

Benzotriazoles
Category Justification and Testing Rationale

CAS Nos. 95-14-7, 29385-43-1 and 64665-57-2

Benzotriazoles Coalition
Synthetic Organic Chemical Manufacturers Association

December, 2001

List of Member Companies in the Benzotriazoles Coalition

The Benzotriazoles Coalition of the Synthetic Organic Chemical Manufacturers Association (SOCMA) includes the following member companies: Bayer Corporation and PMC Specialties Group, Inc.

Executive Summary

The Benzotriazoles Coalition, and its member companies, hereby submit for review and public comment their test plan for the Benzotriazoles category of chemicals under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program.

As discussed in the report that follows, Benzotriazole chemicals are used primarily as chemical intermediates, copper corrosion inhibitors, used in ultra-violet stabilization applications, photographic applications, and as ingredients of de-icing fluids for airplanes.

Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program," in which use of chemical categories is encouraged, the following closely related chemicals constitute a chemical category:

1-H-benzotriazole	(95-14-7)
1-H-benzotriazole, 4 (or 5) methyl	(29385-43-1)
1-H-benzotriazole, 4 (or 5) methyl, sodium salt	(64665-57-2)

Benzotriazole is the parent chemical in this category with the others having a methyl substituent at position 4 or 5. The Sodium salt will dissociate to the methyl benzotriazole in aqueous solution.

Existing data for members of this category indicate that they are of low concern for aquatic and mammalian toxicity, will partition to soil and water and are readily biodegradable. We conclude that there is sufficient data on the members of this, except for the endpoint of Developmental Toxicity. Therefore, to meet requirements of the HPV Chemical Challenge Program, a Teratogenicity Study (OECD 414) on benzotriazole is proposed.

The Benzotriazoles Coalition would like to carry out the work proposed in the test plan, but assistance will be needed by the Agency to achieve these objectives. Extraordinary competition from overseas has placed US companies in a competitive disadvantage in the marketplace.

The Coalition has repeatedly approached importers and requested that they join our efforts, but they have expressed no intent of doing so. After much consideration, the Coalition has reasoned that the most fair, practical way to move forward and fulfill its entire commitment under the HPV Challenge, is through regulatory action, such as a rulemaking under TSCA Section 4.

Introduction

A provision for the use of categories to reduce testing needs is included under EPA's HPV Program. Specifically, categories may be formed based on structural similarity, through analogy, or through a combination of category and analogy for use with single chemicals. The benefits of using a category approach are numerous and include: accelerated release of hazard information to the public; reduction in the number of animals used for testing; and an economic savings as a result of a reduced testing program.

The Benzotriazoles that form this category based on structural similarity, arranged in order of increasing molecular weight, are:

1-H-benzotriazole	(95-14-7)
1-H-benzotriazole, methyl	(29385-43-1)
1-H-benzotriazole, methyl, sodium salt	(64665-57-2)

Development of the Benzotriazoles category

EPA has described a stepwise process for developing categories. These steps include:

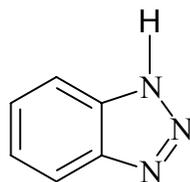
- Grouping a series of like chemicals, including the definition of criteria for the group.
- Gathering data on physicochemical properties, environmental fate and effects, and health effects for each member of the category.
- Evaluating the data for adequacy.
- Constructing a matrix of available and unavailable data.
- Determining whether there is a correlation among category members and data gathered.

Definition of the Benzotriazoles category

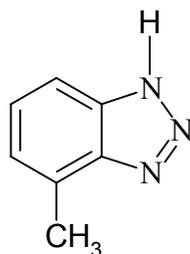
As defined by EPA under the HPV Program, a chemical category is “a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity.” The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing.

Structural Similarity.

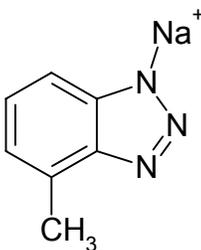
A key factor supporting the classification of these chemicals as a category is their structural similarity. The chemicals within the Benzotriazoles category are defined as illustrated below.



1-H-Benzotriazole
(CAS# 95-14-7)



1-H-Benzotriazole, 4 (or 5)-methyl
(CAS# 29385-43-1)



1-H-Benzotriazole, 4 (or 5)-methyl, sodium salt
(CAS# 64665-57-2)

Figure 1. Chemical Structures

Matrix of SIDS Endpoints

In order to construct a matrix of SIDS endpoints for the members of the Benzotriazoles category, the data on physicochemical properties, environmental fate, ecotoxicity and health effects for each member of the category was collected and evaluated for adequacy. The results of these activities are presented in the tables and text below, as well as the attached IUCLID documents, providing a matrix of available data.

