHHS, 1992; (4) Herbold, 1992; (5) Norpoth, 1977a,b

#### *Mutations*

Up to 5000 micrograms/plate CAS No. 81-11-8, 7336-20-1 and 78447-91-3 tested negative for mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 in the presence and absence of metabolic activation (Zeiger et al., 1987, Herbold, 1992; USDHHS, 1992). CAS No. 81-11-8 tested negative and CAS No. 78447-91-3 had an ambiguous result in *E. coli* WP2uvrA (Norpoth, 1977a,b). The aforementioned studies for CAS No. 81-11-8 and 7336-20-1 were reviewed at SIAM 4.

#### *Chromosome Aberrations*

CAS No. 81-11-8 tested negative for chromosome aberrations and sister chromatid exchanges in Chinese Hamster Ovary (CHO) cells at concentrations up to approximately 1000 micrograms/ml (Loveday et al., 1990). These studies were not described in the dossier accepted at SIAM 4. The study that was reviewed at SIAM 4 was a negative CHO study for CAS No. 7336-20-1 (USDHHS, 1992).

#### **5.4.7 Carcinogenicity**

In a 2 year feeding study, concentrations of CAS No. 7336-20-1 of up to 25,000 ppm (approximately 1000 mg/kg/day for the majority of the study) and 12,500 ppm (approximately 500 mg/kg/day for the majority of the study) had no effect on the incidences of neoplasms at any

site in rats and mice, respectively (USDHHS, 1992). This study was reviewed at SIAM 4 (for CAS No. 81-11-8).

#### **5.4.8 Reproductive Toxicity**

CAS No. 81-11-8 was tested in an OECD Preliminary Reproductive Screen at doses of 40, 200 and 1000 mg/kg/day. This study was reviewed at SIAM 4. The test material had no effect on clinical signs, body weight changes, food consumption or necropsy findings in male or female Sprague-Dawley rats. Testicular and epididymal weights and histopathology in treated animals were similar to controls. There was no effect of treatment on any reproductive or offspring parameter measured (MHW, Japan, 1994).

In a 13-week repeated dose, dietary study, all female mice receiving 100000 ppm CAS No. 7336-20-1 exhibited endometrial atrophy of the uterus and atrophy of the ovaries (USDHHS, 1992). This was not observed at lower doses in mice and was not observed in female rats receiving up to 100000 ppm.

#### **5.4.9 Developmental Toxicity**

In the OECD Preliminary Reproductive Screen with CAS No. 81-11-8 that was reviewed at SIAM 4, there was no effect of treatment with up to 1000 mg/kg/day from 14 days prior to mating to lactation day 3 on number of offspring (total or live), sex ratio, live birth index, viability index, or body weight. No abnormal findings attributable to the test substance were noted in external examination, clinical signs or necropsy of the offspring (MHW, Japan, 1994).

#### **5.4.10 Other Effects**

Studies conducted in cohorts of male workers employed in a factory manufacturing CAS No. 81-11-8 have suggested the possibility of a testosterone-lowering effect of CAS No. 81-11-8 (Grajewski et al., 1996; Quinn et al., 1990; Whelan et al., 1996). When interviewed, there were reports of loss of libido and potency. Since the studies were conducted on a small scale and

there was no clear relationship between testosterone level and reported symptoms of low/libido potency, the reliability of the studies is questionable. None of these studies were reviewed for SIAM 4.

CAS No. 81-11-8 has been tested for uterotrophism in weanling female rats (Smith and Quinn, 1992). Groups of 5-25 animals were injected intraperitoneally with 0.1, 1, 10, 30, 100, 300 or 1000 mg/kg test material (or 10 ml/kg saline vehicle) or administered the same doses by oral gavage using a fixed volume of 10 or 30 ml/kg. Uterus weights of animals given 300 or 1000 mg/kg material i.p. or 1000 or 3000 mg/kg orally were significantly greater than control, suggesting that the material possesses uterotrophic activity. However, the variability of the control uterine weights in the i.p. study questions the validity of the results.

