

SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICALS

Phenolic Benzotriazoles Category

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

2-(2'-Hydroxy-5'-octylphenyl) benzotriazole (CASRN 3147-75-9)

2-(2'-Hydroxy-3',5'-di-t-amylphenyl) benzotriazole (CASRN 25973-55-1)

**2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol
(CASRN 70321-86-7)**

The High Production Volume (HPV) Challenge Program¹ was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set^{1,2}) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance^{2,3} and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including

¹ U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

² U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

³ U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

| | |
|---|---|
| <p>Chemical Abstract Registry Number (CASRN)</p> | <p>CASRN 2440-22-4, CASRN 3147-75-9, CASRN 25973-55-1, CASRN 70321-86-7</p> |
| <p>Chemical Abstract Index Name</p> | <p>Phenol, 2-(2H-benzotriazol-2-yl)-4-methyl-, Phenol, 2-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)-, Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)- Phenol, 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)-</p> |
| <p>Structural Formula</p> | <p>See Section 1.1</p> |
| <p style="text-align: center;">Summary</p> <p>Phenolic benzotriazoles are solids with low water solubilities and low to negligible vapor pressures. They are expected to have low mobility in soil. Volatilization of phenolic benzotriazoles is considered low based on their Henry's Law constant. The rate of hydrolysis of phenolic benzotriazoles cannot be measured due to a lack of water solubility; however the chemical structure of these compounds suggests that hydrolysis is likely to be negligible under environmental conditions. The rate of atmospheric photooxidation is considered rapid for CASRN 2440-22-4 and CASRN 70321-86-7, and moderate for CASRN 3147-75-9 and CASRN 25973-55-1. CASRN 2440-22-4 is expected to have low bioaccumulation potential (B1), CASRN 3147-75-9 and CASRN 25973-55-1 are expected to have high bioaccumulation potential (B3) and CASRN 70321-86-7 is expected to have moderate bioaccumulation potential (B2). However, the relatively low solubility of these compounds may attenuate bioconcentration and bioaccumulation. All four compounds contained in the phenolic benzotriazoles derivatives category are expected to have high persistence (P3), although the phenolic portion of the chemicals resembles many antioxidant phenols which may suggest that that portion of the molecule could oxidize.</p> <p>The acute toxicity of phenolic benzotriazoles is low in rats via the oral, route for all category members. CASRN 2440-22-4 was not irritating to rodent skin and slightly irritating to rabbit eyes. CASRN 2440-22-4 was extremely sensitizing when tested on guinea pigs; however, there was no sensitization or irritation when tested on human volunteers. Following repeated oral exposure of rats to CASRN 2440-22-4 for 90 days, there were liver and kidney effects at 500 mg/kg-day and above; the NOAEL for systemic toxicity was 100 mg/kg-day. No effects were reported for rats administered CASRN 3147-75-9 in the diet for 30 days, with a NOAEL of 5658 mg/kg-day for systemic toxicity. There were blood, liver and kidney effects in rats administered 40 mg/kg-day of CASRN 25973-55-1 in the diet; the NOAEL for systemic toxicity was 20 mg/kg-day. There were liver effects in rats administered 15 mg/kg-day of CASRN 70321-86-7; the NOAEL for systemic toxicity was 2.5 mg/kg-day. There are no specific reproductive toxicity studies. No significant effects on reproductive organs were reported following repeated dietary exposures of rats to two category members (CASRN 2440-22-4 and 70321-86-7). Mice and dogs exposed to CASRN 2440-22-4 in dietary studies also showed no significant effects on</p> | |

reproductive organs. However, effects on reproductive organs were seen following repeated dietary exposures of dogs to CASRN 25973-55-1. A dominant lethal assay showed no male reproductive toxicity in rats treated with CASRN 2440-22-4. In an oral prenatal developmental toxicity study, CASRN 2440-22-4 showed no developmental toxicity in rats and mice; the NOAEL was 1000 mg/kg-day. CASRN 70321-86-7 caused reduced pup weight and delays in skeletal maturation at 1000 mg/kg-day; the NOAEL for developmental toxicity is 300 mg/kg-day. The category members did not induce gene mutations in bacterial tests *in vitro* and did not induce chromosomal aberration when tested *in vivo*. Long-term studies for CASRN 2440-22-4 showed no evidence of carcinogenicity in rats or mice.

The acute hazard of the phenolic benzotriazoles category to fish, aquatic invertebrates and plants is considered to be > 0.17 mg/L.

No data gaps were identified under the HPV Challenge Program.

The sponsor, The Phenolic Benzotriazoles Association (Ciba Specialty Chemicals Corporation and Cytec Industries, Inc.), submitted a Test Plan and Robust Summaries to EPA for the phenolic benzotriazoles category on October 26, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on December 4, 2001

(<http://www.epa.gov/chemrtk/pubs/summaries/phenbenz/c13266tc.htm>). EPA comments on the original submission were posted to the website on June 19, 2002. Public comments were also received and posted to the website.

