

January 13, 2004

Donald A. Lederer  
Product Stewardship Manager  
Solutia, Inc.  
575 Marysville Centre Drive  
St. Louis, MO 63141

Dear Mr. Lederer:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Polyphenyls Category posted on the ChemRTK HPV Challenge Program Web site on August 19, 2003. I commend Solutia, Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Solutia, Inc. advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: [oppt.ncic@epa.gov](mailto:oppt.ncic@epa.gov) and [chem.rtk@epa.gov](mailto:chem.rtk@epa.gov).

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at [tsca-hotline@epa.gov](mailto:tsca-hotline@epa.gov).

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director  
Risk Assessment Division

Enclosure

cc: W. Penberthy  
M. E. Weber

## EPA Comments on Chemical RTK HPV Challenge Submission: Polyphenyl (3- and 4-Phenyl Rings) Category

### Summary of EPA Comments

The sponsor, Solutia, Inc. submitted a test plan and robust summaries to EPA for the polyphenyl (3- and 4-phenyl rings) category dated July 25, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 19, 2003. The category consists of two sponsored chemicals, Mixed Terphenyls (CAS No. 26140-60-3) and Quaterphenyls (CAS No. 29036-02-0). Supplementary data were also submitted for o-, m-, and p-terphenyls (CAS Nos. 84-15-1, 92-06-0, and 92-94-4, respectively).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The description of the category members on page 8 of the test plan under Section II (Common Structure) seems fairly clear. However, the composition ranges of some of the tested substances differ from the definitions on page 8. In addition, the composition ranges of some tested mixtures are inconsistent between the test plan and the IUCLID data set. Information on the biphenyl content of current products should be more completely addressed. Finally, the submitter needs to discuss variations in the isomeric content of the quaterphenyls (to the extent that this information is known).
2. Category Justification. EPA reserves judgment on the submitter's grouping of terphenyls and quaterphenyls in a single category. For mammalian toxicity, toxicokinetic information and/or repeated-dose toxicologic studies on quaterphenyls are needed to determine the potential for read-across among these substances. For all endpoints, information on the isomeric content of the quaterphenyls and whether any manufactured products contain biphenyl is desirable.
3. Physicochemical Properties. EPA reserves judgment on these endpoints pending receipt of information on biphenyl content of the manufactured products and variations in the isomeric content of the quaterphenyls. In addition, the submitter needs to check discrepancies and/or inconsistencies in vapor pressure values and the water solubility value for p-terphenyl.
4. Environmental Fate. Adequate information is provided for biodegradation and stability in water. Depending on the variation in isomeric content of the quaterphenyls, the submitter may wish to provide photodegradation and fugacity calculations for relevant quaterphenyl isomers. In addition, if commercial terphenyl mixtures contain biphenyl, the submitter needs to address any possible differences in fate endpoints compared with terphenyl mixtures that do not contain biphenyl.
5. Health Effects. EPA reserves judgment on the health effects endpoints pending receipt of information on toxicokinetics for both terphenyls and quaterphenyls and/or repeated-dose toxicity data for quaterphenyls as well as biphenyl content of the manufactured products and variations in the isomeric content of the quaterphenyls.
6. Ecological Effects. EPA reserves judgment on these endpoints pending receipt of information on the biphenyl content of the manufactured products, variations in the isomeric content of quaterphenyl mixtures, and clarification of the water solubility value. Also, the submitter needs to provide robust summaries of the SAR estimates using the neutral organic-predicted equations to satisfy these endpoints.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

### **EPA Comments on the Polyphenyl (3 and 4-phenyl Rings) Category Challenge Submission**

#### **Category Definition**

The submitter proposes a category containing two members that are each predominantly composed of mixed isomers of 3- and 4-ring polyphenyls, Mixed Terphenyls (CAS No. 26140-60-3) and Quaterphenyls (CAS No. 29036-02-0) (see definition on page 8, under Section II, Category Justification, Common Structure). Mixed Terphenyls contain 60-90% terphenyls and 10-30% quaterphenyls while Quaterphenyls contain 80-90% quaterphenyls and 10-20% terphenyls. The submitter states that these commercial compositional ratios define the category members rather than the CAS No. definition.

