

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### Bridged Alkyl Phenol Category

#### SPONSORED CHEMICALS

|  |                        |
|--|------------------------|
| <b>4,4'-(1-Methylethylidene)bis[2-(1,1-dimethylethyl)]phenol</b> | <b>CASRN 79-96-9</b>   |
| <b>4,4'-Butylidenebis(6-<i>t</i>-butyl-<i>m</i>-cresol)</b>      | <b>CASRN 85-60-9</b>   |
| <b>4,4'-Thiobis(6-<i>t</i>-butyl-<i>m</i>-cresol)</b>            | <b>CASRN 96-69-5</b>   |
| <b>2,2'-Methylenebis(4-methyl-6-nonyl)phenol</b>                 | <b>CASRN 7786-17-6</b> |

The High Production Volume (HPV) Challenge Program<sup>1</sup> 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<sup>1,2</sup>) 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<sup>2,3</sup> 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 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

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

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

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

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.

|   |  |
|---|--|
| <b>Chemical Abstract Service Registry Numbers (CASRN)</b> | 79-96-9<br>85-60-9<br>96-69-5<br>7786-17-6   |
| <b>Chemical Abstract Index Names</b>                      | Phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)-<br>Phenol, 4,4'-butylidenebis[2-(1,1-dimethylethyl)-5-methyl-<br>Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-<br>Phenol, 2,2'-methylenebis[4-methyl-6-nonyl- |
| <b>Structural Formula</b>                                 | <b>See Section 1</b>   |

### Summary

The bridged alkyl phenols category consists of four members with negligible water solubility and negligible vapor pressure. All four category members are expected to have low mobility in soil. Volatilization of the bridged alkyl phenols is considered low based on their estimated Henry's Law constants. The rate of hydrolysis of bridged alkyl phenols is considered negligible. The rate of atmospheric photooxidation is considered rapid; however, this is not expected to be an important environmental fate process since these substances are not expected to exist in the vapor phase in the atmosphere. The bridged alkyl phenols are expected to have moderate persistence (P2) and low bioaccumulation potential (B1); however, one substance, CASRN 79-96-9 is expected to have a high bioaccumulation potential (B3).

### Human Health Hazard

Due to differences in chemical structure and toxicity as well as uncertainties regarding read across (CASRN 7786-17-6), the sponsored chemicals are divided into the following three subcategories for human health:

- Subcategory I: CASRN 96-69-5
- Subcategory II: CASRN 79-96-9  
CASRN 85-60-9
- Subcategory III: CASRN 7786-17-6

#### ***Subcategory I***

Acute oral toxicity to rats and acute dermal toxicity to rabbits is low for CASRN 96-69-5. In a 13-week repeated-dose toxicity study, dietary administration in rats resulted in changes in hematological parameters at ~ 60 mg/kg-bw/day and higher; the NOAEL for systemic toxicity is ~ 30 mg/kg-bw/day. In a second 13-week dietary study in mice, CASRN 96-69-5 exposure resulted in changes in hematology at ~ 145 - 165 mg/kg-bw/day and higher; the NOAEL for systemic toxicity is ~ 60-65 mg/kg-bw/day. In a chronic study, CASRN 96-69-5 administered to rats in the diet for 104 weeks resulted in signs of liver toxicity and changes in hematological parameters at ~ 40 mg/kg-bw/day and higher; the NOAEL for systemic toxicity is ~ 20 mg/kg-bw/day. Another 104-week dietary study in mice showed significant decreases in hematological parameters in males at ~ 145 mg/kg-bw/day (highest concentration tested); the NOAEL for systemic toxicity is ~ 60 mg/kg-bw/day. No reproductive toxicity studies are available;

however, in a two-month oral study with CASRN 96-69-5 that assessed male reproductive toxicity, decreased sperm production and histopathological changes in seminiferous tubules of rats and mice at 41-57 and 82-99 mg/kg-bw/day, respectively (lowest doses tested) were observed. No effects to reproductive organs were reported in the chronic studies. In an oral gavage prenatal developmental toxicity study in rabbits, anorexia and spontaneous abortions were observed in dams treated at 20 mg/kg-day; the NOAEL for maternal toxicity is 2 mg/kg-day. Significant decreases in mean pup weight and litter size occurred at 2 mg/kg-day; the NOAEL for developmental toxicity is 0.2 mg/kg-day. CASRN 96-69-5 did not induce gene mutations in bacteria or chromosomal aberrations either in mammalian cells *in vitro* or *in vivo*. CASRN 96-69-5 is not irritating to rabbit skin but is irritating to rabbit eyes. CASRN 96-69-5 is a skin sensitizer based on data from the mouse local lymph node assay. No evidence of carcinogenicity was observed with CASRN 96-69-5 exposure in rats during a two-year dietary study.

No data gaps have been identified for Subcategory I under the HPV Challenge Program.

### ***Subcategory II***

Acute oral and dermal toxicity of Subcategory II is low in rats. In 90-day repeated-dose toxicity studies, signs of liver toxicity and lymph node lesions were seen in rats administered CASRN 85-60-9 in the diet at 25 mg/kg-bw/day and higher; the NOAELs for systemic toxicity ranged from 2.5 – 5 mg/kg-bw/day. A repeated-dose toxicity study with CASRN 85-60-9 conducted to evaluate male reproductive parameters revealed decreased sperm production and histopathological changes in the seminiferous tubules following oral exposure in rats and mice for 2 months at 41-58 and 80-95 mg/kg-bw/day, respectively (lowest doses tested). No data are available for developmental toxicity endpoints. CASRN 85-60-9 did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

Reproductive toxicity in females and developmental toxicity are identified as data gaps for Subcategory II under the HPV Challenge Program.

### ***Subcategory III***

No data were provided for CASRN 7786-17-6.

Acute, repeated-dose, reproductive, developmental, and genetic toxicity (gene mutations and chromosomal aberrations) are identified as data gaps for Subcategory III under the HPV Challenge Program.

### **Hazard to the Environment**

The 96-hr LC<sub>50</sub> values of CASRN 96-69-5 for fish ranges from 0.13 to 0.51 mg/L. The 48-hr EC<sub>50</sub> of CASRN 96-69-5 for aquatic invertebrates ranges from 0.16 to 0.70 mg/L.

Aquatic plant and chronic aquatic invertebrate endpoints are identified as data gaps under the HPV Challenge Program.

The sponsor, Rubber and Plastic Additives Panel of the American Chemistry Council, submitted a Test Plan and Robust Summaries to EPA for the hindered phenols category on December 18, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 15, 2002 (<http://www.epa.gov/HPV/pubs/summaries/hndrdphn/c13382tc.htm>). EPA comments on the original submission were posted to the website on December 10, 2002. Public comments were also received and posted to the website. In response to EPA comments on the original submission, the sponsor subsequently divided the hindered phenols category into two separate categories (styrenated phenols and bridged alkyl phenols) and two stand-alone chemicals. The sponsor submitted a test plan and robust summaries for bridged alkyl phenols category dated July 10, 2003, which were posted to the ChemRTK website on July 23, 2003. EPA comments on submissions for the bridged alkyl phenols category were posted to the website on March 20, 2007.

### **Category Justification**

The similarities in structure, reactivity, uses and physicochemical and environmental fate properties support grouping the four bridged alkyl phenols into one category. However, in EPA's comments on the sponsor's submission for bridged alkyl phenols, EPA noted that differences in physical-chemical properties and toxicities associated with CASRN 96-69-5 justify the exclusion of this chemical from the proposed bridged alkyl phenols category for ecological effects. Upon further review, this argument is more appropriate for human health effects endpoints because exposure includes contact of CASRN 96-69-5 with biological fluids in mammalian systems. Support for this argument is provided by results from repeated-dose oral toxicity studies. In particular, the hematological system appears to be particularly sensitive to CASRN 96-69-5, whereas the liver appears to be the primary target organ for CASRN 85-60-9.

Further, the lengths of the alkyl chains and their positions relative to the hydroxyl groups for CASRN 7786-17-6 differ from the positions for CASRNs 79-96-9 and 85-60-9. Therefore, it is possible that CASRN 7786-17-6 may exhibit differences in toxicity compared with CASRNs 79-96-9 and 85-60-9.

Based on the above considerations, the bridged alkyl phenols category is consequently divided into three subcategories for the purpose of assessing human health hazard. Subcategory I consists of CASRN 96-69-5; Subcategory II consists of CASRNs 79-96-9, and 85-60-9; and Subcategory III consists of CASRN 7786-17-6.

No subcategories are needed for ecotoxicity; however, read across is appropriate for all members except CASRN 7786-17-6.

### **Justification for Supporting Chemical**

The sponsor suggested using CASRN 128-37-0 as a supporting chemical. However, based on differences in chemical structure (particularly the position of alkyl groups relative to the hydroxyl group) in addition to differences in doses at which liver and other toxicity is observed, EPA has decided that this chemical is not appropriate as a supporting chemical for human health effects. The supporting chemical is also not needed for hazards to the environment.