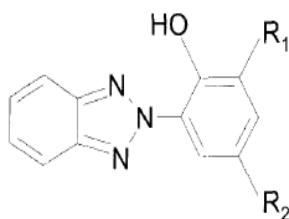
The sponsor provided EPA with a response to comments on December 20, 2002 and submitted revised documents February 18, 2004, which were posted to the ChemRTK website on August 7, 2003 and April 7, 2004, respectively. The phenolic benzotriazoles category consists of the following four chemicals:

Sponsored Chemicals

| | |
|---|------------------|
| 2-(2'-Hydroxy-5'-methylphenyl) benzotriazole | CASRN 2440-22-4 |
| 2-(2'-Hydroxy-5'-octylphenyl) benzotriazole | CASRN 3147-75-9 |
| 2-(2'-Hydroxy-3',5'-di- <i>t</i> -amylphenyl) benzotriazole | CASRN 25973-55-1 |
| 2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol | CASRN 70321-86-7 |

Category Justification

The four members of the phenolic benzotriazoles category have the identical molecular base structure of a benzotriazole group. They also have in common a phenolic group attached to the benzotriazole structure at the same location but the substituents (R1 and R2) on the phenolic group vary.

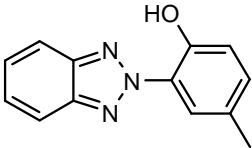
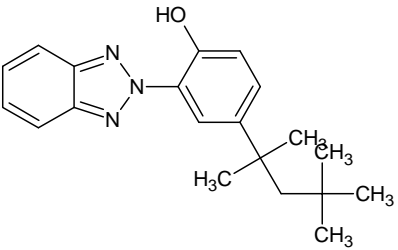
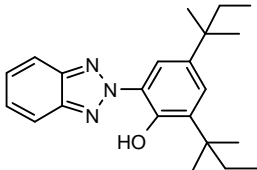
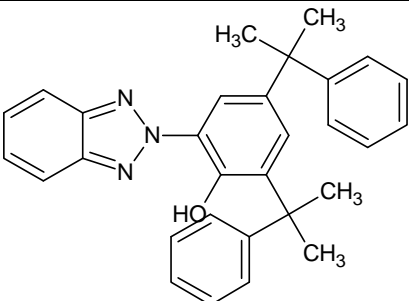


The submitter's primary justification for the category is twofold: (1) the similarity of the structural backbone of all members (phenolic benzotriazoles), and (2) the similar or regular pattern of the chemical, physical and toxicological properties of the members. The Agency concluded that the submitter adequately supports the grouping of the category members with the information provided the HPV Challenge Program.

Existing mammalian and ecotoxicity data for two of the members (CASRN 2440-22-4 and 70321-86-7) are extrapolated to the other two members of the category. No specific reproductive toxicity test data were available for any of the chemicals in the category. In accordance with HPV Challenge Program guidance, EPA concluded that histological evaluation of reproductive organs from the available 90-day and longer repeated-dose toxicity studies address the reproductive toxicity endpoint.

1 Chemical Identity

1.1 Identification and Purity

| Table 1. Sponsored Chemicals | | |
|--|------------|--|
| Chemical Name | CASRN | Structure |
| 2-(2'-Hydroxy-5'-methylphenyl) benzotriazole | 2440-22-4 |  |
| 2-(2'-Hydroxy-5'-octylphenyl) benzotriazole | 3147-75-9 |  |
| 2-(2'-Hydroxy-3',5'-di-<i>t</i>-amylphenyl) benzotriazole | 25973-55-1 |  |
| 2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol | 70321-86-7 |  |

The sponsor did not discuss purity of the chemicals in this category in the Test Plan

1.2 Physical-Chemical Properties

The physical-chemical properties of phenolic benzotriazoles are summarized in Table 2. Phenolic benzotriazoles are solids with low water solubilities and low to negligible vapor pressures.

Table 2. Physical-Chemical Properties of Phenolic Benzotriazoles¹

| Property | 2-(2'-Hydroxy-5'-methylphenyl) benzotriazole | 2-(2'-Hydroxy-5'-octylphenyl) benzotriazole | 2-(2'-Hydroxy-3',5'-di- <i>t</i> -amylphenyl) benzotriazole | 2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol |
|--|---|--|--|--|
| CASRN | 2440-22-4 | 3147-75-9 | 25973-55-1 | 70321-86-7 |
| Molecular Weight | 225.25 | 323.44 | 351.50 | 447.58 |
| Physical State | Solid | Solid | Solid | Solid |
| Melting Point | 131–133°C (measured) | 106–108°C (measured) | 80–83°C (measured) | 139–143°C (measured) |
| Boiling Point | 358°C (measured) ³ | 454.6°C (estimated) ² | 477.8°C (estimated) | 599.8°C (estimated) |
| Vapor Pressure | 1.9×10 ⁻⁶ mm Hg at 25°C (estimated) ² | 9.8×10 ⁻⁹ mm Hg (estimated) ² | 4.3×10 ⁻⁹ mm Hg (estimated) ² | 4.18×10 ⁻¹³ mm Hg (estimated) ² |
| Water Solubility | 0.173 mg/L at 20°C (measured) | <1 mg/L (measured); 0.274 mg/L (estimated) ² | 0.042 mg/L at 25°C (estimated) ² | <0.04 mg/L at 20°C (measured); 0.0031 mg/L (estimated) ² |
| Dissociation Constant (pK _a) | Not applicable | Not applicable | Not applicable | Not applicable |
| Henry's Law Constant | 6.2×10 ⁻¹⁴ atm-m ³ /mole (estimated) ² | 4.45×10 ⁻¹³ atm-m ³ /mole (estimated) ² | 6.52×10 ⁻¹³ atm-m ³ /mole (estimated) ² | 1.37×10 ⁻¹⁵ atm-m ³ /mole (estimated) ² |
| Log K _{ow} | 4.2 (measured) | 6.2 (estimated) | 7.3 (estimated) | >6.5 (measured); 7.7 ² (estimated) |

¹Ciba Specialty Chemicals Corp and Cytec Industries, Inc. February 24, 2004. Revised Robust Summary for Phenolic Benzotriazoles Category. <http://www.epa.gov/HPV/pubs/summaries/phenbenz/c13266tc.htm>.