The possibility of an uterotrophic effect of CAS No. 7336-20-1 also was tested in female rats. Once daily subcutaneous injection of 10 or 30 mg/animal (approx. 230 or 750 mg/kg bw) for 3 days had no effect on uterus weight (Hostetler et al., 1996). In rats and mice administered up to 100000 ppm CAS No. 7336-20-1 in the diet for 13 weeks and up to 12500 ppm (mice) and 25000 ppm (rats) for 2 years, there is no evidence of uterotrophism (USDHHS, 1992). Conversely, uterine weights of mice administered 100000 ppm for 13 weeks were less than control, in keeping with the observation of reduced body weight. In vitro studies on relative binding affinity of the synthetic estrogen diethylstilbestrol (DES) and CAS No. 7336-20-1 to the human estrogen receptor in a breast cell line were positive and negative (respectively), indicating that CAS No. 7336-20-1 does not possess estrogenic activity (unlike DES) (Hostetler et al., 1996).

In conclusion, although some reports suggest that CAS No. 81-11-8 causes uterotrophism, more reliable studies with the sodium salt of the molecule (CAS No. 7336-20-1) indicate that this material does not possess estrogenic activity.

#### **5.4.11 Test Plan for Mammalian Toxicity**

Adequate oral acute toxicity tests performed on all category members indicate that members of this category are of low acute toxicity. Although not required, skin and eye irritation studies have been performed on the majority of the category members. These studies show that the materials are generally not irritating to skin and are slightly to moderately irritating to eyes. Repeated dose toxicity studies performed CAS No. 7336-20-1 indicate 13-week dietary NOAELs of > 1500 mg/kg/day in rats and mice. No additional acute or repeated dose toxicity testing is planned.

Ames and mammalian cell mutation tests performed on the category members were all negative, with the exception of an ambiguous result with CAS No. 78447-91-3 in *E. coli*. In vitro cytogenicity studies performed on CAS Nos. 81-11-8 and 7336-20-1 were negative. These data, along with the negative result of a long term toxicity/carcinogenicity tests performed on CAS No. 7336-20-1 indicate a low potential for these materials for genetic toxicity. No additional genetic toxicity testing is planned.

A reproductive toxicity test performed on CAS Nos. 81-11-8 showed no effect of treatment with 1000 mg/kg on fertility of rats. No embryotoxic or teratogenic effects were reported in rabbits treated with up to 1000 mg/kg CAS Nos. 81-11-8 or 7336-20-1. In conclusion, results of reproductive/developmental toxicity testing indicate that these materials are not selectively toxic to the reproductive system or developing fetus.

## **6. Summary**

### Physical properties

Adequate measured information are available for melting points, which are high (>200-300 degrees C) and consistent with the category members being organic salts. As metal organic salts or inner salts, the category members exist in ionic form and not as discrete molecules. Therefore, these materials do not boil without first undergoing decomposition at or above their melting points. Nor do they exert significant vapor pressure, other than that attributable to volatile impurities or additives that may be present, such as water. Sufficient estimated data predict that log Pow values of the category members will be low or negative (Range 0.2 to –

3.00). Water solubilities determined for three category members or surrogates are adequate to predict the water solubility of the remaining member for which data are not available. No further testing is therefore planned for physical properties

#### Environmental fate properties

Members of this category are not readily biodegradable. Since category members do not volatilize, atmospheric photodegradation is not an important degradative pathway, and conducting atmospheric photodegradation modeling or studies would not be useful. Available data indicate that these materials undergo photodegradation in the hydrosphere as well as slow biodegradation. Level III fugacity modeling indicates that when released to the environment, category members will partition predominately to soil and water, and negligibly to the atmosphere. Further environmental fate testing is not planned.