## 1. Chemical Identity

### 1.1 Identification and Purity

The structures and representative structures are provided in Table 1. The bridged alkyl phenols category consists chemicals in which two molecules of mono or di-substituted alkyl (C1, C4, and/or C9) phenols are “bridged” or linked by a single atom (carbon or sulfur). The carbon atom linking the alkyl phenol groups contains hydrogen, propyl, or methyl substitutions. Although purities are listed for individual study summaries for several category members, only CASRN 96-69-5 includes a range of purities (95 – 99 +) for the commercial products.

| <b>Table 1. Representative Chemical Structures of the Bridged Alkyl Phenols Category</b> |              |  |
|--|--------------|--|
| <b>Chemical Name</b>   | <b>CASRN</b> | <b>Structure</b>                               |
| <b>SPONSORED CHEMICALS</b>   |              |  |
| Phenol, 4,4'-(1-methyl-ethylidene)bis[2-(1,1-dimethylethyl)-                             | 79-96-9      |  |
| Phenol, 4,4'-butylidenebis[2-(1,1-dimethylethyl)-5-methyl-                               | 85-60-9      |  |
| Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-                                     | 96-69-5      |  |
| Phenol, 2,2'-methylenebis[4-methyl-6-nonyl-  | 7786-17-6    |  |
|  |              | Representative C9 alkyl structure <sup>1</sup> |

<sup>1</sup> **Please Note:** The branched C9 structure shown here is used to represent CASRN 7786-17-6, especially for the

**Table 1. Representative Chemical Structures of the Bridged Alkyl Phenols Category**

| Chemical Name | CASRN | Structure |
|---------------|-------|-----------|
|---------------|-------|-----------|

purposes of estimating physical-chemical and fate properties. It differs from the structure depicted by the sponsor in the Test Plan, in that it contains the branched tripropylene-based C9 substituent instead of the linear C9 alkyl group. The sponsor does not indicate if the source of the C9 alkyl is based on tripropylene alkylation. However, the branched structure shown is more representative of the C9 alkyl groups generally present in commercial chemical substances.

## 1.2 Physical-Chemical Properties

The physical-chemical properties of the bridged alkyl phenols category are summarized in Table 2. The bridged alkyl phenols are solids with negligible water solubility and negligible vapor pressure.

| <b>Table 2. Physical-Chemical Properties of the Bridged Alkyl Phenols Category<sup>1</sup></b> |   |  |  |  |
|--|---|--|--|--|
| Property   | Phenol, 4,4'-(1-methylethylidene) bis[2-(1,1-dimethylethyl)-    | Phenol, 4,4'-butylidenebis[2-(1,1-dimethylethyl)-5-methyl-             | Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-                                     | Phenol, 2,2'-methylenebis[4-methyl-6-nonyl                             |
| CASRN  | 79-96-9   | 85-60-9  | 96-69-5  | 7786-17-6  |
| Molecular Weight   | 340.51  | 382.59   | 358.54   | 480.78   |
| Physical State   | Solid   | Solid; white powder <sup>2</sup>                                       | Solid; white <sup>3</sup>  | Solid; tan <sup>4</sup>  |
| Melting Point (°C)   | 113–115.5 (measured)  | 210 (measured); 209 (measured) <sup>2</sup>                            | 156–158 (measured); 163 (measured) <sup>3</sup>  | 251.8 (measured)   |
| Boiling Point (°C)   | >300 (estimated)  | 282 (decomposes)   | 207.4 (decomposes)   | >300 (estimated)   |
| Vapor Pressure (mm Hg at 25°C)   | $6.6 \times 10^{-9}$ (estimated) <sup>5</sup>                   | $<1.0 \times 10^{-10}$ (estimated) <sup>5</sup>                        | $6.3 \times 10^{-7}$ at 70°C (measured); $<1.0 \times 10^{-10}$ (estimated) <sup>5</sup> | $<1.0 \times 10^{-10}$ (estimated) <sup>5</sup>                        |
| Water Solubility (mg/L at 25°C)  | 0.014 (estimated) <sup>5</sup>                                  | <0.1 at 18°C (measured); $4.1 \times 10^{-5}$ (estimated) <sup>5</sup> | <0.1 (measured); $9.0 \times 10^{-4}$ (estimated) <sup>5</sup>                           | $4.2 \times 10^{-8}$ (estimated) <sup>5</sup> ; Insoluble <sup>4</sup> |
| Dissociation Constant (pK <sub>a1</sub> )  | 11.29 (estimated) <sup>6</sup> ; 11.44 (estimated) <sup>6</sup> | 11.29 (estimated) <sup>6</sup> ; 11.49 (estimated) <sup>6</sup>        | 10.50 (estimated) <sup>6</sup> ; 10.64 (estimated) <sup>6</sup>                          | 11.71 (estimated) <sup>6</sup> ; 11.71 (estimated) <sup>6</sup>        |
| Henry's Law Constant (atm·m <sup>3</sup> /mole)  | $<1.0 \times 10^{-10}$ (estimated) <sup>5</sup>                 | $<1.0 \times 10^{-10}$ (estimated) <sup>5</sup>                        | $<1.0 \times 10^{-10}$ (estimated) <sup>5</sup>  | $<1.0 \times 10^{-10}$ (estimated) <sup>5</sup>                        |

| Property            | Phenol, 4,4'-(1-methylethylidene) bis[2-(1,1-dimethylethyl)- | Phenol, 4,4'-butylidenebis[2-(1,1-dimethylethyl)-5-methyl- | Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl- | Phenol, 2,2'-methylenebis[4-methyl-6-nonyl |
|---------------------|--|--|--|--|
| CASRN               | 79-96-9  | 85-60-9  | 96-69-5  | 7786-17-6                                  |
| Log K <sub>ow</sub> | 7.46 (estimated) <sup>5</sup>                                | 9.09 (estimated) <sup>5</sup>                              | 8.24 (estimated) <sup>5</sup>                        | 12.81 (estimated) <sup>5</sup>             |

<sup>1</sup> Rubber and Plastic Additives Panel of the American Chemistry Council. Test Plan and Robust Summary for the Bridged Alkyl Phenols Category. July 2003. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/hndrdphn/c13382tc.htm> as of May 6, 2010.

<sup>2</sup> Hawley, G.G. 2007. The Condensed Chemical Dictionary. 15<sup>th</sup> edition. John Wiley Sons, Inc., New York: p. 200.

<sup>3</sup> Lide, D.R. 2008. CRC Handbook of Chemistry and Physics 89<sup>th</sup> edition. CRC Press.

<sup>4</sup> Chemtura Corporation. 2008. Technical Information: Naugawhite®, Rubber Antioxidant (2,2'-Methylenebis(6-Nonyl-p-Cresol). Available online from:

[http://www.chemtura.com/deployedfiles/staticfiles/product/Business%20Units/Polymer\\_Additives-en-us/BU%20Documents/Technical%20Data%20Sheets/Miscellaneous%20Rubber%20Additives/Rubber%20Antioxidants/Naugawhite%20TDS%20.pdf](http://www.chemtura.com/deployedfiles/staticfiles/product/Business%20Units/Polymer_Additives-en-us/BU%20Documents/Technical%20Data%20Sheets/Miscellaneous%20Rubber%20Additives/Rubber%20Antioxidants/Naugawhite%20TDS%20.pdf) as of May 10, 2010.

<sup>5</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from:

<http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm>. As of May 10, 2010.

<sup>6</sup> SPARC. 2010. Online pK<sub>a</sub> and Property Calculator, v.4.2.1405-s4.2.1408. Available online from: <http://ibmlc2.chem.uga.edu/sparc/> as of May 10, 2010.

## 2. General Information on Exposure

### 2.1 Production Volume and Exposure

According to the 2006 IUR submissions, the Bridged Alkyl Phenol category chemicals had an aggregated production and/or import volume in the United States between 500,000 pounds and 2 million pounds.

- CASRN 85-60-9: <500,000 pounds
- CASRN 96-69-5: 500,000 to <1 million pounds
- CASRN 7786-17-6: <500,000 pounds

CASRN 79-96-9 was not reported in the 2006 IUR. For CASRNs 85-60-9 and 7786-17-6, no industrial processing and uses and commercial and consumer uses were reported. Industrial processing and uses for CASRN 96-69-5 were claimed confidential. No commercial and consumer uses were reported.