²U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA entering measured data where applicable. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

³Measured value is 225°C at 10 mm Hg which NOMO5 (PC Nomograph program) converts to 358°C at 760 mm Hg.

2 General Information on Exposure

2.1 Production Volume and Use Pattern

During calendar year 2005, the four chemicals in the phenolic benzotriazoles category had an aggregated production and/or import volume in the United States of 3.5 million to 31 million pounds (500 to 1 million pounds for CASRN 2440-22-4 and 1 to 10 million pounds for each of the other chemicals in the category).

Information in the IUR indicated that the industrial processing and uses and some commercial/consumer uses for these chemicals were claimed confidential. Non-confidential information in the IUR indicated that the industrial processing and use of CASRN 3147-75-9 includes surface active agents in a variety of industries. Non-confidential information in the IUR indicated that the commercial/consumer use categories containing the chemicals include paints and coatings (CASRN 25973-55-1), rubber and plastic products (CASRN 3147-75-9), and electrical and electronic products (CASRN 3147-75-9). The HPV submission for the phenolic benzotriazoles category states that the chemicals are primarily used as industrial additives for a variety of polymers and in light-stabilized coatings. All four phenolic benzotriazoles category

chemicals have been cleared by the FDA for use in food contact polymers and adhesives or antioxidants and stabilizers.

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of these chemicals to the environment.

Phenolic benzotriazoles are expected to have low mobility in soil. The rate of biodegradation is considered slow based on the results of ready biodegradation tests. The rate of volatilization of phenolic benzotriazoles from water and moist soil is considered low based on their estimated Henry's Law constants. The rate of hydrolysis is considered negligible under environmental conditions. CASRN 2440-22-4 is expected to have low bioaccumulation potential (B1), CASRN 3147-75-9 and CASRN 25973-55-1 are expected to have high bioaccumulation potential (B3) and CASRN 70321-86-7 is expected to have moderate bioaccumulation potential (B2). However, the relatively low solubility of these compounds may limit their potential for bioconcentration and bioaccumulation. Phenolic benzotriazoles are expected to have high potential for persistence (P3) as indicated by low percent degradation in ready biodegradation tests. However, the phenolic portion of the chemicals resembles many antioxidant phenols which may suggest that that portion of the molecule could oxidize. The environmental fate characteristics of phenolic benzotriazoles are summarized in Table 3.

| Property | 2-(2'-Hydroxy-5'-methylphenyl) benzotriazole | 2-(2'-Hydroxy-5'-octylphenyl) benzotriazole | 2-(2'-Hydroxy-3',5'-di- <i>t</i> -amylphenyl) benzotriazole | 2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol |
|------------------------------|--|---|---|---|
| Photodegradation Half-life | 1.39 hours (estimated) | 4.02 hours (estimated) | 8.1 hours (estimated) | 1.06 hours (estimated) |
| Hydrolysis Half-life | Could not be determined due to low water solubility | Cannot be determined due to low water solubility | Cannot be determined due to low water solubility | Cannot be determined due to low water solubility |
| Biodegradation | 0–2% after 28 days (not readily biodegradable) ² | 0–1% after 28 days (not readily biodegradable) ² | 2–8% after 28 days (not readily biodegradable) ² | 3–8% after 28 days (not readily biodegradable) ² |
| Bioconcentration | BCF = 123–494 (carp; 1,000 µg/L); BCF = 130–295 (carp; 100 µg/L); BCF = 44–220 (carp; 10 µg/L) (measured) ⁵ | BCF = 1.21×10 ⁴ (estimated) ³ | BCF = 1.04×10 ⁴ (estimated) ³ | BCF = 2,755 (estimated) ³ |
| Log K _{oc} | 5.0 (estimated) ³ | 6.6 (estimated) ³ | 7.1 (estimated) ³ | 9.3 (estimated) ³ |
| Fugacity (Level III Model) | | | | |
| Air (%) | 3.1 | 4.0×10 ⁻⁵ | 2.3×10 ⁻⁴ | 0.0 |
| Water (%) | 4.9 | 3.5 | 2.2 | 2.2 |
| Soil (%) | 87.3 | 44.6 | 40.4 | 40.1 |
| Sediment (%) | 4.6 | 51.9 | 57.5 | 57.7 |
| Persistence ⁴ | P3 (high) | P3 (high) | P3 (high) | P3 (high) |
| Bioaccumulation ⁴ | B1 (low) | B3 (high) | B3 (high) | B2 (moderate) |

¹Ciba Specialty Chemicals Corp and Cytec Industries, Inc. February 24, 2004. Revised Robust Summary for Phenolic Benzotriazoles Category. <http://www.epa.gov/HPV/pubs/summaries/phenbenz/c13266tc.htm>.