#### Aquatic toxicity

Adequate fish and invertebrate toxicity tests have been performed on the majority of the category members. LC/EC50 values in fish and *Daphnia magna* are > 100 mg/l. Algae toxicity studies performed with CAS Nos. 81-11-8 and 7336-20-1 indicate EC50 values  $\geq$  76 mg/l. The results indicate a low potential of toxicity towards aquatic species. Results of *Daphnia* and algae toxicity studies with CAS Nos. 81-11-8 and 7336-20-1 are expected to be predictive of those for CAS No. 3709-43-1. No additional aquatic testing is necessary.

#### Mammalian toxicity

Adequate tests have been performed for the acute toxicity, repeated dose toxicity, and genetic toxicity endpoints. All reproductive/developmental toxicity tests that have been conducted indicate that these materials are not reproductive or developmental toxicants.

## **7. References**

Bayer AG (no year listed), as cited in the SIDS dossier on CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

Bayer AG (no year listed), as cited in an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

Bayer AG (no year listed), as cited in an IUCLID document for CAS No. 78447-91-3 published on 06.11.2003 and updated on 08.09.2003.

Bayer AG (1986). Unpublished data from a laboratory notebook, dated 19.06.1986.

Bayer AG (1989a). Final report: Water solubility, CAS No 78447-91-3. Study number A 88/0068/01. March 14, 1989 (unpublished study).

Bayer AG (1989b). Institut fuer Umweltanalyse and Bewartungen. Study E-NR 89160246 (unpublished study).

Bayer AG (1989c). Study of the acute oral toxicity in male and female Wistar rat. Report No. 18306, dated 28.8.1989 (unpublished study).

Bayer AG (1989d). Report No. 17819, dated 14.3.1989 (unpublished study).

Bayer AG (1991a). Berechnung UWS-Produktsicherheit [product safety sheet], as cited in an IUCLID Dataset for CAS No. 81-11-8 that was accepted at SIAM 4 and posted on the OECD website.

Bayer AG (1991b). Berechnung UWS-Produktsicherheit [product safety sheet], as cited in an IUCLID Dataset for CAS No. 78447-91-3 published by Bayer AG on 6.11.2003 and updated on 08.09.1993.

Ciba-Geigy (1986). Biodegradative elimination, acute fish toxicity and bacterial sludge toxicity. Fat No. 90159A. Division of Dyes and Chemicals Research and Development, Series 367, Run Number 3938 (unpublished study).

Ciba-Geigy (1989a). Biological breakdown of Dinitrostilbendisulfonic acid. Test number 72A/89 (unpublished study).

Ciba-Geigy (1989b). Oxygen Consumption Test with Industrial Sludge. Study Number 72A/89 (unpublished).

Ciba-Geigy AG (1986). Unpublished data, April 1986.

Ciba-Geigy AG (2005). Unpublished data.

Ciba-Geigy Limited (1986a). Final Report. FAT 90159/A. Acute dermal irritation/corrosion study in the rabbit. Experimental Toxicology GU 2.1, Project Number 851038, dated February 27, 1986.

Ciba-Geigy Limited (1986b). Final Report. FAT 90159/A. Acute eye irritation/corrosion study in the rabbit. Experimental Toxicology GU 2.1, Project Number 851037, dated February 26, 1986.

EA, Japan (1994). Investigation of the ecotoxicological effects of OECD high production volume chemicals. Office of Health Studies, Environmental Health Department, Environmental Agency, Japan (HPV/SIDS test), as cited in a SIDS dossier for CAS No. 81-11-8, Sponsor Country: Japan, dated March 2002, and a SIAR for CAS No. 81-118 presented at SIAM 4, May 20-22, 1996.

ETAD. 1992. Ecological properties of aromatic aminosulfonic acids. Internal Research Project 3018 (unpublished study). May, 1992.

Fraunhofer-Institut fuer Umweltchemie and Oekotoxikologie (FGH)(1989). Fish, Acute Toxicity (Fische, Akute Toxizitaet) (unpublished study).

Grajewski B. et al. (1996). Evaluation of reproductive function among men occupationally exposed to a stilbene derivative. I. Hormone and physical status. *Am. J. Ind. Med.* **29**, 49-57.