### 2.2 Environmental Exposure and Fate

The environmental fate properties of the bridged alkyl phenols are provided in Table 3. The bridged alkyl phenols category members are expected to have low mobility in soil. Two members of the bridged alkyl phenols category – CASRN 85-60-9 and CASRN 96-69-5 – were not readily or inherently biodegradable. CASRN 85-60-9 was not inherently biodegradable in a

shake flask method for ultimate biodegradation, degrading 0–5% after 35 days at a nominal concentration of 20.7 mg/L as measured by CO<sub>2</sub> evolution. CASRN 96-69-5 was found not readily biodegradable in a closed bottle test (OECD 301D), degrading 1.9% in 14 days at a nominal concentration of 100 ppm. CASRN 96-69-5 was also found not to be inherently biodegradable in a Thompson-Duthie-Sturm semi-continuous activated sludge (SCAS) test procedure, degrading 11% in 90 days at a nominal concentration of 3 mg/L. Structural similarities suggest that the two remaining members of the bridged alkyl phenols will also be not readily or inherently biodegradable. The use of the four members of the bridged alkyl phenols as antioxidants suggests they have the potential to oxidize to the quinone like other sterically-hindered phenols, which may lower their persistence in the environment. The rate of hydrolysis is expected to be negligible under environmental pH and temperature. The rate of volatilization of all members is considered low based on their Henry's Law constants. The bridged alkyl phenols are expected to have moderate persistence (P2) and low bioaccumulation potential (B1), with the exception of CASRN 79-96-9, which is expected to have a high bioaccumulation potential (B3).

| <b>Property</b>            | <b>Phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)-</b> | <b>Phenol, 4,4'-butylidenebis[2-(1,1-dimethylethyl)-5-methyl-</b> | <b>Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-</b>  | <b>Phenol, 2,2'-methylenebis[4-methyl-6-nonyl-</b> |
|----------------------------|--|---|--|--|
| CASRN                      | 79-96-9  | 85-60-9   | 96-69-5  | 7786-17-6  |
| Photodegradation Half-life | 1.3 hours (estimated) <sup>2</sup>                                 | 0.6 hours (estimated) <sup>2</sup>                                | 1.0 hours (estimated) <sup>2</sup>   | 2.0 hours (estimated) <sup>2</sup>                 |
| Hydrolysis Half-life       | No data  | No data   | 37% degradation in 168 hours at pH 7 at 23°C   | No data  |
| Biodegradation             | No data  | 0–5% in 35 days (not inherently biodegradable)                    | 1.9% biodegradation in 14 days (measured, not readily biodegradable) <sup>3</sup> ; 11% biodegradation in 90 days (not inherently biodegradable) | No data  |
| Bioaccumulation Factor     | BAF = 7,666 (estimated) <sup>2</sup>                               | BAF = 198.4 (estimated) <sup>2</sup>                              | BCF = 0.1 to 11 (measured in carp) <sup>3</sup> ; BAF = 308 (estimated) <sup>2</sup>   | BAF = 1.3 (estimated) <sup>2</sup>                 |
| Log K <sub>oc</sub>        | 6.3 (estimated) <sup>2</sup>                                       | 7.1 (estimated) <sup>2</sup>                                      | 6.3(estimated) <sup>2</sup>  | 9.0 (estimated) <sup>2</sup>                       |

| <b>Table 3. Environmental Fate Characteristics of the Bridged Alkyl Phenols Category<sup>1</sup></b> |  |   |   |  |
|--|--|---|---|--|
| <b>Property</b>  | <b>Phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)-</b> | <b>Phenol, 4,4'-butylidenebis[2-(1,1-dimethylethyl)-5-methyl-</b> | <b>Phenol, 4,4'-thiobis[2-(1,1-dimethylethyl)-5-methyl-</b> | <b>Phenol, 2,2'-methylenebis[4-methyl-6-nonyl-</b> |
| Fugacity (Level III Model) <sup>2</sup>  | <0.1   | <0.1  | <0.1  | <0.1   |
| Air (%)  | 1.85   | 4.26  | 3.29  | 12.3   |
| Water (%)  | 45.4   | 46.3  | 55.3  | 84.5   |
| Soil (%)   | 52.7   | 49.4  | 41.4  | 3.21   |
| Sediment (%)   |  |   |   |  |
| Persistence <sup>4</sup>   | P2 (moderate)  | P2 (moderate)   | P2 (moderate)   | P2 (moderate)                                      |
| Bioaccumulation <sup>4</sup>   | B3 (high)  | B1 (low)  | B1 (low)  | B1 (low)   |

<sup>1</sup> Rubber and Plastic Additives Panel of the American Chemistry Council. Test Plan and Robust Summary for the Bridged Alkyl Phenols Category. July 2003. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/hndrdphn/c13382tc.htm> as of May 10, 2010.

<sup>2</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from:

<http://www.epa.gov/opptintr/exposure/pubs/episutedl.htm> as of May 10, 2010.

<sup>3</sup> National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from:

[http://www.safe.nite.go.jp/english/kizon/KIZON\\_start\\_hazkizon.html](http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html) as of May 10, 2010.

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

### **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 member are read-across (RA) to the untested members of the category.

#### ***Acute Oral Toxicity***

##### ***Subcategory I***

##### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

Sprague-Dawley rats (males and females in groups of five animals/dose) were administered CASRN 96-69-5 (25% suspension in corn oil) as a single oral dose at 2510, 3160, 3980 or 5010 mg/kg and observed for up to 14 days. Mortalities were observed in female rats at all dose levels and in high-dose male rats.

**LD<sub>50</sub> = 4150 mg/kg**

### *Subcategory II*

#### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

Sprague-Dawley rats (males and females of unspecified group numbers) were administered CASRN 85-60-9 (identified in the robust summary as Santowhite Powder, > 96% purity) as a 20% suspension in corn oil at dose levels of 6310 or 7940 mg/kg. The duration of post-dosing observation was not specified, but was at least 3 days. Mortalities were observed (doses of mortalities not provided).

**LD<sub>50</sub> > 7940 mg/kg**

### *Subcategory III*

No data

### *Acute Dermal Toxicity*

#### *Subcategory I*

#### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

New Zealand Albino rabbits (one male at the low and high doses, one male and one female at the middle dose) were administered CASRN 96-69-5 (> 96% purity) as a 40% suspension in corn oil via single 24-hour occlusive dermal application at doses of 3160, 5010 or 7940 mg/kg-bw and observed for up to 14 days. The single male rabbit at the highest dose died at an unspecified time post-treatment. No other mortalities were observed.

**LD<sub>50</sub> > 5010 and < 7940 mg/kg-bw**

#### *Subcategory II*

#### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

New Zealand White rabbits (unspecified numbers of males and females/dose) were administered CASRN 85-60-9 (identified as Santowhite Powder, > 96% purity) as a 40% suspension in corn oil via single dermal application at doses of 5010 or 7940 mg/kg-bw and observed for 14 days. No mortalities were observed.

**LD<sub>50</sub> > 7940 mg/kg-bw**

#### *Subcategory III*

No data

### *Repeated-Dose Toxicity*

#### *Subcategory I*

#### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

(1) In a National Toxicology Program (NTP) study, F344/N rats (10/sex/concentration) were administered CASRN 96-69-5 (99% purity) in the diet for 13 weeks at concentrations of 0, 250, 500, 1000, 2500 or 5000 ppm (males: 0, 15, 30, 60, 165 and 315 mg/kg-bw/day, respectively; females: 0, 15, 35, 70, 170 and 325 mg/kg-bw/day, respectively). All rats survived the 13 weeks of treatment. Decreased food consumption was noted in male and female rats at the highest dose. Statistically significant ( $p < 0.01$ ) effects in males and females at the highest dose included decreased mean final body weights, increased absolute and relative liver weight, increased serum alanine aminotransferase activities, alkaline phosphatase activities (males) and increased incidences of lesions in the liver (hyperplasia in the bile duct, Kupffer cell hypertrophy and necrosis), kidney (necrosis and pigmentation) and lymph nodes (macrophage hyperplasia). At 5000 ppm, there were also increases in total leukocyte counts in females and segmented neutrophil counts in males and females ( $p \leq 0.01$ ), which were consistent with an inflammatory response. At 2500 ppm, Kupffer cell hypertrophy in the liver was also noted in males and females. None of these histopathological lesions were observed in controls. Also at 2500 ppm, increased serum alkaline phosphatase activity in males, increased serum alanine aminotransferase activity in males and females and increased relative liver weight in males were observed ( $p \leq 0.01$  for all). Decreased hematocrit and hemoglobin concentrations ( $p \leq 0.05$  or  $0.01$ ) were observed in male rats at exposure concentrations  $\geq 1000$  ppm (with a dose response for hemoglobin), which was suggestive of mild anemia. Neurotoxicity was assessed only at 1000 and 2500 ppm; dose-related increased forelimb and hindlimb grip strength was noted in both male and female exposed rats at both doses ([http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults)).

**LOAEL ~ 60 mg/kg-bw/day** (based on decreased hemoglobin concentrations and increases in forelimb/hindlimb grip strength)

**NOAEL ~ 30 mg/kg-bw/day**

(2) In an NTP study, B6C3F<sub>1</sub> mice (10/sex/concentration) were administered CASRN 96-69-5 (99% purity) in the diet for 13 weeks at concentrations of 0, 100, 250, 500, 1000 or 2500 ppm (males: 0, 15, 30, 65, 145 and 345 mg/kg-bw/day, respectively; females: 0, 15, 35, 60, 165 and 340 mg/kg-bw/day, respectively). All mice survived the 13 weeks of treatment. There were no treatment-related clinical signs. At the highest exposure concentration (2500 ppm), decreased food consumption was noted in male rats during the first 3 weeks and in female rats during most of the study. Significantly depressed ( $p < 0.01$ ) mean final body weights were noted in female mice at concentrations  $\geq 500$  ppm and in male mice at the highest dose. Significantly increased absolute and relative liver weights were also noted at the highest dose ( $p < 0.01$ ). Significantly increased absolute and relative spleen weights were noted in males at concentrations  $\geq 500$  ppm ( $p < 0.05$  at 500 and 1000 ppm;  $p < 0.01$  at 2500 ppm) and in females at 2500 ppm ( $p < 0.01$ ); relative spleen weight was also significantly ( $p < 0.01$ ) increased in 1000 ppm females. Differences in other organ weights were considered related to reductions in mean body weights. At 2500 ppm, male and female mice exhibited significant ( $p < 0.01$ ) increases in the incidence liver lesions (bile duct hyperplasia, Kupffer cell hypertrophy), and males also exhibited a significantly increased ( $p < 0.05$ ) incidence of macrophage hyperplasia in mesenteric lymph nodes. None of the histopathologic lesions were seen in control rats. Erythrocyte counts and mean volumes and hematocrit and hemoglobin concentrations were significantly ( $p < 0.05$ ) lower in males and females at the highest dose relative to control values. Hematocrit and erythrocyte counts were also lower in 1000 ppm males ( $p < 0.01$ ) and females ( $p < 0.5$ ), suggestive of anemia ([http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults)).

