May 29, 2009

Douglas Winkelmann
Technical Contact
ExxonMobil Chemical Company
13501 Katy Freeway
Houston, TX 77079

Dear Mr. Winkelmann:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for sec-Butyl ether, posted on the ChemRTK HPV Challenge Program Web site on January 19, 2007. I commend ExxonMobil Chemical Company 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 ExxonMobil advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. EPA has moved energetically from the HPV Challenge Program to the Chemical Assessment and Management Program, or ChAMP (www.epa.gov/champ), and is relying on Challenge chemical sponsors to provide, as expeditiously as possible, the data that are the key to this effort.

Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov. If you have any questions about this response, please contact me at 202-564-8617. 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.

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

Sincerely,

/s/

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
R. Lee
J. Willis

**EPA Comments on Chemical RTK HPV Challenge Submission:**
**sec-Butyl Ether**

## Summary of EPA Comments

The sponsor, ExxonMobil Chemical Company, submitted a test plan and robust summaries to EPA for sec-butyl ether (CAS No. 6863-58-7) dated November 28, 2006. EPA posted the submission on the ChemRTK HPV Challenge website on January 19, 2007. The submission identified two proposed analogs: n-butyl ether (CAS No. 142-96-1) and diisopropyl ether (CAS No. 108-20-3). The submission also provides data for several proposed metabolites of sec-butyl ether: sec-butyl alcohol (CAS No. 78-92-2), methyl ethyl ketone (CAS No. 78-93-3), 3-hydroxy-2-butanone (CAS No. 513-86-0), and 2,3-butanediol (CAS No. 513-85-9).

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

1. Analog Justification. The justification for the use of metabolite data for the human health endpoints is inadequate. However, data for the proposed structural analogs can be used to address these endpoints for the purposes of the HPV Challenge program.

2. Physical Chemical Properties. EPA agrees with the submitter that there are sufficient data for melting point, vapor pressure, and log $K_{ow}$ for the purposes of the HPV Challenge Program. EPA recommends that the submitter replace the submitted estimated boiling point value with available measured values. The submitter needs to provide a measured water solubility value.

3. Environmental Fate. EPA agrees that there are sufficient data available to satisfy the stability in air, stability in water, and fugacity endpoints for the purposes of the HPV Challenge Program. The submitted biodegradation data are inadequate; the submitter needs to provide measured data.

4. Health Effects. Adequate data were submitted to address the human health endpoints for the purposes of the HPV Challenge program. The submitter needs to address deficiencies in the robust summaries.

5. Ecological Effects. EPA disagrees that there are sufficient data available to satisfy the aquatic toxicity endpoints for the purposes of the HPV Challenge Program. The submitter needs to provide adequate acute fish, invertebrate, and algal data on the sponsored chemical or adequate data on an appropriate analog for all three end points.

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

## EPA Comments on the Sec-Butyl Ether Challenge Submission

### Analog Justification

The submitter proposes to use measured data for several proposed metabolites of the sponsored substance, including sec-butyl alcohol (CAS No. 78-92-2), methyl ethyl ketone (CAS No. 78-93-3), 3-hydroxy-2-butanone (CAS No. 513-86-0) and 2,3-butanediol (CAS No. 513-85-9) to fulfill the health effects endpoints for sec-butyl ether. In addition, the submitter proposes to use data for two structural analogs, n-butyl ether (CAS No. 142-96-1) and diisopropyl ether (CAS No. 108-20-3) for several endpoints.

*The use of health effects data for proposed metabolites*. The test plan provided information on the toxicokinetics and metabolic fates of sec-butyl alcohol and methyl ethyl ketone, but no data on the *formation* of these products. The submitter postulates that sec-butyl ether will hydrolyze to sec-butanol, which then is oxidized to methyl ethyl ketone, but provided no supporting data. In fact, this hydrolysis is unlikely because ethers are chemically resistant to hydrolysis. Metabolic cleavage of ethers generally proceeds via oxidation. The test plan does not address this or other metabolic pathways, either for the

sponsored substance or for other branched alkyl ethers. Therefore, the proposed use of metabolite data is not supported for the assessment of health effects.