²Ciba Specialty Chemicals Corp and Cytec Industries, Inc. October 29, 2001. Robust Summary for Phenolic Benzotriazoles Category. <http://www.epa.gov/chemrtk/pubs/summaries/phenbenz/c13266tp.pdf>

³U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

⁴Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

⁵National Institute of Technology and Evaluation. 2002. Biodegradation and Bioconcentration of Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

Conclusion: Phenolic benzotriazoles are solids with low water solubilities and low to negligible vapor pressures. They are expected to have low mobility in soil. Volatilization of phenolic benzotriazoles is considered low based on their Henry's Law constant. The rate of hydrolysis of phenolic benzotriazoles cannot be measured due to a lack of water solubility; however the chemical structure of these compounds suggests that hydrolysis is likely to be negligible under environmental conditions. The rate of atmospheric photooxidation is considered rapid for CASRN 2440-22-4 and CASRN 70321-86-7, and moderate for CASRN 3147-75-9 and CASRN 25973-55-1. CASRN 2440-22-4 is expected to have low bioaccumulation potential (B1), CASRN 3147-75-9 and CASRN 25973-55-1 are expected to have high bioaccumulation potential (B3) and CASRN 70321-86-7 is expected to have moderate bioaccumulation potential (B2). However, the relatively low solubility of these compounds may attenuate bioconcentration

and bioaccumulation. All four compounds contained in the phenolic benzotriazoles derivatives category are expected to have high persistence (P3), although the phenolic portion of the chemicals resembles many antioxidant phenols which may suggest that that portion of the molecule could oxidize.

3 Human Health Hazard

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

Tif Ralf (SPF) rats (5/sex/dose) were administered the test substance (suspended in PEG 400) via gavage at 4640, 7750 and 10,000 mg/kg-bw and observed for 14 days. Two females in the 10,000 mg/kg-bw group died within the first 7 days. No treatment-related effects were observed at necropsy.

LD₅₀ > 10,000 mg/kg-bw

2-(2'-Hydroxy-5'-octylphenyl) benzotriazole (CASRN 3147-75-9)

Male Wistar rats (20/dose) were administered an aqueous suspension of test substance at 125, 250, 500 and 1000 mg/kg-bw via gavage at and observed for 14 days. No mortality was observed.

LD₅₀ > 1000 mg/kg-bw

2-(2'-Hydroxy-3,5-di-tert-amylphenyl) benzotriazole (CASRN 25973-55-1)

Tif Ralf (SPF) rats (5/sex/dose) were administered the test substance (30% suspension in PEG 400) via gavage at 1392, 1800 and 2325 mg/kg-bw and observed for 14 days. No deaths occurred during the 14-day test period. No treatment-related effects were observed at necropsy.

LD₅₀ > 2325 mg/kg-bw

2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol (CASRN 70321-86-7)

Tif Ralf (SPF) rats (5/sex/dose) were administered the test substance (suspension in PEG 400) via gavage at 1000, 2150, 4640 and 7750 mg/kg-bw and observed for 14 days. No mortality occurred. No treatment-related effects were observed at necropsy.

LD₅₀ > 7750 mg/kg-bw

Acute Inhalation Toxicity

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

Charles River rats (5/sex) were administered the test substance via air-dust mixture at 1420 mg/m³ (1.42 mg/L) for 4 hours and observed for 14 days following treatment. No deaths occurred within 14 days. No test substance-related effects were noted.

LC₅₀ > 1420 mg/m³ (1.42 mg/L)

Acute Dermal Toxicity

2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol (CASRN 70321-86-7)

Albino rats (5/sex/dose) were exposed to the test substance dermally under a semi-occlusive dressing for 24 hours. Following removal of the dressing at 24 hours and cleaning of the application site, the rats were observed for 14 days. No mortalities occurred during this study. Necropsy examination did not reveal any gross pathologic alterations.

LD₅₀ > 2000 mg/kg-bw

Repeated-Dose Toxicity

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

(1) Beagle dogs (6/sex/group) were administered the test substance in their diet at 1000, 3000 or 10,000 ppm for 13 weeks (corresponding to approximately 32, 96, and 320 mg/kg-bw/day for males and 35, 105, and 350 mg/kg-bw/day for females). After exposure to the test material for 3 months, one animal per dose group was fed a control diet for a recovery period of 1 month. No mortality and no local or systemic toxicity was reported. At 10,000 ppm, a decrease in body weight gain and food consumption was reported (magnitude of change and significance not reported). One female animal from the 10,000 ppm group was emaciated. Only enzyme level changes are reported; alanine aminotransferase activity was increased in the 3000 and 10,000 ppm groups and gamma glutamyl transpeptidase activity was increased in the 10,000 ppm group. Male and female reproductive organs were evaluated. No effects were seen on male reproductive organs. Absolute ovary weights were decreased at all doses (significance not stated); however, there were no histopathological changes related to treatment. The robust summary concludes that there were no treatment-related gross or histopathological changes.

LOAEL ~320 mg/kg-bw/day (based on decreased body weight)

NOAEL ~ 96 mg/kg-bw/day

(2) Wistar rats (10/sex/dose) were administered the test substance via the diet at 0, 0.2, 1, or 5% (approximately 0, 100, 500 or 2500 mg/kg-bw/day) for 90 days. There was no effect on mortality. Body weight gain and food consumption were only decreased in the first 2 weeks of the study in animals fed the 1 and 5% diet. No differences in body weight were observed in the later part of the study. At the 5% level there was a decreased number of erythrocytes and increased number of leukocytes in male rats ($0.05 > P > 0.01$). Relative liver weights were significantly increased in both males and females fed both 1 and 5% diets ($P < 0.01$). Relative kidney weights were increased significantly in both males and females fed the 5% diet. Relative spleen weights were increased significantly in high-dose females ($0.05 > P > 0.01$) and testes weights were decreased in 1 and 5% diet males ($0.05 > P > 0.01$). Distinct histopathological changes were seen in the kidneys of both male and female rats and liver of 2 high dose males.