**LOAEL ~ 145-165 mg/kg-bw/day** (based on decreases in hematocrit and erythrocyte counts)

**NOAEL ~ 60-65 mg/kg-bw/day**

(3) In an NTP study, groups of F344/N rats (115 males and 75 females per dose level) were fed a diet that provided ~ 0, 20, 40 or 100 mg/kg-bw/day CASRN 96-69-5 (99% purity) to males and 0, 20, 45 or 120 mg/kg-bw/day to females for 104 weeks. Endpoints monitored included clinical signs, body weight and food consumption. Hematology, clinical chemistry and urinalysis tests were conducted at 3, 9 and 15 months (15 rats/sex/dose). Also at 15 months, an additional 10 male and 10 female rats from each group were evaluated for histopathology (along with hematology and clinical chemistry) and 40 male rats per group were evaluated for neurotoxic effects. Survival rates and body weights were generally comparable between groups throughout the study. Food consumption, behavior and general health and appearance of exposed males and female rats were similar to those of the controls. Slight decreases in hematocrit levels, hemoglobin concentrations and erythrocyte counts were observed in one set of mid- and high-dose males at 15 months ( $p \leq 0.05$  or  $\leq 0.01$ ). Similar decreases in hematocrit level and hemoglobin concentration occurred in females at the highest dose at 9 months ( $p \leq 0.01$ ). Mean erythrocyte hemoglobin concentrations in females at the highest dose were lower than those of controls at 9 and 15 months ( $p \leq 0.01$ ). Platelet counts were slightly increased in one set of males and females at the highest dose evaluated at 15 months ( $p \leq 0.01$ ). Serum activities of alkaline phosphatase, alanine aminotransferase and sorbitol dehydrogenase in high-dose males were greater than those in controls at 3, 9 and 15 months ( $p \leq 0.01$ ). Alkaline phosphatase activities in both sets of 40 mg/kg-bw/day males evaluated at 15 months were greater than those of controls ( $p \leq 0.01$ ). Serum activities of alanine aminotransferase and sorbitol dehydrogenase were greater in females at the highest dose than those of controls at 3, 9 and 15 months ( $p \leq 0.01$ ). Neurotoxicity tests did not show alterations on motor nerve excitability or conduction,

neuromuscular transmission or muscle contractility that could be attributed to treatment with CASRN 96-69-5. In addition, there were no microscopic lesions in the sciatic nerve, quadriceps muscle or teased nerve preparations of sciatic nerve that could be attributed to administration of the chemical. Histopathological evaluations at 15 months and at termination showed increased incidences of Kupffer cell hypertrophy, hepatocyte cytoplasmic vacuolization and mixed cell foci in mid- and high-dose rats ([http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults)).

**LOAEL ~ 20 mg/kg-bw/day** (based on hematological effects and signs of liver toxicity)

**NOAEL = Not established**

(4) In an NTP study, groups of B6C3F<sub>1</sub> mice (80/sex/dose level) were fed a diet that provided 0, 250, 500 or 1000 ppm (~ 0, 30, 60 or 145 mg/kg-bw/day CASRN 96-69-5 (99% purity) to males or 0, 45, 110 or 255 mg/kg-bw/day to females) for 104 weeks. Endpoints monitored included clinical signs, body weight, food consumption and gross and microscopic evaluation of all major organs and tissues. Hematology, clinical chemistry and urinalysis tests were also conducted on 9 or 10 mice/sex/group at 3, 9 and 15 months. The survival rates of exposed male and female mice were similar to those of the controls. The final mean body weights of males and females at the highest dose were 8% and 18% lower than those of the controls, respectively. Food consumption by exposed males was similar to that by controls; treated females seemed to have consumed more food than controls. There were no clinical findings attributed to administration of CASRN 96-69-5. Hematocrit level, hemoglobin concentration and erythrocyte count were significantly lower in high-dose males than in controls at the 15-month interim evaluation ( $p \leq 0.01$ ). Serum alkaline phosphatase activities were slightly greater in males at the highest dose (relative to controls) at 3 and 9 months ( $p \leq 0.01$ ), as was the serum alkaline phosphatase activity in high-dose females at 9 months ( $p \leq 0.01$ ). Serum levels of total bilirubin in all groups of exposed males were significantly greater than those in controls at 9 and 15 months. In the absence of liver histopathology, the toxicological significance of this finding is unknown. The only significant histopathological finding was an increased incidence of myelofibrosis in highest dose females ([http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults)).

**LOAEL (males) ~ 145 mg/kg-bw/day** (based on hematological effects)

**NOAEL (males) ~ 60 mg/kg-bw/day**

**LOAEL (females) ~ 255 mg/kg-bw/day** (based on myelofibrosis)

**NOAEL (females) ~ 110 mg/kg-bw/day**

### ***Subcategory II***

#### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

(1) Sprague-Dawley rats (15 male and female rats/concentration) were administered CASRN 85-60-9 (> 95% purity) in the diet for 90 days at concentrations of 0, 100, 500 or 1000 ppm (males, 0 and ~ 6, 30 and 60 mg/kg-bw/day, respectively; females, 0 and ~ 5, 25 and 50 mg/kg-bw/day, respectively). There were no significant clinical signs and no mortalities. Slightly reduced food consumption and body weights, altered serum alanine aminotransferase and aspartate transaminase, increased liver weight and (unspecified) microscopic liver and lymph node changes were noted in 1000 ppm rats. Rats in the 500 ppm group also exhibited altered serum alanine aminotransferase and aspartate transaminase, increased liver weight and (absolute/relative unspecified) microscopic liver and lymph node lesions.

**LOAEL ~ 25 mg/kg-bw/day** (based on signs of liver toxicity and lymph node lesions)

**NOAEL ~ 5 mg/kg-bw/day**

(2) Carworth Farms rats (6/sex/dose group) were administered CASRN 85-60-9 in the diet for 90 days at concentrations of 0, 50, 500 or 5000 ppm (males, 0 and ~ 3, 30 or 300 mg/kg-bw/day, respectively; females, 0 and ~ 2.5, 25 or 250 mg/kg-bw/day, respectively). There were no deaths during the study. At 5000 ppm, rats showed reduced weight gain and food consumption, and hematology tests done on days 45 and 90 revealed an increase in leukocytes. At this dose, rats also had increased relative liver weight, yellowish livers, fatty infiltration and necrosis. At 500 ppm, rats also had yellowish livers, increased relative liver weight and some fatty infiltration. No abnormalities were reported at the lowest dose (<http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384> – Fiche# OTS0545986).

**LOAEL ~ 25 mg/kg-bw/day** (based on signs of liver toxicity)

**NOAEL ~ 2.5 mg/kg-bw/day**

(3) Sprague-Dawley rats (10/sex/concentration) were administered CASRN 85-60-9 (> 95% purity) in the diet for 28 days at concentrations of 0, 1000, 2500, 5000 or 10,000 ppm (males, 0 and ~ 60, 150, 300 and 600 mg/kg-bw/day, respectively; females, 0 and ~ 50, 125, 250 and 500 mg/kg-bw/day, respectively). There were no significant clinical signs and no mortalities. Reduced food intake and body weights were observed in males and females at concentrations  $\geq$  2500 ppm. Upon necropsy, increased absolute and relative liver weights and liver discoloration were noted in all male and female rats at all exposure levels. Histopathological examination revealed hepatocellular vacuolation in all exposed dose groups and hepatocellular degeneration/necrosis was also noted at exposure levels  $\geq$  2500 ppm.

**LOAEL ~ 50 mg/kg-bw/day** (based on signs of liver toxicity; lowest dose tested)

**NOAEL = Not established**

(4) Sprague-Dawley rats (Crj: CD) (10/sex/concentration) were administered CASRN 85-60-9 (98.5% purity) via gavage at 0, 5, 25 and 125 mg/kg-day for at least 28 days. Clinical signs were recorded daily and body weight/food consumption was evaluated. Hematological parameters as well as clinical biochemistry were evaluated. Status of thyroid hormones was also evaluated. Changes in gait, posture, response to handling, occurrence of clonic/tonic movements were also evaluated. A functional observation battery tested sensory reactivity to stimuli, assessed grip strength and motor activity. Spermatology, estrous cycling, organ weights and histopathology were also evaluated. Soft stools and diarrhea were observed in some male and female rats at 125 mg/kg-day. White blood cell and platelet counts were increased at 125 mg/kg-day ( $p < 0.05$ ). Several enzyme levels were also increased at 125 mg/kg-day. Several enzymes were increased in males and/or females at 125 mg/kg-day ( $p < 0.05$ ). Total cholesterol, triglyceride, glucose, albumin and albumin-globulin ratios were decreased in male and/or females at 25 and/or 125 mg/kg-day ( $p < 0.05$ ). At 125 mg/kg-day, serum thyroid-stimulating hormone was increased (both sexes) and serum triiodothyronine and thyroxin were decreased in males ( $p < 0.05$ ). No abnormalities were observed in sperm or estrous cycle analyses. Relative liver weights increased at 25 (males) and 125 mg/kg-day (males and females) ( $p < 0.05$ ). Thyroid weights were increased in female rats at 125 mg/kg-day (and slightly increased in males at this dose; significance not stated). Follicular epithelial cell hypertrophy was seen in thyroids in 4 females at 125 mg/kg-day. Centrilobular hepatocyte hypertrophy was seen in all rats at 125 mg/kg-day (not at lower doses). Lipid droplets were seen in hepatocytes in one male rat at 5 mg/kg-day,

in 10 males and 4 females at 25 mg/kg-bw/day, and in all rats at 125 mg/kg-bw/day (Yamasaki et al., 2008).