Correlation of Physicochemical Properties

The physicochemical properties of the members of the Benzotriazoles category are presented in **Table 1**. The Benzotriazoles are non-flammable, colorless or pale colored solids with low vapor pressure and low partition coefficients. The similarities in the other physicochemical properties of these chemicals are explained by similarities in their chemical structure, and provide justification of this group of chemicals as a category within the HPV Challenge Program.

All members of the category have measured or calculated data on physicochemical properties. There are no data gaps; no additional testing is needed to meet requirements of the HPV Chemical Challenge Program.

Correlation of Environmental Fate

The HPV Challenge Program requires that hydrolysis, photodegradation, biodegradation and environmental transport information be presented for each chemical or bridged to each member of a category. The EPIWIN modeling Program was used to calculate the photodegradation and fugacity for each chemical in the category. The members of this category have photodegradation half-lives of 3-10 days.

Adequate biodegradation data exist for all chemicals in this category. All are categorized as “readily biodegradable” with degradation rates $\geq 70\%$ after 28 days.

Partitioning to soil and water fractions (vs. air and sediment) is expected according to Fugacity Level III calculations. Default “input values” of 1000 kg/hr were used for the modeling.

Hydrolysis data on benzotriazole demonstrates that it is a weak acid and somewhat soluble in water. The pKa for this reaction is 8.2 (Boyer, 1961). The reaction suggests that benzotriazole will be less soluble in pH <7 (such as rainwater) and more soluble in solutions >7 (such as seawater) than in distilled water. Benzotriazole reacts with solutions of alkali metal hydroxides producing soluble alkali salts (NTIS PB-266 366, 1977). Sodium tolyltriazole is sold as aqueous solution; it is stable in water, it does not hydrolyze.

Data is available or bridged for all Environmental Fate endpoints for this category (See **Table 2**). No additional testing is needed to meet requirements of the HPV Chemical Challenge Program.

Correlation of Ecotoxicity

The HPV Challenge Program requires that an acute aquatic toxicity test in fish, invertebrates, and algae be performed or bridged to each member of a category. Existing data indicate that the members of the Benzo and tolyl triazoles have low toxicity to fish ($LC_{50} = 21 - >175$ mg/l), *Daphnia* ($EC_{50} = 35-280$ mg/l), and algae ($EC_{50} = 26-231$ mg/l).

No additional aquatic toxicity tests are proposed for this category as it has been adequately characterized for purposes of the HPV Chemical Challenge Program.

Correlation of Health Effects

Acute Mammalian Toxicity

Acute oral, dermal and inhalation toxicity data for the category is summarized in **Table 4**. All chemicals have test data, all show moderate toxicity following oral administration and low toxicity following dermal administration.

Dose response studies by the oral route, conducted by Sherwin-Williams Company in 1976, show that benzotriazole is slightly more toxic than tolyltriazole and since the slopes of both dose response curves are similar it was predicted that mechanism of action is similar for both chemicals (NTIS PB-266 366, 1977). Investigations of dermal toxicity at 2000 mg/kg in rabbits resulted in essentially identical results for the benzo- and tolyl-triazole (NTIS PB-266 366, 1977).

The similarity in the order of toxicity for these chemicals is consistent with their similar chemical structure and physicochemical properties and supports the scientific justification of these chemicals as a category within the HPV Challenge Program.

The HPV Challenge Program requires that either an acute test be performed or bridged to each member of a category. Adequate acute oral and dermal toxicity tests exist for all members of the category and inhalation testing has been conducted on two of the chemicals. The acute toxicity of the category has been adequately evaluated with respect to acute toxicity endpoints, and no additional acute toxicity testing is proposed for purposes of the HPV Challenge Program.

Repeat Dose Toxicity

A summary of the repeat dose toxicity data for the Benzotriazoles category is presented in **Table 4**.

Repeat dose studies (28 d or 18-24 month studies) have been conducted with two of the Benzotriazoles and demonstrate an apparent reduction in toxicity with increasing molecular weight. The repeat dose toxicity of the sodium salt (CAS#64665-57-2) is expected to be similar to the repeat dose toxicity of tolyl triazole (29385-43-1), since the sodium salt will dissociate to the methyl benzotriazole in aqueous solution.

By bridging existing data to the one chemical where no data was found, the repeat dose aspect of the category has been evaluated adequately, and no additional testing is proposed to meet requirements of the HPV Challenge Program.

Mutagenicity

A summary of the mutagenicity information for the Benzotriazole category is presented in **Table 4**. The weight of evidence for the members of this category indicates these chemicals are not mutagenic or clastogenic. By bridging existing data to the sodium salt, which will dissociate to the methyl benzotriazole in aqueous solution, the mutagenicity aspect of the category has been evaluated adequately, and no additional testing is proposed to meet requirements of the HPV Challenge Program.

Reproductive and Developmental Toxicity.

