

Celanese Chemicals



201-15973

July 25, 2005

Oscar Hernandez, Director
Risk Assessment Division
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

RECEIVED
08/01/05
05 JUL 26 AM 9:14

Dear Mr. Hernandez:

Thank you for your comments of June 6, 2005 on our HPV submission for Methoxymethanol (CAS# 4461-52-3).

Celanese Ltd. is pleased to provide the Agency with responses to their comments. We are forwarding responses to each of EPA's specific comments along with a revised Test Plan and a set of revised Robust Summaries.

Should you need additional information or have any questions, please contact me at 972-443-4836.

Sincerely,

Celanese

Prakash Surana, Ph.D.
Product Stewardship Coordinator

201-15973

Response to EPA's Comments on the HPV Challenge Submission

Methoxymethanol

CAS 4461-52-3

RECEIVED
05 JUL 26 AM 9:10

EPA COMMENTS ON THE METHOXYMETHANOL CHALLENGE SUBMISSION

Test Plan

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

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

Response: Agreed

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

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

Response: Agreed

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

COMMENT: 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).

Response: The equilibrium and kinetic constants for these species have all been reported and many verified by independent work. The dilution model has been verified both for the Japanese test substance and the Celanesc commercial product and results of these calculations are provided that span several orders of magnitude. At concentrations of test material of 1000 mg/L or less, the methoxymethanol molecule is less than 1% of the total test substance with the bulk of the material in the form of methanol or methylene glycol (the hydrated form of formaldehyde). Likewise, the relative concentrations of these species in the dilutions of test material dosed to the test animals has been calculated. More importantly, assuming 100% absorption and distribution only in the blood, the relative maximum quantities of methanol, methylene glycol, methoxymethanol and free formaldehyde have been calculated. These show that even at the high dose, that methoxymethanol represents only about 3% of the administered test substance and this percentage decreases exponentially with decreasing dose.

Additional information concerning the kinetics of these reactions has been added to support the proposed rapid establishment of equilibrium after dilution. We trust these calculations and tables, based on reliable published data, will fulfill EPA's request for additional information about speciation and the effects of dilution on the relative concentrations of chemical species.

A paragraph was also added to the executive summary noting the presence of these calculations and the conclusions.

COMMENT: *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.

Response: This term was in quotes to correspond with the EPA HPV template. The term "in vivo" has been removed from the text and the title of the section has also been changed to "Genetic Toxicity: Clastogenicity".

Ecological Effects (fish, invertebrates, and algae)

COMMENT: *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).

Response: Tables have been inserted to provide the requested information. At Methyl Formcel concentrations up to 1000 mg/L (the maximum recommended testing concentration), less than 1 % of the test material is in the form of methoxymethanol. This information, combined with the ESOSAR results indicating a low intrinsic toxicity of the methoxymethanol molecule, validate our approach to using formaldehyde data to address the aquatic toxicity endpoints. Please see the earlier response to "analog justification" for more details. Regarding the short duration of the algal studies, this is clear in the robust summary. Although it was a shorter study, formaldehyde is so reactive that all the formaldehyde (and methylene glycol) probably reacts with algae in the first few hours of the study and a longer duration study would not be more informative.

COMMENT: 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.

Response: The sponsor is well aware that the ECOSAR model is not robust in the case of hemiacetals such as methoxymethanol due to the rapid hydrolysis of hemiacetals to their corresponding aldehyde and alcohol. As speciation and relative toxicity of the various species in these equilibrium mixtures is an issue in estimating the aquatic toxicity of methoxymethanol, and as the intrinsic toxicity of the methoxymethanol molecule itself to aquatic species cannot be determined due to rapid hydrolysis, the only way to assess the potential contribution of the methoxymethanol molecule is by modeling. This modeling of methoxymethanol ecotoxicity is considered a necessary step in accepting formaldehyde toxicity as the determinant of methoxymethanol aquatic toxicity.

In recognition of the Agencies comment, language has been added to the test plan and robust summaries to point out the purpose of this modeling and that it is not considered to be an estimate of the aquatic toxicity of methoxymethanol in water solutions. In addition, the order of the robust summaries has been changed to place these ECOSAR estimates at the end of each section and remove the "critical" flag from them.

Specific Comments on the Robust Summaries

Health Effects

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

Response: The year the study was conducted is not an IUCLID field. The year field in IUCLID is reserved for the year of the guideline or version of the study guidance document. In many cases the year can be determined from the reference, but in some cases the year of study conduct is not available. The OECD 422 study, for example, is provided on the MHLW, Japan website but has no date on the summary report. Likewise, published articles may describe results of a study in satisfactory detail without providing the date of study completion.

COMMENT: *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.

Response: Positive and negative control substances have been listed. The higher value for cytotoxicity to *E. coli* was an error and has been replaced with the correct value resolving the discrepancy.

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

Response: Neither the study report in Japanese nor the English study summary provided a list of organs examined and the actual testing protocol was not available. It was, however, specified that the OECD 422 guideline was followed. As this guideline is specifically designed to provide an evaluation of reproductive and developmental endpoints, it can reasonably be assumed that a full range or reproductive and developmentally related organs were examined. A statement to this effect has been added to the repeated dose and reproductive toxicity robust summaries.

Ecological Effects

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

Response: References for all studies cited have been added

COMMENT: *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.

Response: Invertebrates: All details available in the original publication for the daphnid study were added to the robust summary including statistical methodology and full references. The reference for the study was expanded to include the full title of the article.

Response: Fish: All available details as given in the formaldehyde SIDS document and other available secondary sources (such as the CICAD) have been provided in the robust summary. Although the source document is not readily available, there are numerous fish studies cited in the ECB formaldehyde IUCLID supporting the selected study as being representative.