**LOAEL = 25 mg/kg-day** (based on signs of liver toxicity)

**NOEL = 5 mg/kg-day**

(5) Carworth Farms rats (6/sex/dose group) were administered CASRN 85-60-9 (identified as Santowhite Powder) in the diet for 30 days at concentrations of 0, 500, 2500 or 12,500 ppm (males, 0 and ~30, 150 or 750 mg/kg-bw/day, respectively; females, 0 and ~25, 125 or 625 mg/kg-bw/day, respectively). At the highest dose, all rats had reduced weight gain, but there was no mortality. Relative liver weight was increased in high-dose rats and in some mid-dose rats. Necropsy of 12,500 ppm rats revealed vacuoles around the central vein of the liver, which were interpreted as beginning fatty infiltration; vacuoles were also seen in some rats at 2500 ppm, but not in 500 ppm rats ([http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384 – Fiche#\\_OTS\\_0545986](http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384-Fiche#_OTS_0545986)).

**LOAEL ~ 125 mg/kg-bw/day** (based on signs of liver toxicity)

**NOEL ~ 25 mg/kg-bw/day**

### ***Subcategory III***

No data

## ***Reproductive Toxicity***

### ***Subcategory I***

#### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

(1) In a study evaluating male reproductive toxicity, male Crj:CD-1(ICR) mice (8 mice/group) were administered CASRN 96-69-5 (purity > 98%) in the diet at 0.06, 0.125 and 0.25% (~ 81.6-99.0, 164-196 and 351-495 mg/kg-bw/day) for 2 months (Takahashi and Oishi, 2006). Separate experiments were conducted – one using 0, 0.06 and 0.125% and a second experiment using a different 0% control group plus a 0.25% treatment group. Body weight and food intake were occasionally measured. Clinical signs of toxicity were recorded each day and blood was collected. Kidney and liver weights were measured only at 0.25%. Preputial glands, testes, epididymides, prostate glands, seminal vesicles with coagulation glands, kidneys and liver were weighed. Extensive histopathological examinations of testes were conducted, which included evaluation of seminiferous tubules (counts, vacuolization, detachment, scattering, atrophy, reduced spermatogenesis, luminal dilatation, etc), Leydig cells (counts, vacuolization, degeneration, necrosis, proliferation) and Sertoli cells (vacuolization). Testosterone concentrations in serum were determined, and sperm content and daily sperm production (DSP) were determined.

At 0.25%, relative liver weight was significantly increased ( $p < 0.01$ ), and fatty liver was seen in 37.5% of the mice at necropsy (not statistically significant). Also at 0.25%, most mice (62.5%) did not have parametrial adipose tissues ( $p < 0.01$ ). At the highest dose, testicular weight was not significantly reduced although absolute weights of epididymides, seminal vesicles, prostate glands and preputial glands were significantly decreased ( $p < 0.05$  or  $0.01$ ); relative weights of

preputial glands were also significantly lower than controls ( $p < 0.01$ ). Also at the highest dose, severe exfoliation of seminiferous tubules was observed in 62.5% of the mice ( $p < 0.01$ ); sloughing of seminiferous tubules was seen in 75% of mice ( $p < 0.01$ ); vacuolization and proliferation of Leydig cells and dilated lumen of the seminiferous tubules were each seen in 50% of the mice ( $p < 0.05$ ). At 0.125%, lumen dilatation was seen in 75% of mice ( $p < 0.01$ ) and sloughing was seen in one animal (not significant). Serum testosterone was increased ( $p < 0.01$ ) only at the middle dose (0.125%); variability in testosterone levels may have been due to differences in social dominance hierarchies and may not be treatment-related. At 0.06%, one mouse each exhibited lumen dilatation of seminiferous tubules and sloughing (not significant). Mice exhibited dose-related decreases in DSP ( $p < 0.01$ ) (Takahashi and Oishi, 2006).

**LOAEL (males) ~ 82-99 mg/kg-bw/day** (based on decreased sperm production, dilated lumen and sloughing of seminiferous tubules)

**NOAEL (males) = Not established**

(2) Male F344 rats (8 rats/group) were administered CASRN 96-69-5 (purity > 98%) in the diet at 0.06 or 0.25% (~ 41-57.3 or 155-230 mg/kg-bw/day) for 2 months (Takahashi and Oishi, 2006). Separate experiments (with two different control groups) were conducted for each concentration. Evaluations were the same as those described for study summary (1) in this section, except that spleen weights were also measured at 0.25%. At 0.25%, absolute (but not relative) spleen weights were lower ( $p < 0.05$ ). At 0.25%, relative testicular weight was significantly increased whereas relative weights of seminal vesicles with coagulation glands and ventral/dorsolateral prostate glands were decreased ( $p < 0.05$ ). Absolute dorsolateral prostate glands were also decreased at this dose ( $p < 0.05$ ). At the highest dose, 2 rats had enlarged cecum. Exfoliation of seminiferous tubules was seen in 6 and 7 animals at 0.06 and 0.25%, respectively ( $p < 0.01$ ). Sloughing of seminiferous tubules was seen in 5 animals at 0.25% ( $p < 0.01$ ) and in only one animal at 0.06% (not significant). At 0.25%, one animal exhibited a degenerated tubule and 2 exhibited germ cell loss. Although overall DSP was not decreased, DSP per gram testis was slightly decreased at 0.25% ( $p < 0.05$ ) (Takahashi and Oishi, 2006).

**LOAEL (males) ~ 41-57 mg/kg-bw/day** (based on exfoliation of seminiferous tubules)

**NOAEL (males) = Not established**

(3) In the previously-described repeated-dose toxicity study of male and female F344/N rats and male and female B6C3F<sub>1</sub> mice administered CASRN 96-69-5 in the diet for 13 weeks or 2 years (NTP studies), gross and microscopic examinations of reproductive organs and tissues revealed no evidence of treatment-related adverse effects.

## ***Subcategory II***

### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

(1) Male Crj:CD-1(ICR) mice (8 mice/group) were administered CASRN 85-60-9 (purity > 95%) in the diet at 0.06, 0.125 and 0.25% (approximately 80.4-95.4, 205-206 and 340-450 mg/kg-bw/day) for 2 months (Takahashi and Oishi, 2006). Separate experiments were conducted (with separate control groups) – one using treatment groups of 0.06 and 0.125% and a second experiment using a 0.25% treatment group. Evaluations were the same as those described for study summary (1) for CASRN 96-69-5, Subcategory I in the *Reproductive Toxicity* section.

Body weights at termination were lower at the mid-dose ( $p < 0.01$ ) but not at the other doses. At 0.25%, relative liver weight was significantly increased ( $p < 0.01$ ), and fatty liver was seen in all mice at necropsy ( $p < 0.01$ ). At 0.25%, relative weights of seminal vesicles with coagulation glands, prostate glands and preputial glands were all lower than controls ( $p < 0.05$ ); at the same dose, absolute weights of these same organs plus epididymides were also decreased ( $p < 0.01$  for prostate glands,  $p < 0.05$  for the other organs). At lower doses, relative weights exhibited an opposite trend – they were higher than controls for most organs; statistical significance was reached at 0.125% for testes ( $p < 0.05$ ), seminal vesicles with coagulation glands ( $p < 0.05$ ), prostate glands ( $p < 0.01$ ) and epididymides ( $p < 0.01$ ). Also at 0.25%, severe exfoliation of seminiferous tubules was observed in 75% of the mice ( $p < 0.01$ ); sloughing of seminiferous tubules was seen in 50% of mice ( $p < 0.05$ ); dilated lumen of the seminiferous tubules was seen in 75% of the mice ( $p < 0.01$ ). Two mice exhibited proliferation of Leydig cells at 0.25% (not statistically significant), but none showed proliferation at lower doses. At 0.125%, 2 animals exhibited exfoliation and 3 had dilated lumens (not significant); at 0.6%, one animal had presence of giant cells and 2 had dilated lumens (not significant). Also at 0.25%, serum testosterone was lower than controls (not significant) but variability in testosterone levels may be due to differences in social dominance hierarchies and therefore, may not be treatment-related. Mice exhibited dose-related decreases in DSP and DSP/g testis when evaluated in the experiment using 0.06 and 0.125% ( $p < 0.01$ ) (Takahashi and Oishi, 2006).