The submitter uses several commercial mixtures as representative of the category members. However, the composition ranges of some of the representative compounds discussed both in the test plan and in the IUCLID data set differ from the definitions on page 8. Also, there are differences in the description of the content of individual products. The submitter also notes that there are variations in the isomeric content of the quaterphenyls but does not discuss the extent of these variations. The submitter needs to address these discrepancies and include more information on the isomeric content of the quaterphenyls, if available.

The commercial terphenyl mixtures whose data are used to represent the Mixed Terphenyls are: (1) Therminol 75 (also called MCS-1980), which contains 61-62% terphenyls, 34% quaterphenyls, and 4% higher boilers; (2) Santowax R (also called Therminol 88), which contains 81-82% terphenyls, 16-17% quaterphenyls, and 2% higher boilers; (3) Santowax MP (>99% terphenyls); and (4) Santowax OM (96% terphenyls and 4% quaterphenyls). According to information provided in the test plan (page 7), Santowax R, Therminol 75, and Santowax MP predominantly contain meta- and para-isomers of terphenyl with <1-10% of the o-isomer. However, from the one test substance description provided in the IUCLID data set, Therminol 75 predominantly contains the m-isomer (89%) versus 8% for the p-isomer and 3% for the o-isomer. The IUCLID data set describes Santowax MP and Santowax OM products that contain terphenyls and quaterphenyls in proportions that are outside the ranges defined by the submitter on page 8 of the test plan. Also, the IUCLID data set states that Santowax OM contains  $\leq$  5% biphenyl, which has its own toxicity that might have influenced the results of the submitted health effects toxicity tests. Although the test plan states that the sponsor produces Therminol 75 (MCS-1980) and Santowax R (Therminol 88) and Solutia, Inc. may be the only manufacturer, the sponsor needs to more clearly address whether biphenyl is contained in currently manufactured terphenyls or quaterphenyls.

Data for the individual terphenyl isomers, o-terphenyl (CAS No. 84-15-1), m-terphenyl (CAS No. 92-06-8), and p-terphenyl (CAS No. 92-94-4), have also been provided as support for the category.

To represent the quaterphenyl category member, the submitter uses two commercial quaterphenyl mixtures. Santotar 9 and Santowax Q are described on page 7 of the test plan as containing 90% quaterphenyls and 10% mixed terphenyls. The IUCLID data set, however, states that Santotar 9 contains 95% quaterphenyls plus higher polyphenyls and <1% terphenyls. Information in the IUCLID data set is also not consistent with the terphenyl content range in the quaterphenyl mixtures as defined on page 8 of the test plan.

## **Category Justification**

The submitter bases the grouping of the category members on structural and functional similarities between the individual terphenyl and quaterphenyl isomers. The submitter bases the category on some similarities among the category members in physicochemical properties (although they acknowledge differences among individual isomers) and somewhat greater similarities in environmental fate properties. The submitter also notes similarities in acute mammalian and acute aquatic toxicities.

EPA acknowledges that the structures of these compounds are similar given the lack of benzene ring substituents. Also, there do appear to be some similarities in the submitted data and estimations. Acute oral LD<sub>50</sub> values in rats are similar for the mixed terphenyls and quaterphenyls (considering the purest of the terphenyl mixtures): >5000 mg/kg for Santowax MP (<0.5% o-, 75% m-, and 24% p-terphenyls plus 1% quaterphenyls) and 5650 mg/kg for Santowax Q (95% quaterphenyls plus 5% mixed terphenyls). No deaths occurred at the limit dose of 5000 mg/kg for the mixed terphenyls and only one animal died out of five (mixed sex) exposed to quaterphenyls. For both substances, hypoactivity was observed in some animals, but no abnormal findings were observed in survivors at gross necropsy. It should be noted, however, that similarity in acute toxicities is not a good indicator of similarities in other human health endpoints. In addition, the submitted ecological toxicity data show similarities in relative magnitudes of the measured and calculated EC50s and LC50s for the mixed terphenyls and quaterphenyls, provided that the calculated values are accurate (see comments below under Test Plan, Ecological Effects). Finally, the terphenyl and quaterphenyl compounds have generally similar estimated distributions in the environment (e.g., mainly into soil and sediments).