Consideration was given to effects on reproductive organs in repeated exposure studies to determine whether reproductive toxicity studies were needed. The 78 week oral study of 1H-benzotriazole in Fischer 344 rats did not find any evidence of pathology in the reproductive organs. The 104 week oral study of 1H-benzotriazole in B6C3F1 mice did not find any evidence of pathology in the reproductive organs. The reproductive organs examined were: prostate/testis/epididymis of males and uterus/ovaries of females. These chemicals are covered by the chronic data discussed to meet requirements of the HPV Challenge Program and no further testing for reproductive toxicity is proposed.

No data was found on the Developmental toxicity of benzo- and tolyl- triazole. Therefore, to meet requirements of the HPV Chemical Challenge Program, a Teratogenicity Study (OECD 414) on benzotriazole is proposed. Benzotriazole was chosen because it is slightly more toxic than tolyltriazole and will provide the worst case scenario.

Conclusion.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for all available data, published and unpublished. It has performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to fill certain data gaps. The use of animals in this proposed test plan has been minimized.

Based upon the data provided in this report and the attached IUCLID documents, the physicochemical and toxicological properties of the Benzotriazoles category members are similar and follow a regular pattern as a result of that structural similarity. Therefore, the EPA definition of a chemical category has been met.

Summary Endpoint Matrix / Test Plan

All endpoints of the category has been adequately characterized, except for Developmental Toxicity, therefore to fulfill requirements of the HPV Chemical Challenge Program, a Teratogenicity Study (OECD 414) on benzotriazole is proposed.

The summary endpoint matrix is included as **Table 5** of this document.

Background Information: Manufacturing and Commercial Applications

Manufacturing

Triazoles (Benzo and Toly1) are produced by the reaction of unsubstituted and substituted aromatic amines with other nitrogen donors. The formed product(s) are further purified before distribution to the market place.

Commercial Applications

Benzotriazoles are used primarily as chemical intermediates, copper corrosion inhibitors, in ultra-violet stabilization applications, photographic applications, and as ingredients of de-icing fluids for airplanes.

Shipping/Distribution

Triazoles (Benzo and Toly1) are shipped throughout the world from Manufacturing plants.

Worker/Consumer Exposure

The Benzotriazoles industry has a long safety record in handling these chemicals by both the manufacturers and users. Exposure of workers handling the Benzotriazole materials is likely to be highest in the area of packaging. These materials are powders or liquids of very low vapor pressure, thus during the packaging process there is a low potential for inhalation exposure except as nuisance dust. Depending on handling procedures and filling equipment, dermal contact to the liquid is also possible.

**Table 1. Matrix of Available and Adequate Data on the Benzotriazoles Category
Physico-chemical Properties**

Chemical	1-H-Benzotriazole	1-H-Benzotriazole, 4 (or 5)-methyl	1-H-Benzotriazole, 4 (or 5)-methyl, sodium salt
CAS#	95-14-7	29385-43-1	64665-57-2
Molecular Weight:	119.1	133.2	155
Physical State	Yellow solid or powder	Beige granules	Clear yellow to amber liquid
MeltingPoint	100°C	76-87°C	-5 to -10°C
Boiling Point	204°C @ 20 hPa	160°C @ 2.67hPa	~ 106°C @ 1013 hPa
Relative Density	1.19 g/cm ³ @ 100°C	1.13 g/cm ³ @ 100°C	1.18 g/cm ³ @ 20°C
Vapor Pressure	0.000797 hPa @ 25°C (EPIWIN)	0.00001 hPa @ 25°C 0.000797 hPa @ 25°C (EPIWIN)	.0533 hPa @ 20°C < 0.00001 hPa @ 25°C (EPIWIN)
PartitionCoefficient (logP_{ow})	1.34	1.71	0.658
Water Solubility	1-5 mg/l @24°C	<0.1g/l @18°C	55 vol % @20°C

EPIWIN = EPIWIN modeling Program. Meylan, W. and Howard, P. (1999)

**Table 2. Matrix of Available and Adequate Data on the Benzotriazoles category
Environmental Fate**

Endpoint	1-H-Benzotriazole 95-14-7	1-H-Benzotriazole, 4 (or 5)-methyl 29385-43-1	1-H-Benzotriazole, 4 (or 5)-methyl, sodium salt 64665-57-2
Photodegradation T _{1/2} =	10.7 days (AOP)	3.9 days (AOP)	3.1 days (AOP)
Hydrolysis	pKa = 8.2	No data found	Stable. Sodium tolyltriazole dissolves in water, it does not hydrolyze. Sold as aqueous solution
Biodegradation	90% after 28 D	77% after 28 D	70% after 28 D
Fugacity Level III			
Air (%)	4.6	2.8	<0.001
Water (%)	42.3	39.3	43.5
Soil (%)	53.1	57.8	56.4
Sediment (%)	0.0869	0.0934	0.0754