**LOAEL (males) ~ 80-95 mg/kg-bw/day** (based on decreased sperm production, presence of giant cells and dilated lumens)

**NOAEL (males) = Not established**

(2) Male F344 rats (8 rats/group) were administered CASRN 85-60-9 (purity > 95%) in the diet at 0.06 or 0.25% (~ 40.7-57.7 or 159-230 mg/kg-bw/day) for 2 months (Takahashi and Oishi, 2006). Separate experiments (with two different control groups) were conducted for each dietary concentration. Evaluations were the same as those described for study summary (1) for CASRN 96-69-5, Subcategory I in the *Reproductive Toxicity* section, except that spleen weights were also measured at 0.25%. At 0.25%, relative liver weights were approximately 50% higher than controls, as were absolute weights ( $p < 0.01$ ), and all rats at this dose had fatty livers ( $p < 0.01$ ). At 0.25%, relative testicular weight was significantly increased ( $p < 0.05$ ) whereas relative weights of seminal vesicles with coagulation glands and ventral/dorsolateral prostate glands were decreased ( $p < 0.01$ ). Absolute weights of these organs (seminal vesicles, prostate glands, preputial glands, epididymides) were also decreased at this dose ( $p < 0.05$  or  $< 0.1$ ). At 0.06%, however, absolute (and some relative) weights of the reproductive organs tended to be higher (instead of lower) than controls, although none were statistically significant. One rat at each of the doses had vacuolated Sertoli cells. Exfoliation of seminiferous tubules was seen in 1 and 7 animals at 0.06 and 0.25%, respectively ( $p < 0.01$  at the high dose only). At 0.25%, sloughing of seminiferous tubules was seen in 6 animals ( $p < 0.01$ ), and 5 rats exhibited disappearance of germ cells. DSP and DSP per gram testis was slightly decreased at 0.25% ( $p < 0.05$ ) (Takahashi and Oishi, 2006).

**LOAEL (males) ~ 41-58 mg/kg-bw/day** (based on signs of testicular toxicity)

**NOAEL (males) = Not established**

(3) In the previously-described repeated-dose toxicity study of male and female Sprague-Dawley rats administered CASRN 85-60-9 in the diet for 90 days, gross and microscopic examinations of

reproductive organs and tissues revealed no evidence of treatment-related adverse effects up to approximately 60 mg/kg-bw/day in males and 50 mg/kg-bw/day in females.

### *Subcategory III*

No data

### *Developmental Toxicity*

#### *Subcategory I*

##### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

Pregnant New Zealand White rabbits (13/dose) were administered CASRN 96-69-5 (suspended in 0.5% gum tragacanth) by gavage at 0, 0.2, 2.0 or 20 mg/kg-day on gestation days 6 – 18. Clinical signs and body weights were monitored during pregnancy. Rabbits were sacrificed on gestation day 29 and the uterus was immediately dissected for evaluation of the fetuses and counting of resorption sites and corpora lutea. Fetuses were weighed and examined externally and internally for abnormalities and processed for evaluation of skeletal abnormalities. Pregnancy rate was not significantly affected. One rabbit at 2.0 mg/kg-day and four rabbits at 20 mg/kg-day showed anorexia and subsequent abortion; the trend for abortion was statistically significant. Also, litter size was reduced and the incidence of embryonic deaths was significantly increased at 20 mg/kg-day. Mean weight gain of high-dose rabbits that did not abort was not significantly different from that of controls. Among rabbits with viable litters, there were no conclusive effects on litter size, fetal loss or litter weight. Mean pup weight in the mid-dose, but not high-dose group, was significantly ( $p < 0.05$ ) lower than controls (~ 15% lower than controls). The apparent lack of effects in the high-dose group could have been related to alterations in the sample composition due to groups with total litter loss. There were no statistically significant treatment-related effects on incidences of visceral and skeletal anomalies and skeletal variants (<http://www.srcinc.com/what-we-do/databaseforms.aspx?id=384> – Fiche# OTS0542114).

**LOAEL (maternal toxicity) = 20 mg/kg-day** (based on anorexia and spontaneous abortions)

**NOAEL (maternal toxicity) = 2 mg/kg-day**

**LOAEL (developmental toxicity) = 2 mg/kg-day** (based on decreased mean weight of offspring)

**NOAEL (developmental toxicity) = 0.2 mg/kg-day**

#### *Subcategory II*

No data

#### *Subcategory III*

No data

## *Genetic Toxicity – Gene Mutations*

### *In vitro*

#### *Subcategory I*

##### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were incubated with CASRN 96-69-5 (99% pure) at concentrations ranging from 0.1 to 500 µg/plate in the presence and absence of metabolic activation. Cytotoxicity was observed at 500 µg/plate with metabolic activation and at 100 µg/plate without metabolic activation. The solvent was dimethylsulfoxide and various positive controls were used with and without metabolic activation. No explicit information was provided in the sponsor's summary regarding results of the assays with positive controls.

**CASRN 96-69-5 was not mutagenic in this assay.**

(2) In an NTP study, *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 were incubated with CASRN 96-69-5 at concentrations ranging from 0.1 to 500 µg/plate in the presence and absence of metabolic activation. Solvent and positive controls were used. Positive controls responded appropriately ([http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults)).

**CASRN 96-69-5 was not mutagenic in this assay.**

#### *Subcategory II*

##### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

(1) *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were incubated with CASRN 85-60-9 (> 95% pure) at 0.1, 1.0, 10, 100 or 500 µg/plate in the presence and absence of metabolic activation. No information was provided in the sponsor's summary regarding solvent and positive controls.

**CASRN 85-60-9 was not mutagenic in this assay.**

(2) *Saccharomyces cerevisiae* strain D4 were incubated with CASRN 85-60-9 (> 95% pure) at 0.1, 1.0, 10, 100 or 500 µg/plate in the presence and absence of metabolic activation. No information was provided in the sponsor's summary regarding solvent and positive controls.

**CASRN 85-60-9 was not mutagenic in this assay.**

#### *Subcategory III*

No data

## *Genetic Toxicity – Chromosomal Aberrations*

### *In vitro*

#### *Subcategory I*

##### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

(1) Chinese hamster lung cells were incubated with CASRN 96-69-5 (> 97% pure) in DMSO at 1.25, 2.5 or 5.0 mg/mL in the presence and absence of metabolic activation. There is no mention of positive controls in the sponsor's summary. The cytotoxic concentration was 5.0 mg/mL both with and without activation.

**CASRN 96-69-5 did not induce chromosomal aberrations in this assay.**

(2) In an NTP study, Chinese hamster ovary (CHO) cells were incubated with CASRN 96-69-5 in DMSO at 3 – 12.5 µg/mL in the absence (18.5 hours) and presence (2 hours) of metabolic activation. Solvent and positive controls were included and responded appropriately ([http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults)).

**CASRN 96-69-5 did not induce chromosomal aberrations in this assay.**

#### *Subcategory II*

##### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

CHO cells were incubated with CASRN 85-60-9 at 2, 4 or 8 µg/mL in the absence of metabolic activation or at 12.5, 25 or 50 µg/mL in the presence of metabolic activation. Negative and positive controls were included but no information on responses for the controls was included.

**CASRN 85-60-9 did not induce chromosomal aberrations in this assay.**

#### *Subcategory III*

No data

### *In vivo*

#### *Subcategory I*

##### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

Groups of Fisher 344 rats (5/sex/group) were administered a single dose of CASRN 96-69-5 (99% pure) by gavage in corn oil at 0, 700 or 1400 mg/kg-bw and sacrificed at 6, 18 and 30 hours after dosing for evaluation of chromosomal aberrations in bone marrow. Bone marrow was sampled 6, 24 and 48 hours after dosing. Solvent and positive controls were used and responded appropriately.

**CASRN 96-69-5 did not induce chromosomal aberrations in this assay.**

## *Genetic Toxicity – Other*

### *In vitro*

#### *Subcategory I*

##### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

(1) In an NTP study, CHO cells were incubated with CASRN 96-69-5 in DMSO at 0.5 – 16.7 µg/mL in the absence (26 hours) and presence (2 hours) of metabolic activation. Solvent and positive controls were included and responded appropriately. CASRN 96-69-5 induced sister chromatid exchanges at doses that induced cell cycle delays. The test results were considered equivocal ([http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=96-69-5&fuseaction=ntpsearch.searchresults)).

(2) *S. cerevisiae* strain D4 were incubated with CASRN 96-69-5 (95% pure) in DMSO at concentrations ranging from 0.1 to 500 µg/plate in the presence and absence of metabolic activation to evaluate the frequency of mitotic recombinations. Negative and positive controls were included in the assay but their responses were not included. Cytotoxicity was not observed. **CASRN 96-69-5 did not induce mitotic recombinations in this assay.**

#### *Subcategory II*

##### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

Primary rat liver cells were incubated with CASRN 85-60-9 (Santowhite Powder; >96% pure) at concentrations of 1, 5, 10, 50, 100 or 250 µg/L in the absence of metabolic activation to evaluate unscheduled DNA synthesis. No information was provided regarding solvent or positive controls.