Herbold BA (1992). Dinitrostilbenedisulfonic acid K Salmonella/Microsome test. Bayer AG Study No. T 8039628, dated 23.1.1992 (unpublished).

Hostetler KA et al. (1996). *J. Toxicol. Environ. Health* **48**, 141-149.

Huang-Minlon (1948). *J. Am. Chem. Soc.* **70**, 2802-2804.

IUCLID Dataset for CAS No. 3709-43-1 published by the European Chemicals Bureau on 11-Feb-2000.

Klimisch HJ, Andreae M and Tillmann U (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Reg Tox Pharm* 25:1-5.

Kramer JB (1996). Photodegradation of fluorescent whitening agents in sunlit natural waters. *Env. Sci. and Technol.* Dissertation submitted to the Swiss Federal Institute of Technology Zurich, 123 pp.

Krotlinger F (1993a). 4,4'-Diaminostilben-2,2'-disulfonsaure. Study for skin and eye irritation/corrosion in rabbits. Bayer AG, Fachbereich Toxikologie Study No. T6050056, dated 19.4.1993 (unpublished study).

Krotlinger F (1993b). 4,4'-Diaminostilben-2,2'-disulfonsaure Di-Na-Salt ft./Flavonsaure S. Study for skin and eye irritation/corrosion in rabbits. Bayer AG, Fachbereich Toxikologie Study No. T6041047, dated 18.5.1992 (unpublished study).

Loeser E (1979). Bayer AG data, short report, 3. 5. 1979.

Loveday KS, Anderson BE, Resnick MA and Zeiger E (1990). Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. Results with 46 chemicals. *Environ Mol Mutagen* 16:272-303.

Lyman WJ, Reehl WF, Rosenblatt DH (1981). Handbook of Chemical Property Estimation Method. McGraw Hill Book Co.

MHW, Japan (1994). Unpublished report on preliminary reproductive toxicity test of 4,4'-diamino-2,2'-stilbenedisulfonic acid (HPV/SDS test conducted by MHW, Japan).

MITI, Japan (1994). Unpublished data, as cited in a SIDS dossier for CAS No. 81-11-8, Sponsor Country:Japan, dated March 2002, and a SIAR for CAS No. 81-118 presented at SIAM 4, May 20-22, 1996.

Norpoth K (1977a). Report of the examination of eleven different compounds for their mutagenic potency in the oxigenase-enterobacteriaceae test system, Report for Bayer AG, dated 22.7.1977, as cited in an IUCLID Dataset for CAS No. 78447-91-3 published by Bayer AG on 6.11.2003 and updated on 08.09.1993.

Norpoth K (1977b). Report of the examination of eleven different compounds for their mutagenic potency in the oxigenase-enterobacteriaceae test system, Report for Bayer AG, dated 22.7.1977.

Quinn MM et al. (1990). Investigation of reports of sexual dysfunction among male chemical workers manufacturing stilbene derivatives. Am. J. Ind. Med. **18**, 55-68.

RTECS (no date listed), NIOSH USA, WJ 6603000, as cited in an IUCLID Dataset for CAS No. 81-11-8 published by the European Chemicals Bureau on 19-Feb-2000.

RTECS (no date listed), NIOSH USA, WJ 6603000, as cited in an IUCLID document for CAS No. 7336-20-1 published by the European Chemicals Bureau on 19-FEB-2000.

Smith ER and Quinn MM (1992). Uterotropic action in rat of amsonic acid and three of its synthetic precursors. J. Toxicol. Environ. Health. **36**(1), 13-25.

U.S. Dept of Health and Human Services (USDHHS)(1992). Toxicology and carcinogenesis studies of 4,4'-diamino-2,2'stilbene disulfonic acid, disodium salt (CAS No. 7336-20-1) in F344/N rats and B6C3F1 mice. Technical Report Series 412, NIH publication No. 92-3143, dated August, 1992.

Whelan EA et al. (1996). Evaluation of reproductive function among men occupationally exposed to a stilbene derivative. II. Perceived libido and potency. *Am. J. Ind. Med.* **29**, 59-65.