AOP = AOP Program, version 1.89. EPIWIN modeling Program. Meylan, W. and Howard, P. (1999)

Table 3. Matrix of Available and Adequate Data on the Benzotriazoles category Ecotoxicity

Endpoint	1-H-Benzotriazole 95-14-7	1-H-Benzotriazole, 4 (or 5)-methyl 29385-43-1	1-H-Benzotriazole, 4 (or 5)-methyl, sodium salt 64665-57-2
Acute Fish Toxicity 96 hr LC50	<i>B. rerio</i> = >100 mg/l <i>S. gairdneri</i> = 39 mg/l	<i>B. rerio</i> = 65 mg/l <i>L. macrochirus</i> = 31 mg/l <i>P. promelas</i> = 25.5 mg/l <i>S. gairdneri</i> = 21.4 mg/l	<i>L. macrochirus</i> = >173 mg/l <i>S. gairdneri</i> = ~ 25 mg/l <i>B. rerio</i> = 122 mg/l
Acute Invertebrate Toxicity 48 hr EC50	<i>D. magna</i> = 91 - 141 mg/l	<i>D. magna</i> = 35.4 mg/l	<i>D. magna</i> LC50 = 280 mg/l
Algal Toxicity 72 hr EC50	<i>S. subspicatus</i> = 231 mg/l (growth) 102 mg/l (biomass)	<i>S. subspicatus</i> = 62 mg/l (growth) 32 mg/l (biomass)	<i>S. capricornutum</i> = 26.2 mg/l (growth) 32 mg/l (biomass) (96 hr)

**Table 4. Matrix of Available and Adequate Data on the Benzotriazoles category
Mammalian Toxicity**

Endpoint	1-H-Benzotriazole 95-14-7	1-H-Benzotriazole, 4 (or 5)-methyl 29385-43-1	1-H-Benzotriazole, 4 (or 5)-methyl, sodium salt 64665-57-2
Acute Toxicity			
Oral LD50	560-909 mg/kg bw (rat)	1470 - 1830 mg/kg bw (rat)	640-1980mg/kg bw (rat) mg/kg bw (rabbit)
Dermal LD50	> 10,000 mg/kg bw (rabbit)	> 4,000 mg/kg bw (rabbit)	> 2,000 mg/kg bw (rabbit)
Inhalation LC50	> 1.5 mg/l (4 hr) (rat)	> 1.73 mg/l (1 hr) (rat)	No data found
Repeated Dose NOAEL=	12,100 ppm (oral - rat -18 mos) 23,500 ppm (oral - mouse -24 mos)	150 mg/kg bw (oral- rat - 29 D)	No data found
Mutagenicity – gene mutation	Ames – positive HGPRT - negative	Ames – negative	No data found
Mutagenicity – chromosome aberration	Micronucleus test (mouse) - negative	DNA Damage and Repair – negative Micronucleus test (mouse) - negative	No data found
Reproductive Toxicity	No pathology of reproductive organs 12,100 ppm (oral - rat -18 mos) 23,500 ppm (oral - mouse -24 mos)	No data found	No data found
Developmental Toxicity NOAEL =	No data found	No data found	No data found

Table 5. Summary of data for the Benzotriazoles category

Endpoint	1-H-Benzotriazole 95-14-7	1-H-Benzotriazole, 4 (or 5)-methyl 29385-43-1	1-H-Benzotriazole, 4 (or 5)-methyl, sodium salt 64665-57-2
Environmental Fate			
Photodegradation	C	C	C
Hydrolysis	A	R	A/R
Biodegradability	A	A	A
Fugacity	C	C	C
Ecotoxicity			
Acute Fish Toxicity	A	A	A
Acute Invertebrate Toxicity	A	A	A
Algal Toxicity	A	A	A
Mammalian Toxicity			
Acute Toxicity	A	A	A
Repeated Dose	A	A	R
Mutagenicity – gene mutation	A	A	R
Mutagenicity – chromosome aberration	A	A	R
Reproductive Toxicity	A	R	R
Developmental Toxicity	T	R	R

Key for symbols in table:

- A = Adequate data available
- R = Endpoint requirement fulfilled using category approach, SAR
- C = Endpoint requirement fulfilled based on calculated data
- T = Testing to be done

References:

- Boyer, JH. 1961. "Monocyclic triazoles and Benzotriazoles" in Heterocyclic Compounds. Vol. 7. R.C. Elderfield, Ed. J. Wiley & Sons, Inc., New York.
- Meylan, W. and Howard, P. (1999) Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.
- NTIS PB-266 366. 1977. Investigation of Selected Potential Environmental Contaminants: Benzotriazoles. Syracuse Research Corporation for Environmental Protection Agency, Washington, D.C. Office of Toxic Substances.