**CASRN 85-60-9 did not induce unscheduled DNA synthesis in this assay.**

## *Additional Information*

### *Skin Irritation*

#### *Subcategory I*

##### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

Six New Zealand Albino rabbits were administered 0.5 g of CASRN 96-69-5 as a finely ground powder moistened with water to the shaved dorsal skin. The application area was covered with an occlusive wrap for 24 hours. Evaluations were performed at 24, 48, 72 and 168 hours after topical application.

**CASRN 96-69-5 was not irritating to rabbit skin in this assay.**

## *Eye Irritation*

### *Subcategory I*

#### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

Six New Zealand Albino rabbits were administered 100 mg of CASRN 96-69-5 as a finely ground powder to one eye; the other was untreated and served as control. The cornea, iris and conjunctiva were examined immediately after treatment and then at intervals of 10 minutes and 1, 24, 48, 72 and 168 hours. Immediate findings included slight discomfort. At 10 minutes, moderate erythema slight edema and copious discharge were noted. At 1 hour, there was moderate to severe erythema, slight edema and copious discharge. At 24 hours, there was moderate to severe erythema, slight edema and copious discharge containing a slight whitish exudate. At 48 hours, there was gradual improvement. All signs of irritation had subsided by the third day after exposure.

**CASRN 96-69-5 was irritating to rabbit eyes in this assay.**

## *Skin Sensitization*

### *Subcategory I*

#### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

Female BALB/c mice (5/dose) were administered CASRN 96-69-5 at 0.1, 0.5, 1.0, 5.0 and 10.0% (w/v) in acetone at 25  $\mu$ l on the dorsal surface of each ear for three consecutive days. Negative controls that received only the vehicle and positive controls that received 30%  $\alpha$ -hexylcinnamaldehyde were also used. Animals rested for 2 days following the last exposure. On the following day, mice were injected intravenously via the lateral tail vein with 20  $\mu$ Ci [ $H^3$ ]-thymidine in order to measure lymphocyte proliferation and were then euthanized five hours later. The left and right cervical draining lymph nodes were pooled for each animal. No irritation (as determined by an absence of ear swelling) was observed. The concentration of the chemical required to induce a 3-fold increase in lymphocyte proliferation compared with the negative controls was 0.2% (Myers et al., 2007).

**CASRN 96-69-5 was a skin sensitizer in this assay.**

## *Carcinogenicity*

### *Subcategory I*

#### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

In the previously summarized 2-year dietary NTP bioassay of CASRN 96-69-5, there was no evidence of carcinogenic activity in male or female F344/N rats or in male or female B6C3F<sub>1</sub> mice under the conditions of the study.

## *Uterotrophic Assays*

### *Subcategory I*

#### ***4,4'-Thiobis(6-t-butyl-m-cresol) (CASRN 96-69-5)***

In a uterotrophic assay (to test for estrogenicity), ovariectomized adult female mice (8 mice/dose) were administered CASRN 96-69-5 at 0.06 and 0.25% (approximately 64.2-74.4 and 285-313 mg/kg-day) in their diets for 2 months. Mice were killed and uteri were dissected and weighed at termination of feeding. Body weight and food consumption were reported. In addition, radiation body temperature was measured at 3 weeks, and parametrial fat weighed at necropsy. Although there was a trend towards higher uterine weights in treated animals, only the absolute uterine weight was increased at 0.25%. Body temperatures were decreased at both doses ( $p < 0.05$ ). The authors conclude that this chemical may be a weak xenoestrogen *in vivo* (Takahashi and Oishi, 2006).

### *Subcategory II*

#### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

In a uterotrophic assay, ovariectomized adult female mice (8 mice/dose) were administered CASRN 85-60-9 at 0.06 and 0.25% (approximately 62.4-78.6 and 375-383 mg/kg-day) in their diets for 2 months. Mice were killed and uteri were dissected and weighed at termination of feeding. Body weight and food consumption were reported. In addition, radiation body temperature was measured at 3 weeks, and parametrial fat was weighed at necropsy. Absolute and relative uterine weights were increased at 0.25% ( $p < 0.01$  or  $< 0.05$ , depending on statistical test). Absolute and relative parametrial adipose tissue weight was decreased at the high dose ( $p < 0.01$ ), and body temperatures were decreased at both doses ( $p < 0.05$ ). The authors conclude that this chemical is a weak xenoestrogen *in vivo* (Takahashi and Oishi, 2006).

## *Hershberger Assay*

### *Subcategory II*

#### ***4,4'-Butylidenebis(6-t-butyl-m-cresol) (CASRN 85-60-9)***

Castrated male Brl Han:WIST Jcl (GALAS) rats (56 days old) were administered CASRN 85-60-9 (98.5% purity) via gavage at 50, 200 and 1000 mg/kg for 10 consecutive days. A vehicle control given olive oil only was also used. Rats were then injected subcutaneously with 0.2 mg/k-bw/day testosterone propionate (TP) in their backs, and another group (positive control) was injected with TP only. To confirm the reliability of the study, another group received the known androgen antagonist flutamide via gavage plus injections of TP. Body weights of the rats were measured. In addition, the ventral prostates (plus fluid), seminal vesicles (plus fluid), blubocavernosus/levator ani muscles, glans penis and Cowper's glands were weighed. No changes in body weight were observed. The relative weight of the blubocavernosus/levator ani muscle was lower at all doses (plus TP) than with vehicle with no clear dose response. The absolute weight of this muscle was not different from the vehicle plus TP group. In the TP-only group, weights of all accessory sex organs were higher than the organ weights for the vehicle controls. The futamide plus TP group had lower organ weights compared with the rats administered only TP (Yamasaki et al., 2008).

**CASRN 85-60-9 was negative for estrogenic and androgenic activity in this assay.**

### **Conclusions:**

#### ***Subcategory I***

Acute oral toxicity to rats and acute dermal toxicity to rabbits is low for CASRN 96-69-5. In a 13-week repeated-dose toxicity study, dietary administration in rats resulted in changes in hematological parameters at ~ 60 mg/kg-bw/day and higher; the NOAEL for systemic toxicity is ~ 30 mg/kg-bw/day. In a second 13-week dietary study in mice, CASRN 96-69-5 exposure resulted in changes in hematology at ~ 145 - 165 mg/kg-bw/day and higher; the NOAEL for systemic toxicity is ~ 60-65 mg/kg-bw/day. In a chronic study, CASRN 96-69-5 administered to rats in the diet for 104 weeks resulted in signs of liver toxicity and changes in hematological parameters at ~ 40 mg/kg-bw/day and higher; the NOAEL for systemic toxicity is ~ 20 mg/kg-bw/day. Another 104-week dietary study in mice showed significant decreases in hematological parameters in males at ~ 145 mg/kg-bw/day (highest concentration tested); the NOAEL for systemic toxicity is ~ 60 mg/kg-bw/day. No reproductive toxicity studies are available; however, in a two-month oral study with CASRN 96-69-5 that assessed male reproductive toxicity, decreased sperm production and histopathological changes in seminiferous tubules of rats and mice at 41-57 and 82-99 mg/kg-bw/day, respectively (lowest doses tested) were observed. No effects to reproductive organs were reported in the chronic studies. In an oral gavage prenatal developmental toxicity study in rabbits, anorexia and spontaneous abortions were observed in dams treated at 20 mg/kg-day; the NOAEL for maternal toxicity is 2 mg/kg-day. Significant decreases in mean pup weight and litter size occurred at 2 mg/kg-day; the NOAEL for developmental toxicity is 0.2 mg/kg-day. CASRN 96-69-5 did not induce gene mutations in bacteria or chromosomal aberrations either in mammalian cells *in vitro* or *in vivo*. CASRN 96-69-5 is not irritating to rabbit skin but is irritating to rabbit eyes. CASRN 96-69-5 is a skin sensitizer based on data from the mouse local lymph node assay. No evidence of carcinogenicity was observed with CASRN 96-69-5 exposure in rats during a two-year dietary study.

#### ***Subcategory II***

Acute oral and dermal toxicity of Subcategory II is low in rats. In 90-day repeated-dose toxicity studies, signs of liver toxicity and lymph node lesions were seen in rats administered CASRN 85-60-9 in the diet at 25 mg/kg-bw/day and higher; the NOAELs for systemic toxicity ranged from 2.5 – 5 mg/kg-bw/day. A repeated-dose toxicity study with CASRN 85-60-9 conducted to evaluate male reproductive parameters revealed decreased sperm production and histopathological changes in the seminiferous tubules following oral exposure in rats and mice for 2 months at 41-58 and 80-95 mg/kg-bw/day, respectively (lowest doses tested). No data are available for developmental toxicity endpoints. CASRN 85-60-9 did not induce gene mutations in bacteria or chromosomal aberrations in mammalian cells *in vitro*.

#### ***Subcategory III***

No data were provided for CASRN 7786-17-6.