LOAEL ~ 500 mg/kg-bw/day (based on liver and kidney effects)

NOAEL ~ 100 mg/kg-bw/day

Source: TSCATS, Doc#:88-920002920

2-(2'-Hydroxy-5'-octylphenyl) benzotriazole (CASRN 3147-75-9)

Wistar rats (5/sex/group) were administered the test substance via the diet at 0, 1.25, 2.5 and 5% (corresponding to 0, 1286, 2594 and 5658 mg/kg-bw/day) for 30 days. There were no deaths and

no effect on body weight or food consumption during the test period. Hydronephrosis was noted in the high dose (four animals) and control (three animals) groups. The robust summary states this effect is common in this strain of rats. No lesions were noted that were attributable to ingestion of the test substance.

NOAEL = 5658 mg/kg-bw/day (highest dose tested)

2-(2'-Hydroxy-3',5'-di-t-amylphenyl) benzotriazole (CASRN 25973-55-1)

(1) Beagle dogs (3/sex/group) were administered the test substance via the diet at 0, 15, 30, 60, 120 or 240 mg/kg-bw/day daily for 3 months. Decreases in body weight and food consumption were evident in the high-dose group animals. Males were more sensitive than females with mortality of one male dog in the highest dose group. The liver was reported to be the primary target organ for toxicity. Anemia was noted in animals from the 120 and 240 mg/kg dose groups and "slight" changes in blood chemistry parameters included increased serum bilirubin levels and gamma glutamyl transpeptidase (GTP), glutamyl oxalacetic transaminasae (GOT) and alkaline phosphatase activity. In males, decreases in testes, prostate and epididymal weights at the two highest doses. In females, body weight and uterus weight was decreased in the three highest dose groups. Increased liver weights associated with liver damage including icterus (jaundice) were observed upon gross and histopathological examination in a few dogs in the 120 and 240 mg/kg-bw/day dose groups. Microscopically, fatty degeneration of hepatocytes, presence of protein globules in the cytoplasm, Kupffer cell hyperplasia and centrilobular cholestasis were seen. It was reported that the kidneys also exhibited toxicity, but no details were provided. In higher dose groups, some animals showed atrophy of uterus, abnormal spermiogenesis and atrophy of the prostate.

LOAEL = 60 mg/kg-bw/day (based on body weight, liver and kidney effects)

NOAEL = 30 mg/kg-bw/day

(2) Rats (10/sex/group) were administered the test substance via the diet at 0, 100, 200, 400, 800 or 1600 ppm (approximately 5, 10, 20, 40 or 80 mg/kg/day) for 90 days. No mortality occurred. Signs of anemia (decreased hemoglobin and packed cell volume) were seen in males at dietary concentrations of 200 ppm and above (approximately 20 mg/kg-bw/day). In females, this effect was less pronounced. An increase in glucose-6-phosphatase activity was noted at all dietary concentrations. Liver, kidney, spleen and testes weights were increased in higher exposure groups with "an indication" of increased thyroid weights (magnitude and significance of change not reported). The liver was the primary target organ and had a greenish-drab discoloration in males and females at higher exposure levels. Microscopic examination revealed foci of necrosis and slight proliferation of bile duct epithelia. Paraenchymal cells were enlarged. In the kidney, tubular necrosis was reported in some males from the higher dose groups. In females, a treatment-related, yellowish-brown pigmentation in the cytoplasm of the proximal tubular cells was noted.

LOAEL ~ 40 mg/kg-bw/day (based on blood, liver and kidney effects)

NOAEL ~ 20 mg/kg-bw/day

2-(2H-Benzotriazol-2-yl)-4,6-bis (1-methyl-1-phenylethyl) phenol (CASRN 70321-86-7)

Tif: RAIF (SPF) rats (10/sex/dose) were administered the test substance via the diet at 0, 50, 300, 2000 or 10,000 ppm (corresponding to approximately 0, 2.5, 15, 100 or 500 mg/kg-bw/day) for 92-94 days. No treatment-related clinical symptoms or signs of toxicity were observed. There

was no effect on mortality; body weight; hematological, blood chemistry and urinalysis parameters; nor macroscopic findings. A statistically significant increase in absolute and relative (to body and brain weight) liver weight was seen in males and females at 2000 ppm and above and in females at 300 ppm. A slight to moderate hypertrophy and/or cytoplasmic vacuolization of hepatocytes were seen and in females from 300 ppm and above and in both males and females at 2000 ppm and above.

LOAEL ~ 15 mg/kg-bw/day (based on liver effects)

NOAEL ~ 2.5 mg/kg-bw/day

Reproductive Toxicity

Reproductive toxicity tests were not submitted to address the reproductive toxicity endpoint for this category. Evaluation of reproductive organs in repeated-dose toxicity and other studies were used to address the reproductive endpoints for the purposes of the HPV Challenge Program. Therefore, NOAEL/LOAELs for fertility and/or reproductive toxicity cannot be determined for this endpoint.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

(1) In the 90-day dietary toxicity study in dogs described previously, reproductive organs were weighed and examined macroscopically (ovaries or testes and uterus or prostate). No gross or histopathological changes in reproductive organs were seen. The highest dose was approximately 350 mg/kg-bw/day.