Zaitseva NV, Kulikov AL (1980). *Gig. Sanit.* 45, 73-76, as cited in a SIDS dossier for CAS No. 81-11-8, Sponsor Country:Japan, dated March 2002, and a SIAR for CAS No. 81-118 presented at SIAM 4, May 20-22, 1996.

Zeiger E. et al. (1987). *Environ. Mutagen.* **9**, Suppl. 9, 1-110.

## APPENDIX

### STILBENE-BASED FLUORESCENT WHITENING AGENTS MANUFACTURED FROM STILBENE INTERMEDIATES (CATEGORY MEMBERS)

<b>CAS No.</b>	<b>Chemical Name</b>	<b>Common or Trade Name</b>
<b>4404-43-7</b>	4,4'-Bis(6-anilino-1,4-bis(2-hydroxyethyl)amino)-1,3,5-triazin-2-yl)amino]stilbene-2,2-disulfonic acid	C.I. Fluorescent Brightener 28/113, Free acid
<b>4193-55-9</b>	Disodium 4,4'-bis(6-anilino-1,4-bis(2-hydroxyethyl)amino)-1,3,5-triazin-2-yl)amino]stilbene-2,2-disulphonate	C.I. Fluorescent Brightener 28/113, Disodium salt
70942-01-7	potassium sodium 4,4'-bis[6-anilino-4-[bis(2-hydroxyethyl)amino]-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate	C.I. Fluorescent Brightener 28/113
<b>13863-31-5</b>	2,2'-Stilbenedisulfonic acid, 4,4'-bis((4-anilino-6-((2-hydroxyethyl) methyl amino) -s-triazin-2-yl)amino)-, disodium salt	Tinopal 5BM
<b>16090-02-1</b>	disodium 4,4'-bis[(4-anilino-6-morpholino-1,3,5-triazin-2-yl) amino]stilbene-2,2'-disulphonate	C.I. Fluorescent Brightener 260, Disodium salt C.I. Fluorescent Brightener 339
<b>16470-24-9</b>	tetrasodium 4,4'-bis[[4-[bis(2-hydroxy ethyl)amino]-6-(4-sulphonatoanilino)-1,3,5-triazin-2-yl]amino]stilbene-2,2'-disulphonate]	C.I. Fluorescent Brightener 220, Tetrasodium salt
<b>67786-25-8</b>	tetrasodium 4,4'-bis[[4-[bis(2-hydroxy propyl)amino]-6-[(4-sulphonato phenyl)amino]-1,3,5-triazin-2-yl]amino]-stilbene-2,2'-disulphonate	C.I. Fluorescent Brightener 263, Tetrasodium salt
<b>29637-52-3</b>	2,2'-Stilbenedisulfonic acid, 4,4'-bis[[4-[(2-carbamoyl ethyl)(2-hydroxyl ethyl)amino]-6-(p-sulfoanilino)-s-triazin-2-yl]amino]-, tetrasodium salt	C.I. Fluorescent Brightener 235, Tetrasodium salt

**ETAD North America Stilbene Fluorescent Brighteners Intermediates**

**HPV Submission**

**December 21, 2005**

**201-16114A1**

**1. Test Plan and Category Justification (29 pp.)**

H:\SWAs\Test Plan  
Stilbene Intermediate

**2. CAS 81-11-8 (Category Member). IUCLID Data Set (60 pp.)**

H:\SWAs\Interded  
iuclid81118Aug29200

**3. CAS 7336-20-1 (Category Member). IUCLID Data Set (51 pp.)**

H:\SWAs\Intermed  
IUCLID7336201Dec14

**4. CAS 3709-43-1 (Category Member). IUCLID Data Set (23 pp.)**

H:\SWAs\Intermed  
IUCLID3709431Aug 2

**5. CAS 78447-91-3 (Surrogate with supporting data). IUCLID Data Set (24 pp.)**

H:\SWAs\Intermed  
IUCLID78447913Jun:

06 JAN -9 AM 10:43

RECEIVED  
PPF/CMC