However, the submitter does not adequately justify grouping these chemicals in the same category. First, the available data do not always suggest a pattern among the chemicals. For example, it is difficult to compare physicochemical data among mixtures adequately to establish a pattern. Also, differences in both mammalian and ecological toxicity among the three terphenyl isomers suggest that a read-across to quaterphenyls (which may include a greater number of isomers) may be more complicated than a simple extrapolation from 3-ring to 4-ring compounds. Second, key data to establish a read-across approach from terphenyls to quaterphenyls are missing. For example, the submitter did not provide adequate data to compare mammalian toxicities among terphenyls and quaterphenyls (e.g., toxicokinetic data for both compounds or repeated-dose toxicity data on quaterphenyl mixtures should be supplied). Also, lack of data on the variation in isomeric mixtures of the quaterphenyls further complicates a read-across approach. EPA believes that these considerations along with human health and ecological toxicity results that show effects at low doses suggest that the submitter needs to provide further justification for including both mixtures in a single category.

## **Test Plan**

### **Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)**

EPA reserves judgment on physicochemical properties pending receipt of information on biphenyl content of the manufactured products and variations in the isomeric content of the quaterphenyls. On page 6 of the test plan (Introduction), the CAS No. for o-terphenyl should be 84-15-1, not 100-00-5. In addition, the structure presented for m-terphenyl on page 6 is actually the structure for o-terphenyl.

*Vapor pressure.* The submitter provided supporting data for the mixed terphenyl category member. Vapor pressure values of  $3 \times 10^{-4}$  hPa (25°C),  $2.33 \times 10^{-5}$  hPa (25°C), and  $4.56 \times 10^{-7}$  hPa (25°C) were given for

the o-, m-, and p-isomers of terphenyl, respectively, and obtained from standard reference sources (Daubert and Danner, 1989; Neely and Blau, 1985). The values for the o- and m-isomers were extrapolated from measured data; the value for the p-isomer was an estimate obtained from a literature source (Neely and Blau 1985). However, the almost 50-fold difference in the vapor pressures given for o- and p-terphenyl is much larger than would be expected from the small difference in the boiling points between m-terphenyl (363°C) and p-terphenyl (376°C). The submitter needs to check these values, and make any corrections necessary.

*Water solubility.* The submitter provided a value of 0.0018 mg/L at 25°C for p-terphenyl, which was obtained from a standard reference source (Yalkowsky and Dannenfelser, 1992). However, EPA found a different value (0.018 mg/L) in another literature source that cites Yalkowsky and Dannenfelser. The submitter needs to check the water solubility value for p-terphenyl and correct if necessary.

#### Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Adequate information is provided for biodegradation and stability in water. Depending on the variation in isomeric content of the quaterphenyls, the submitter may wish to provide photodegradation and fugacity calculations for relevant quaterphenyl isomers. In addition, if commercial terphenyl mixtures contain biphenyl, the submitter needs to address any possible differences in fate endpoints compared with terphenyl mixtures that do not contain biphenyl.

#### Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

EPA reserves judgment on the health effects endpoints pending receipt of information on toxicokinetics for both terphenyls and quaterphenyls and/or repeated-dose toxicity data for quaterphenyls as well as biphenyl content of the manufactured products and variations in the isomeric content of the quaterphenyls.

Toxicokinetic data can provide information on similarities in absorption, distribution, excretion, and metabolites between the terphenyls and quaterphenyls. In addition, toxicokinetic data on the terphenyls may help explain why the NOAEL from the 235-day study is lower than the NOAELs from the 30-day studies (e.g., are these chemicals persistent within the body?). If toxicokinetic data are not available, the submitter needs to provide repeated-dose toxicity data on quaterphenyls to compare with the data available for terphenyls.

