

June 6, 2005

Prakash Surana  
Technical Contact  
Celanese Limited  
P.O. Box 819063  
Dallas, TX 75381

Dear Mr. Surana:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Methoxymethanol posted on the ChemRTK HPV Challenge Program Web site on March 2, 2004. I commend Celanese Limited 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 Celanese 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 Mark Townsend, Acting Chief of the HPV Chemicals Branch, 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](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: M. E. Weber  
J. Willis

**EPA Comments on Chemical RTK HPV Challenge Submission:  
Methoxymethanol**

**Summary of EPA Comments**

The sponsor, Celanese Limited, submitted a test plan and robust summaries to EPA for methoxymethanol (CAS No. 4461-52-3) dated December 31, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on March 2, 2004.

EPA has reviewed this submission and reached the following conclusions:

1. Physicochemical Properties. The data are adequate for the purposes of the HPV Challenge Program.
2. Environmental Fate. The data are adequate for the purposes of the HPV Challenge Program.
3. Health Effects. While the submitter's approach using analog data may be reasonable, additional supporting information is needed.
4. Ecological Effects. The submitter needs to supply more information to support using formaldehyde data to address these endpoints. The estimated values using ECOSAR for methoxymethanol are invalid as the model is not reliable for hemiacetals.

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

**EPA Comments on the Methoxymethanol Challenge Submission**

**Test Plan**

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

Submitted data for all endpoints are adequate for the purposes of the HPV Challenge Program.

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

Submitted data for all endpoints are adequate for the purposes of the HPV Challenge Program.

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

*Analog Justification.* The submitter proposes to use data for a Japanese test substance to address health endpoints for methoxymethanol, a transient equilibrium species in a methanol-formaldehyde-water mixture marketed in the U.S. as Methyl Formcel. While this may be a reasonable approach, the presentation does not provide sufficient information for understanding the makeup and behavior of these mixtures in relation to the submitter's argument. A key point in that argument is that aqueous dilution (as in administration to an animal or dilution in an aquatic test system) shifts the equilibrium rapidly and wholly to methanol and formaldehyde, which exert any toxicity observed, and attempting to measure toxicity of the transient species will thus be fruitless. In other words, in an actual test system there will be little or no detectable methoxymethanol, and in the testing environment the analog substance and Methyl Formcel will differ only in the relative concentrations of formaldehyde and methanol.

The NMR data furnished in the test plan support this claim only in limited part. Only "Mixture A" is prepared preponderantly from water (initial mole fraction .62), and it still contains 50% methoxymethanol and other methoxylated species. This leaves open the question as to how much dilution would be

required to produce a negligible concentration of methoxylated species. While EPA agrees that the toxicity of this chemical may be driven by release of formaldehyde and methanol, the distribution properties are likely to be different for the parent chemical which in turn may result in a different toxicity profile. In order to support the proposed dilution model, the submitter needs to better characterize the complex equilibria with measured data. For example, measurement of NMR spectra on serially diluted samples of Methyl Formcel could clarify the dilution-concentration relationship. Ideally such information would be obtained on both the Japanese test substance and the US commercial product and related back to the available data. It should also illuminate the rate at which equilibria are re-established (rate information may be available from the existing NMR measurements but was not reported quantitatively in the test plan).

*Genetic Toxicity (Chromosomal Aberrations).* The test plan refers to the *in vitro* CHL cell study as being conducted "*in vivo*"; this error needs to be corrected.

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

*Analog Justification.* The submitter proposes to use formaldehyde data to address these endpoints for methoxymethanol. While this may be a reasonable approach, the presentation does not provide sufficient information to support the submitter's argument. The submitter needs to supply additional information as discussed above under Health Effects. If it can be demonstrated that Methyl Formcel contains negligible methoxymethanol under testing conditions, then adequate formaldehyde data would be sufficient to address the endpoint. EPA notes that the algal data in the OECD formaldehyde data summary were not generated in a guideline-compliant study (test duration 24 hr rather than 96 or 72 hr).

The ECOSAR model used by the sponsor is not reliable because the model does not apply to hemiacetals such as methoxymethanol; the application of ECOSAR to methoxymethanol should be removed from the test plan and robust summaries.

#### **Specific Comments on the Robust Summaries**

##### Health Effects

*General.* None of the robust summaries identifies the year in which the study was performed.

*Genetic Toxicity (Gene Mutations).* The submitter needs to identify the positive and negative controls and any statistical methods used. Also, the discrepancy as to the cytotoxic concentration for *E. coli* (given as both 2,500 and 1,500 µg/plate) needs to be resolved.

*Repeated Dose and Reproductive Toxicity.* The summaries need to include a complete list of organs examined for gross effects and histopathology.

##### Ecological Effects

*General.* The summaries need to include references for all studies cited.

*Fish and Invertebrates* Some of the robust summaries do not state dissolved oxygen levels; water hardness; pH; number of replicates; number of organisms per replicate; organism age, weight, and length; and temperature range.

#### **Followup Activity**

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