(2) In a 2-year dietary toxicity study in rats (0, 100, 300, 1000 and 3000 ppm) and mice (0, 5, 50 and 500 ppm), organ weight analysis performed on the reproductive organs of male and female rats sacrificed after 104 weeks of treatment revealed no differences between control and treatment groups. General histopathology of the reproductive organs of rats and mice sacrificed after 104 weeks of treatment showed no abnormalities. The highest doses tested were approximately 62 mg/kg-bw/day for mice and 169 mg/kg bw/day for rats.

(3) In a Dominant Lethal Assay, male NMRI derived albino mice (20/group) were treated with the test chemical by gavage at a single dose of 0, 1000 or 3000 mg/kg-bw and were mated with untreated females. The vehicle was aqueous carboxymethyl cellulose. Females were necropsied on day 14 of pregnancy. There were no differences in mating ratio, number of implantations, or embryonic deaths between control and treated groups.

2-(2'-Hydroxy-3',5'-di-t-amylphenyl) benzotriazole (CASRN 25973-55-1)

(1) In the 90-day repeated-dose toxicity study conducted in Beagle dogs as described previously, males showed greater signs of toxicity than females. In males, decreases in body weight and in testes and epididymal weights at the two highest doses. In females, body weight and uterus weight was decreased in the three highest dose groups. However, the significance of the body and organ weight changes is not described. Microscopic changes included slight to moderate atrophy of the uterus (60 mg/kg-bw/day and above), abnormal spermiogenesis (30 mg/kg-bw/day and above) and atrophy of the prostate (30 mg/kg-bw/day and above).

(2) In the 90-day repeated-dose dietary toxicity study conducted in rats described previously, there was no treatment-related effect on female body weight or ovary weight (reported as ovary weight per 100 g body weight). Body weights of male rats were significantly reduced at 800 and 1600 ppm (4% and 16%, respectively). Increases in testes weights (reported as testes weight per 100 g body weight) were statistically significant at 400 ($p < 0.05$), 800 and 1600 ppm ($p < 0.01$). The robust summary judged this result to be caused by decreased body weight and not toxicologically significant. Reproductive organs were not evaluated microscopically.

2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-l-phenylethyl) phenol (CASRN 70321-86-7)

In the 90-day repeated-dose dietary toxicity study conducted in rats described previously, reproductive organs were weighed and evaluated microscopically. Reproductive organ weights were not affected at the end of the treatment period. The summary states that there were no histological effects on reproductive organs.

Developmental Toxicity

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

Groups of presumed pregnant female Sprague-Dawley rats and NMRI derived albino mice (number unspecified) received the test substance (in 2% aqueous carboxymethyl cellulose) by gavage at 150, 500 or 1000 mg/kg-bw on days 6-15 of gestation. The robust summary states that no maternal toxicity was evident and the rates of implantation and embryotoxicity were not affected by treatment. The robust summary states there were no teratogenic effects but it does not specify what developmental endpoints were examined.

NOAEL (maternal/developmental toxicity) = 1000 mg/kg-bw/day (highest dose tested)

2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-l-phenylethyl) phenol (CASRN 70321-86-7)

Groups of presumed pregnant female Tif: RAIF (SPF) rats (number not specified) received the test substance by gavage at 300, 1000 or 3000 mg/kg-bw on days 6 through 15 of gestation. No maternal toxicity was evident at any dose. Fetal data indicated a significant reduction in body weight for the 1000 mg/kg-bw dose group (magnitude and significance not specified). In addition, an increased delay of skeletal maturation was noted for this group. However, there were no similar effects in the high dose group so the robust summary categorized these effects as "incidental". One fetus in the high dose group showed an omphalocele (failure of ventral closure during last stages of embryonic development).

NOAEL (maternal toxicity) = 3000 mg/kg-bw/day (highest dose tested)

LOAEL (developmental toxicity) = 1000 mg/kg-bw/day (based on body weight and delay skeletal maturation)

NOAEL (developmental toxicity) = 300 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

An Ames assay was conducted using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations reported as 10, 30, 90, 270

and 810 µg/0.1 mL. There is no discussion of positive or negative controls in the robust summary.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole was not mutagenic in this assay.

2-(2'-Hydroxy-5'-octylphenyl) benzotriazole (CASRN 3147-75-9)

A reverse mutation assay was conducted using *S. typhimurium* strains TA 98, TA100, TA 1535 and TA 1537 and *E. coli* WP2uvrA, with and without metabolic activation and at concentrations of 20.5, 61.7, 185.2, 555.5, 1666.6 and 5000 µg/plate. Appropriate positive and negative controls were used. The results revealed no marked difference in mutagenic activity of the tested concentrations when compared with negative controls; positive controls showed appropriate response.

2-(2'-Hydroxy-5'-octylphenyl) benzotriazole was not mutagenic in this assay.

2-(2'-Hydroxy-3',5'-di-t-amylphenyl) benzotriazole (CASRN 25973-55-1)

An Ames assay was conducted using *S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at 25, 75, 225, 675 and 2025 µg/0.1 mL. The comparison of results between the negative control and test chemical revealed no marked differences. No other description of controls is provided. No evidence of point mutation was detected.

2-(2'-Hydroxy-3',5'-di-t-amylphenyl) benzotriazole was not mutagenic in this assay.

