

August 24, 2005

Edwin L. Mongan, III  
Manager, Environmental Stewardship  
E.I. du Pont de Nemours & Company, Inc.  
1007 Market Street  
DuPont 6082  
Wilmington, DE 19898

Dear Mr. Mongan:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Methylamine posted on the ChemRTK HPV Challenge Program Web site on April 13, 2004. I commend E.I. du Pont de Nemours & Company, 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 DuPont 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  
N. Patel  
J. Willis

## **EPA Comments on Chemical RTK HPV Challenge Submission: Monomethylformamide (N-methylformamide)**

### **Summary Of EPA Comments**

The sponsor, E.I. du Pont de Nemours & Company, Inc., submitted a test plan and robust summaries to EPA for monomethylformamide (MMF, CAS No. 123-39-7) dated March 30, 2004. The submission also includes information on the proposed analog *N,N*-dimethylformamide (DMF, CAS No. 68-12-2). EPA posted the submission on the ChemRTK HPV Challenge Web site on April 13, 2004.

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

1. Analog Justification. DMF is a reasonable analog for MMF.
2. Physicochemical Properties. The submitted data are adequate for all endpoints for the purposes of the HPV Challenge Program.
3. Environmental Fate. The submitted data for the photodegradation, stability in water, and fugacity endpoints are adequate for the purposes of the HPV Challenge Program. The submitter needs to provide ready biodegradation data to address this endpoint.
4. Health Effects. All endpoints have been addressed for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.
5. Ecological Effects. All endpoints have been addressed for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

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

### **EPA Comments On The Monomethylformamide Challenge Submission**

#### **Test Plan**

##### Analog Justification

Although the submitter used DMF as an analog for MMF, its suitability could not be adequately determined from the submitted information. EPA reviewed additional information from the literature and DMF data published in the OECD SIDS Initial Assessment Report (SIAR) completed in 2003 (<http://cs3-hq.oecd.org/scripts/hpv/>). On the basis of physicochemical properties, information on metabolism (SIAR 2003), the specificity and consistency of the liver as the target organ, and similar reproductive and developmental toxicity of MMF and DMF, EPA agrees that DMF is a reasonable analog for MMF.

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

Adequate data are available for all SIDS endpoints for the purposes of the HPV Challenge Program.

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

The submitted data for the photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program. The submitted biodegradation data (Zahn-Wellens test) are

for inherent biodegradability of the chemical. For the purposes of the HPV Challenge Program, the submitter needs to provide ready biodegradation data according to OECD TG 301.

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

The submitted MMF data are adequate to address acute and developmental toxicity endpoints. MMF data submitted for other endpoints were inadequate; however, adequate DMF data for repeated-dose, reproduction, and genetic toxicity address these remaining endpoints. The submitter needs to address deficiencies in the robust summaries.

*Reproductive Toxicity.* The study on MMF was not adequate because it was conducted by an intraperitoneal route of administration and provided limited information. In addition, EPA considers questionable the data from the DMF one-generation reproductive toxicity study conducted at the Industrial Bio-Test Laboratories, and disagrees with the submitter's conclusions from this study. The material related to this study should be deleted from the test plan. The continuous breeding study satisfies the endpoint.

*Developmental Toxicity.* The submitter needs to remedy the following inconsistency in the discussion of maternal and fetal effects on page 6 of the test plan. The first sentence of the first paragraph states that "Extensive testing...shows that DMF affects the embryo/fetus only under conditions which will affect the maternal animal." Later in the paragraph is the statement that "DMF given orally to rabbits produced both maternal and fetal effects with fetal anomalies being produced at doses that had little maternal effect (Merkle and Zeller, 1980)." [The SIAR for DMF clearly summarizes developmental effects on pages 5 and 21.] In addition, at the bottom of page 6 the test plan states that "No effects on fertility or fetal parameters were observed at 1000 ppm", which ignores information from the robust summary indicating a reduction in F2 pup weight at 1000 ppm and a statistically significant (Fail et al.) reduction in the F2 liver weights.

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

The submitted data for all endpoints are adequate for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

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

#### Health Effects

*Repeated-Dose Toxicity.* The robust summary for the 90-day inhalation study of DMF (high reliability) needs the method used to generate the test atmosphere, and the incidence and statistical significance of apparent treatment-related responses.

*Genetic Toxicity (gene mutations).* Information missing in the in vitro bacterial reverse mutation assay on DMF (high reliability) includes the number of replicate plates used per concentration, the criteria for a positive response, a description of the response observed in the positive controls, whether statistical methods were used to analyze the results, and summary data for the number of revertants.

*Genetic Toxicity (chromosomal aberrations).* The summary for the DMF *in vitro* study in CHO cells (NTP, 1992, high reliability) is missing several critical data elements, including the concentrations of DMF, the rationale for the selection of the test concentrations (e.g., cytotoxicity), number of replicates per concentration, number of cells analyzed, scoring criteria, and identity of and results for positive controls.

*Reproductive Toxicity.* Tables for the continuous breeding study with DMF (Study No. 2) need to include the statistical significance of the entries. The second to the last paragraph on page 84 needs to mention the statistical significance of the reduction in the F2 liver weights.

*Developmental Toxicity.* The robust summaries of the key MMF studies in rats and rabbits have the following deficiencies: the summary did not report data for the observed changes in maternal body weight gain or fetal weight; although the summary indicated that statistical analyses were performed, the statistical significance of observed changes in maternal body weight gain, fetal body weight, fetal viability, fetal variations, and fetal malformations was not clearly indicated (this information is available in the published literature).

#### Ecological Effects

*Fish.* The submitter needs to verify the concentrations provided for the 96-hour acute toxicity study in fathead minnows (DuPont Co., 1985): the summary lists two concentration levels of 100 mg/L.

*Algae.* Information is needed on the initial concentration of the algal cells, the lighting intensity and spectral range used and the magnitude of the increase in cell concentration within 72 hours.

#### **Followup Activity**

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

#### **References**

Fail, P.A. et al.: *Reprod. Toxicol.* 12 (3), 317-322, 1998.