#### Ecological Effects (fish, invertebrates, and algae).

EPA reserves judgment on ecological effects pending receipt of information on variations in the isomeric content of quaterphenyl mixtures, the biphenyl content of manufactured products, and clarification of the water solubility value discussed in the physicochemical properties section of EPA's comments.

In addition to measured data, the submitter provided ECOSAR predictions for the two sponsored chemicals, mixed terphenyls and quaterphenyls, and three non-sponsored chemicals, o-, m-, and p-terphenyls. The summaries in which these predictions were provided indicated that the esters class was used as the basis for the predictions. However, when EPA entered the CAS Nos. for these five chemicals into the same version of ECOSAR that was apparently used by the sponsor (i.e., v.0.99), ecotoxicity predictions were based on the neutral organics class. The submitter needs to address this discrepancy.

## Specific Comments on the Robust Summaries

### Environmental Fate

The phrases “3-membered” and “4-membered” are misleading and ideally should be deleted from the summaries for mixed terphenyls and quaterphenyls.

*Stability in water.* The submitter needs to provide more explanation in the robust summaries (as it did with mixed terphenyl, and quaterphenyl) as to why o-, m-, and p-terphenyl do not undergo hydrolysis.

### Health Effects

For mixed terphenyls, some of the robust summaries for non-critical studies were missing reference citations.

*Acute Toxicity.* A robust summary for an acute oral toxicity study in rats exposed to Santowax Q (95% quaterphenyls, 5% mixed terphenyls) was acceptable but had several discrepancies. The summary did not provide results for mortality by sex or for clinical signs by dose. The protocol was equivalent to OECD Guideline 401 except that the group size was 5 mixed sex per dose rather than 5/sex/dose.

*Repeated-Dose Toxicity.* A robust summary for a 235-day bioassay in rats exposed to Santowax OM (95% mixed terphenyls) was acceptable, but was deficient in some areas. The summary was missing the magnitude of body weight effects and the protocol differed from OECD Guideline 408 in the use of a slightly smaller group size (9 rather than 10/sex/group), the use of fewer parameters for hematology and histopathology examinations, and the lack of analyses for clinical chemistry and ophthalmoscopy. The submitter should discuss whether the results may have been influenced by the 5% biphenyl content in the test substance.

*Genetic Toxicity.* A robust summary for a negative chromosomal aberration assay in rats exposed by intraperitoneal injection to Therminol 75 (62% mixed terphenyls and 34% quaterphenyls) apparently had an error; lines 10 and 11 of the Methods fields refer to the numbers of *slides* counted for mitotic index and chromosomal aberrations, when it is likely that *cells* was the intended word.

### Ecological Effects

*Fish.* The submitter needs to provide the number of fish tested per concentration and mortality per concentration for the mixed terphenyl compound, Therminol 75, in *P. promelas*. The submitter needs to clarify how the water solubility of 0.75 mg/L was estimated in this study. This test is considered the key study because it's the only test conducted at or below the reported water solubility.

*Invertebrates.* Missing study details noted in the summaries for studies of the mixed terphenyl compounds MCS 1980 and Therminol 88 include percent mortality per concentration and in the case of Therminol 88 the amount of acetone used in the test solution.

The reported EC<sub>50</sub> values were apparently based on mortality for both studies, although this was not clearly stated in the summaries. If this was the case, these values should be specified as LC<sub>50</sub> values instead of EC<sub>50</sub> values.

The summaries for the supporting chemicals, o-, m-, and p-terphenyl, lack the substance purity.

*Algae.* The summary for the study of Therminol 88 and Therminol 75 lacks the results of cell counts and specifics on the composition of the culture medium.

*Chronic Toxicity to Fish.* The LOEC is missing from the study of the mixed terphenyl compound, Therminol 75.

For each endpoint using SAR, the submitter needs to provide robust summaries of the SAR estimations using the neutral organic-predicted equations, and stating the log  $K_{ow}$  used.

**Followup Activity**

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.