2-(2H-Benzotriazol-2-yl)-4,6-bis (1-methyl-1-phenylethyl) phenol (CASRN 70321-86-7)

In a reverse mutation assay, *S. typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 were exposed to the test chemical at 25, 75, 225, 675 and 2025 µg/0.1 mL with and without metabolic activation. Appropriate positive and negative controls were used. The results revealed no marked difference in mutagenic activity of the tested concentrations when compared with negative controls; positive controls showed appropriate response.

2-(2H-Benzotriazol-2-yl)-4,6-bis (1-methyl-1-phenylethyl) phenol was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

Chinese hamsters (6 females and 4 males/dose) were administered the test chemical by gavage for 2 consecutive days at doses of 500, 1000 and 2000 mg/kg-bw; injected intra peritoneally with colcemide 2 hours after administration of the second dose and sacrificed 4 hours later. Bone marrow was harvested and analyzed for chromosomal aberrations. Chromosomes from animals treated with the test chemical showed no aberrations; two metaphase figures were observed in the negative control and there was a significant increase in aberrations in the positive controls.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

5 rats and 5 mice (sex and strain not specified) were administered 0.1 cm³ per mouse or 0.4 cm³ per rat of a 5 % suspension of the chemical in gum arabic on a clipped spot on the back for 5 consecutive days. The report concludes there was no local irritation and no systemic toxicity. No other study details were provided.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4) was not irritating to rodent skin.

Eye Irritation

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

100 mg was instilled in the eyes of six rabbits (sex and strain not provided). Irritation was noted in 2 of the 6 rabbits. The report concludes that the chemical is “minimally” irritating to rabbit eye mucosa.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4) was slightly irritating to rabbit eyes.

Skin Sensitization

(1) On day 1 of a guinea pig maximization test, 0.1 mL of three pairs of intradermal injections were made into the shaved neck adjuvant/saline mixture, test article in Oleum arachidis, and test article in adjuvant saline mixture). On day 8, approximately 0.4g of a paste containing 1, 5, 10 or 30% (w/w) chemical in Vaseline, was cutaneously applied to the neck for 48 hours using an occlusive dressing. After 2 additional weeks (week 3 and 4) without treatment, a challenge cutaneous application of the chemical in vaseline was applied for 24 hours using an occlusive dressing on the animals' flanks. Under these experimental conditions, 80-90% of the animals tested showed skin reactions 24 and 48 hours after removing the dressing. The chemical was classified as an “extreme” sensitizer in albino guinea pigs.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4) caused skin sensitization in guinea pigs.

Source: TSCATS, Doc#:88-920001579

(2) Patch testing of 59 volunteers with 0.5 ml of 5% test material in dimethyl phthalate produced no irritation following initial application. The patch test was repeated three times weekly for three weeks followed by a similar challenge exposure in the sixth week. Two of the original 66 subjects displayed positive reactions during subsequent exposures during the induction phase, but one was reacting to dimethyl phthalate and the other reacted to a different test chemical and still had “congestion” on their skin at the time of challenge so was excluded. Five subjects dropped out. The 59 subjects (12 men, 47 women) completing the test showed no irritation or sensitization.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4) caused no skin sensitization in humans.

Carcinogenicity

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

(1) In a lifetime carcinogenicity study, 50 strain Tif: MAGf(SPF)mice/sex/group were given the test substance in the diet for 24 months at concentrations of 5, 50 or 500 ppm (corresponding to 0.8, 6.5 and 64 and 0.8, 6.7 and 62 mg/kg bw/day for males and females, respectively). There was no effect on mortality, bodyweight, food consumption, and clinical signs of toxicity. No systemic toxicity was observed. The robust summary concludes that it can be inferred that the test substance did not produce inflammatory, degenerative, proliferative or neoplastic lesions. **NOAEL (systemic toxicity) ~ 62 mg/kg-bw/day** (no effect at highest dose tested)

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole was not carcinogenic in this assay.

(2) In a long-term feeding study, 50 CFY strain rats/sex/group were administered the test substance for 104 weeks at concentrations of 0, 100, 300, 1000 or 3000 ppm (corresponding to 0, 4, 14, 47 and 142 mg/kg-bw/day in males and 6, 17, 58, and 169 mg/kg bw/day in females). Although not statistically significant, marginally lower survival rate was noted in males in the highest dose group. A statistically significant ($P < 0.05$) decreased bodyweight gain (magnitude of change not reported) in males in this group over the last 52 weeks of treatment was reported. The robust summary concludes that administration of the test substance did not have an effect on the spontaneous tumors.

LOAEL (systemic toxicity) = 142 mg/kg-bw/day (reduced body weight gain in males)

NOAEL(systemic toxicity) = 47 mg/kg-bw/day

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole was not carcinogenic in this assay.