**Table 4. Summary of the Screening Information Data Set – Human Health Data**

| Endpoints  | Subcategory I  | Subcategory II  |  | Subcategory III  |
|--|--|---|--|--|
|  | SPONSORED<br>CHEMICAL<br>4,4'-Thiobis<br>(6- <i>t</i> -butyl- <i>m</i> -cresol)<br><br>(96-69-5) | SPONSORED<br>CHEMICAL<br>4,4'-Butylidenebis-<br>(6- <i>t</i> -butyl- <i>m</i> -cresol)<br><br>(85-60-9) | SPONSORED<br>CHEMICAL<br>Phenol, 4,4'-<br>(1-methylethylidene)-<br>bis[2-(1,1-dimethyl-<br>ethyl)]-<br>(79-96-9) | SPONSORED<br>CHEMICAL<br>Phenol, 2,2'-methylene-<br>bis(4-methyl-6-nonyl)<br><br>(7786-17-6) |
| Acute Oral Toxicity<br>LD <sub>50</sub> (mg/kg-bw)   | 4150   | > 7940  | No Data<br>> 7940<br>(RA)  | No Data  |
| Acute Dermal Toxicity<br>LD <sub>50</sub> (mg/kg-bw)   | > 5010 < 7940  | > 7940  | No Data<br>> 7940<br>(RA)  | No Data  |
| Repeated-Dose Toxicity<br>NOAEL/LOAEL<br>Oral (mg/kg-bw/day)   | Rat<br>NOAEL ~ 20<br>LOAEL ~ 40  | Rat<br>NOAEL = NE<br>LOAEL = 5  | No Data<br>NOAEL = NE<br>LOAEL = 5<br>(RA)   | No Data  |
| Reproductive Toxicity<br>– Fertility<br>NOAEL/LOAEL<br>Oral (mg/kg-bw/day)<br>Systemic Toxicity<br>Reproductive Toxicity | No Data  | No Data   | No Data  | No Data  |
| Reproductive Toxicity<br>– Male Parameters<br>NOAEL/LOAEL<br>Oral (mg/kg-bw/day)   | Rat<br>NOAEL = Not<br>established<br>LOAEL = 41-57   | Rat<br>NOAEL = Not<br>established<br>LOAEL = 41-58  | No data<br>Rat<br>NOAEL = Not<br>established<br>LOAEL = 41-58<br>(RA)  | No data  |
| Devel Toxicity<br>NOAEL/LOAEL<br>Oral (mg/kg-bw/day)<br>Maternal Toxicity<br>Developmental Toxicity                      | Rabbit<br>NOAEL = 2<br>LOAEL = 20<br>NOAEL = 0.2<br>LOAEL = 2.0                                  | No Data   | No Data  | No Data  |

**Table 4. Summary of the Screening Information Data Set – Human Health Data**

|  | Subcategory I  | Subcategory II  |  | Subcategory III  |
|--|--|---|--|--|
|  | <b>SPONSORED CHEMICAL</b><br>4,4'-Thiobis<br>(6- <i>t</i> -butyl- <i>m</i> -cresol)<br><br>(96-69-5) | <b>SPONSORED CHEMICAL</b><br>4,4'-Butylidenebis-<br>(6- <i>t</i> -butyl- <i>m</i> -cresol)<br><br>(85-60-9) | <b>SPONSORED CHEMICAL</b><br>Phenol, 4,4'-<br>(1-methylethylidene)-<br>bis[2-(1,1-dimethyl-<br>ethyl)]-<br>(79-96-9) | <b>SPONSORED CHEMICAL</b><br>Phenol, 2,2'-methylene-<br>bis(4-methyl-6-nonyl)<br><br>(7786-17-6) |
| <b>Endpoints</b>   |  |   |  |  |
| <b>Genetic Toxicity – Gene Mutation</b><br><i>In vitro</i>           | Negative   | Negative  | No Data<br>Negative<br>(RA)  | No Data  |
| <b>Genetic Toxicity – Chromosomal Aberrations</b><br><i>In vitro</i> | Negative   | Negative  | No Data<br>Negative<br>(RA)  | No Data  |
| <b>Genetic Toxicity – Chromosomal Aberrations</b><br><i>In vivo</i>  | Negative   | –   | –  | –  |
| <b>Additional Information</b>  |  |   |  |  |
| <b>Skin Irritation</b>   | Not irritating   | –   |  |  |
| <b>Eye Irritation</b>  | Slightly irritating  | –   | –  | –  |
| <b>Skin Sensitization</b>  | Positive   | –   |  |  |
| <b>Uterotrophic assay</b><br><i>(in vivo)</i>                        | Weak estrogenicity   | Weak estrogenicity  |  |  |
| <b>Hershberger assay</b><br><i>(in vivo)</i>                         | –  | Negative  |  |  |

Measured data (bold face); (RA) = Read Across; – indicates that endpoint was not addressed for this substance; NE = Not established

#### 4. Hazard to the Environmental

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. For the category member phenol, 2,2'-methylenebis(4-methyl-6-nonyl) CASRN 7786-17-6), no aquatic toxicity testing is required for fish, aquatic invertebrates, or aquatic plant because of the low water solubility and high log  $K_{ow}$  value.

##### *Acute Toxicity to Fish*

###### ***4,4'-Thiobis(6-*t*-butyl-*m*-cresol) (CAS No. 96-69-5)***

(1) Fathead minnow (*Pimephales promelas*) were exposed to 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in acetone at nominal concentrations of 0, 0.1, 0.18, 0.32, 0.56 or 1.0 mg/L under static conditions for 96 hours. Analytical monitoring of test substance concentration was not performed. No effects were seen at the 0.1 mg/L concentration.

**96-h LC<sub>50</sub> = 0.36 mg/L**

(2) Rainbow trout (*Salmo gairdneri*) were exposed to 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in acetone at nominal concentrations of 0, 0.1, 0.14, 0.18, 0.24, 0.32 or 0.42 mg/L under static conditions for 96 hours. Dissolved oxygen and pH were monitored. Analytical monitoring of test substance concentration was not performed. No effects were seen at the 0.1 mg/L concentration.

**96-h LC<sub>50</sub> = 0.16 mg/L**

(3) Rainbow trout (*Salmo gairdneri*) were exposed to 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in acetone at nominal concentrations of 0, 0.075, 0.10, 0.16, 0.21, 0.32, 0.42, 0.56 or 0.75 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 0.13 mg/L**

(4) Bluegill sunfish (*Lepomis macrochirus*) were exposed to 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in acetone at nominal concentrations of 0, 0.14, 0.18, 0.24, 0.32, 0.56, 0.75 or 1.0 mg/L under static conditions for 96 hours. No effects were seen at the 0.14 mg/L concentration.

**96-h LC<sub>50</sub> = 0.24 mg/L**

(5) Bluegill sunfish (*Lepomis macrochirus*) were exposed to 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in acetone at nominal concentrations of 0, 0.24, 0.32, 0.42, 0.56, 0.75, 1.0, 1.4 or 1.8 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 0.51 mg/L**

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

###### ***4,4'-Thiobis(6-*t*-butyl-*m*-cresol) (CAS No. 96-69-5)***

(1) Water fleas (*Daphnia magna*) were exposed to 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in dimethylformamide at nominal concentrations of 0, 0, 0.063, 0.125, 0.25, 0.5 or 1.0 mg/L under static conditions for 48 hours. No effects were seen at the 0.063 mg/L concentration.

**48-h EC<sub>50</sub> = 0.16 mg/L**

(2) Water fleas (*Daphnia magna*) were exposed to 4,4'-thiobis(6-*t*-butyl-*m*-cresol) in acetone at nominal concentrations of 0, 0, 0.18, 0.56, 1.0, 3.2, 5.6, 10 or 32 mg/L under static conditions for 48 hours. No effects were seen at the 0.18 mg/L concentration.

**48-h EC<sub>50</sub> = 0.70 mg/L**

***Toxicity to Aquatic Plants***

No adequate data are available for bridged alkyl phenols category.

**Conclusions:** The 96-hr LC<sub>50</sub> values of CASRN 96-69-5 for fish ranges from 0.13 to 0.51 mg/L. The 48-hr EC<sub>50</sub> of CASRN 96-69-5 for aquatic invertebrates ranges from 0.16 to 0.70 mg/L.

| Table 5. Summary of Aquatic Toxicity Data                    |  |  |   |   |
|--|--|--|---|---|
| Endpoints  | 4,4'-Thiobis-<br>(6- <i>t</i> -butyl- <i>m</i> -cresol)<br><br>(96-69-5) | Phenol,<br>4,4'-(1-methyl-<br>ethylidene)bis<br>[2-(1,1-dimethyl-<br>ethyl)]-<br>(79-96-9) | 4,4'-Butylidenebis<br>(6- <i>t</i> -butyl- <i>m</i> -<br>cresol)<br><br>(85-60-9) | Phenol,<br>2,2'-methylenebi<br>s(4-methyl-<br>6-nonyl)<br><br>(7786-17-6) |
| <b>Fish</b><br>96-h LC <sub>50</sub> (mg/L)                  | <b>0.13 – 0.51</b>   | 0.13 – 0.51<br>(RA)  | 0.13 – 0.51<br>(RA)   | Data not<br>Required  |
| <b>Aquatic Invertebrates</b><br>48-h EC <sub>50</sub> (mg/L) | <b>0.16 - 0.70</b>   | 0.16 - 0.70<br>(RA)  | 0.16 - 0.70<br>(RA)   | Data not<br>Required  |
| <b>Aquatic Plants</b><br>72-h EC <sub>50</sub> (mg/L)        | No Adequate Data   | No Data  | No Data   | Data not<br>Required  |
| <b>Aquatic Invertebrates</b><br>21-day Chronic               | No Data  | No Data  | No Data   | Data not<br>Required  |

Measured data (bold face); (RA) = read-across

## 5. References

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