*The use of health effects data on proposed analogs.* Although no toxicological data were submitted for the human health endpoints for the sponsored substance, the use of data for the proposed analogs, n-butyl ether and diisopropyl ether, is supported by their similar physicochemical properties and their structural similarity to the sponsored substance. Diisopropyl ether in particular would resemble the sponsored substance in its expected metabolism. The weight of the evidence suggests that diisopropyl ether is a reasonable analog substance for the purposes of the HPV Challenge Program.

*Ecological toxicity*. The analog justification for using n-butyl ether is adequate for these endpoints. However, the submitted data for n-butyl ether are inadequate (see below).

*Other endpoints*. The submitter uses measured data for n-butyl ether as supplemental data for the water solubility endpoint, and proposes to address the biodegradation endpoint with data for diisopropyl ether and n-butyl ether. EPA considers these proposals inadequate for the reasons stated below.

**Test Plan**

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

Adequate data are available for melting point, vapor pressure, and log $K_{ow}$ for the purposes of the HPV Challenge program.

*Boiling point*. The submitter reported an estimated boiling point of 116˚C. Estimated boiling point values below 300˚C may not be substituted for measured data. However, EPA located measured values of 121˚C (Drake, Nathan L.; J. Am. Chem. Soc. 1935 V57, p. 2623-5 CAPLUS (identified in CAS Experimental Properties (EPROP) on-line search)) and 122˚C (Karas, L.; Kirk-Othmer Encyclopedia of Chemical Technology. (2005). NY, NY: John Wiley & Sons; Ethers. Online Posting Date: March 19, 2004). With the inclusion of this information, the data will be adequate for this endpoint.

*Water solubility*. The submitter provided measured and estimated water solubility data. The test plan states that the measured data are for n-butyl ether; however, in the robust summary, this same value is listed for sec-butyl ether. The submitter needs to resolve this discrepancy. EPA found wide variation among estimated values for this substance. The submitted estimated water solubility value is inadequate; the submitter needs to provide a measured value using OECD TG 105.

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

Adequate data are available for melting point, vapor pressure, and log $K_{ow}$ for the purposes of the HPV Challenge program.

*Biodegradation*. The submitter provided estimated biodegradation data for sec-butyl ether and measured data for the proposed analog diisopropyl ether. Estimated data are not sufficient. Although the proposed analog is structurally analogous to sec-butyl ether, the test submitted for the former was OECD TG 301D, which is the least vigorous of the 301 tests. For this reason, EPA does not consider the analog data to adequately represent the biodegradation potential of sec-butyl ether. The submitter needs to provide measured biodegradation data according to OECD TG 301.

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

No data were submitted for the sponsored substance to address the human health endpoints. EPA agrees that data for the two structural analog substances, n-butyl ether and diisopropyl ether, can be used together to address the SIDS endpoints in a weight-of-evidence approach. Adequate data were

submitted to address all SIDS endpoints for the purposes of the HPV Challenge program. The submitter needs to address deficiencies in the robust summaries.

Ecological Effects (fish, invertebrates and algae)

*Toxicity to Fish, Invertebrates, Algae.* ECOSAR-estimated values for sec-butyl ether, together with adequate measured n-butyl ether data, could satisfy these endpoints for the sponsored substance. However, the submitted data for n-butyl ether are inadequate. Measured data for n-butyl ether were submitted only for the fish endpoint, and that fish study was too short in duration (48 hours vs.the required 96 hours) to be considered adequate for the purposes of the HPV Challenge Program. The submitter needs to provide adequate measured data for the sponsored chemical following the methods of OECD TG 201, 202, and 203 in combination with the guidance in the OECD Series on Testing and Assessment, Number 23, on the testing of substances that volatilize readily from water.

**Specific Comments on the Robust Summaries**

Health Effects

*Repeated Dose Toxicity.* The submitter needs to include specific information (e.g. change in organ weights) on the female reproductive organs from the 13-week inhalation repeated-dose study with diisopropyl ether to inform the reproductive toxicity endpoint.

*Reproductive Toxicity.* The submitter needs to prepare a robust summary that summarizes information on the male and female reproductive organs from the 13-week inhalation repeated-dose study with diisopropyl ether to address this endpoint.

**Followup Activity**

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