Conclusion: The acute toxicity of phenolic benzotriazoles is low in rats via the oral, route for all category members. CASRN 2440-22-4 was not irritating to rodent skin and slightly irritating to rabbit eyes. CASRN 2440-22-4 was extremely sensitizing when tested on guinea pigs; however, there was no sensitization or irritation when tested on human volunteers. Following repeated oral exposure of rats to CASRN 2440-22-4 for 90 days, there were liver and kidney effects at 500 mg/kg-day and above; the NOAEL for systemic toxicity was 100 mg/kg-day. No effects were reported for rats administered CASRN 3147-75-9 in the diet for 30 days, with a NOAEL of 5658 mg/kg-day for systemic toxicity.. There were blood, liver and kidney effects in rats administered 40 mg/kg-day of CASRN 25973-55-1 in the diet; the NOAEL for systemic toxicity was 20 mg/kg-day. There were liver effects in rats administered 15 mg/kg-day of CASRN 70321-86-7; the NOAEL for systemic toxicity was 2.5 mg/kg-day. There are no specific reproductive toxicity studies. No significant effects on reproductive organs were reported following repeated dietary exposures of rats to two category members (CASRN 2440-22-4 and 70321-86-7). Mice and dogs exposed to CASRN 2440-22-4 in dietary studies also showed no significant effects on reproductive organs. However, effects on reproductive organs were seen following repeated dietary exposures of dogs to CASRN 25973-55-1. A dominant lethal assay showed no male reproductive toxicity in rats treated with CASRN 2440-22-4. In an oral prenatal developmental toxicity study, CASRN 2440-22-4 showed no developmental toxicity in rats and mice; the NOAEL was 1000 mg/kg-day. CASRN 70321-86-7 caused reduced pup weight and delays in skeletal maturation at 1000 mg/kg-day; the NOAEL for developmental toxicity is 300 mg/kg-day. The category members did not induce gene mutations in bacterial tests *in vitro* and

did not induce chromosomal aberration when tested *in vivo*. Long-term studies for CASRN 2440-22-4 showed no evidence of carcinogenicity in rats or mice.

Table 4. Summary of Human Health Data

| Endpoints | 2-(2'-Hydroxy-5-methylphenyl)benzotriazole (2440-22-4) | 2-(2'-Hydroxy-5'-octylphenyl)benzotriazole (3147-75-9) | 2-(2'-Hydroxy-3,5-di-tert-amylphenyl)benzotriazole (25973-55-1) | 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol (70321-86-7) |
|--|---|--|--|---|
| Acute Oral Toxicity LD ₅₀ (mg/kg-bw) | > 10,000 | > 10,000 | > 2325 | > 7750 |
| Repeated-Dose Toxicity NOAEL/LOAEL (mg/kg-bw/day) | NOAEL ~ 100 LOAEL ~ 500 | (30 days) NOAEL = 5,658 | NOAEL ~ 20 LOAEL ~ 40 | NOAEL ~ 2.5 LOAEL ~ 15 |
| Reproductive Toxicity | No effects on reproductive organs in the repeated-dose study | No Data | No effects on reproductive organs in the rat repeated-dose study | No effects on reproductive organs in the repeated-dose study |
| Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) | | | | |
| Maternal Toxicity | NOAEL = 1000 | No Data NOAEL = 1000 (RA) | No Data NOAEL = 3000 (RA) | NOAEL = 3000 |
| Developmental Toxicity | NOAEL = 1000 | NOAEL = 1000 (RA) | LOAEL = 1000 NOAEL = 300 (RA) | LOAEL = 1000 NOAEL = 300 |
| Genetic Toxicity – Gene Mutation <i>In vitro</i> | Negative | Negative | Negative | Negative |
| Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i> | Negative | No Data Negative (RA) | No Data Negative (RA) | No Data Negative (RA) |
| Additional Information – Carcinogenicity | No evidence of carcinogenicity in mice or rats No systemic toxicity in mice, low in rats | – | – | – |

Bold = measured data; (RA) = Read Across

4 Hazards to the Environment

Based on EPA's comments on the original submission, a study to evaluate the acute toxicity to fish was conducted on the least hydrophobic category member for which measured solubility data were available (i.e., CASRN 2440-22-4). EPA indicated that if no effects were seen in this test at the limit of solubility, no further aquatic toxicity testing would be needed.

Acute Toxicity to Fish

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (CASRN 2440-22-4)

Rainbow trout (*Oncorhynchus mykiss*) were exposed to 2-(2'-hydroxy-5'-methylphenyl) benzotriazole at nominal concentrations of 0.022, 0.037, 0.061, 0.10 and 0.17 mg/L for 96 hours under static conditions. The highest concentration tested approximated the water solubility limit of the compound. The concentrations were measured in the exposure solutions. At test termination, no mortality or adverse effects were observed in the test.

96-h LC₅₀ > 0.17 mg/L

Conclusion: The acute hazard of the phenolic benzotriazoles category to fish, aquatic invertebrates and plants is considered to be > 0.17 mg/L.

| Table 5. Summary of Environmental Effects – Aquatic Toxicity Data | | | | |
|--|---|--|---|---|
| Endpoints | 2-(2'-Hydroxy-5'-methylphenyl) benzotriazole (2440-22-4) | 2-(2'-Hydroxy-5'-octylphenyl) benzotriazole (3147-75-9) | 2-(2'-Hydroxy-3',5'-di-<i>t</i>-amylphenyl) benzotriazole (25973-55-1) | 2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol (70321-86-7) |
| Fish 96-h LC₅₀ (mg/L) | > 0.17 (m) | No Data > 0.17 (m) (RA) | No Data > 0.17 (m) (RA) | No Data > 0.17 (m) (RA) |
| Aquatic Invertebrates 48-h EC₅₀ (mg/L) | No Data ¹ | No Data ¹ | No Data ¹ | No Data ¹ |
| Aquatic Plants 72-h EC₅₀ (mg/L) | No Data ¹ | No Data ¹ | No Data ¹ | No Data ¹ |

(m) = measured data (i.e., derived from testing); ¹ In test plan comments EPA indicated that if no effects were seen in the fish test with 2-(2'-hydroxy-5'-methylphenyl)benzo-triazole (2440-22-4) at the limit of solubility, no further aquatic toxicity testing would be needed.