May 6, 2009

Pamela F. Cosse
Technical Contact
The Dow Chemical Company
Building 1803
Midland, MI 48674

Dear Ms. Cosse:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 2-amino-2-hydroxymethyl-1,3-propanediol, posted on the ChemRTK HPV Challenge Program Web site on December 22, 2006. I commend The Dow 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 Dow 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:
Tris(hydroxymethyl)aminomethane

Summary of EPA Comments

The sponsor, Dow Chemical Company, submitted a test plan and robust summaries to EPA for tris(hydroxymethyl)aminomethane (TRIS AMINO, CAS No. 77-86-1) dated November 14, 2006. EPA posted the submission on the Chem RTK HPV Challenge Web site on December 22, 2006. The submission also includes data for two proposed analogs, 2-amino-2-methyl-1,3-propanediol (AMPD, CAS No. 115-69-5) and 2-amino-2-methyl-1-propanol (AMP, CAS No. 124-68-5).

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

1. Analog Justification. The test plan provides sufficient evidence for the use of the analogs for data for aquatic invertebrates. For human health effects, the available information is not considered conclusive, but the Agency believes that AMP has higher toxicity than the other two substances and that it can represent a worst-case analog.

2. Physicochemical Data. Adequate data are available for melting point, boiling point, log Kow, and water solubility for the purposes of the HPV Challenge Program. The submitter needs to provide adequate measured data for the vapor pressure endpoint.

3. Environmental Fate and Pathways. Adequate data are available for stability in air and stability in water for the purposes of the HPV Challenge Program. The submitter needs to provide revised fugacity data. EPA reserves judgment on the biodegradation data until additional study details are provided.

4. Health Effects. Although the sponsor suggests that developmental/reproductive toxicity testing may be necessary, EPA believes this is not needed and that, with the addition of other available information, adequate data will be available for all of the human health endpoints for the purposes of the HPV Challenge Program.

5. Ecological Effects. Once all missing critical elements have been submitted, the data provided on acute fish and invertebrates testing as a whole will be sufficient for the purposes of the HPV Challenge Program. The algal test concentration was given as 100 micrograms per liter in the IUCLID document and 100 milligrams per liter in the test plan. The submitter needs to address this substantial discrepancy.

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

EPA Comments on the Tris(Hydroxymethyl)Aminomethane
Challenge Submission

Analog Justification

The submitter proposes AMPD and AMP as analogs for the sponsored chemical. The rationale (Test Plan, pages 4-7) includes: (1) structural similarity ("same backbone"), and (2) similar physical chemical, environmental fate, ecotoxicity, and mammalian toxicity profiles. However, many of the physical chemical properties offer poor support for the similarity argument. The available environmental fate data are insufficient to make a judgment. Although AMPD (but not AMP) could be an adequate analog for biodegradation, ready biodegradability data were not submitted for AMPD. For ecological effects, the information suggests that AMP is more toxic than TRIS AMINO or AMPD.

For human health effects, acute toxicity data are not a robust indicator of toxicological similarity among possible analogs. Other available human health data are difficult to compare (i.e., repeated-dose data for TRIS AMINO using the intravenous route versus other data for AMP and AMPD using conventional, oral routes of exposure). Finally, the test plan offers no evidence that AMP or AMPD may be converted in

vivo to TRIS AMINO. Nonetheless, the available information, while not conclusive, does suggest that AMP has higher toxicity than AMPD or TRIS AMINO, likely owing to the relatively higher lipid solubility of AMP, and that it can thus be considered a worst-case analog. The apparent lack of toxicity in the known use of TRIS AMINO in humans also supports this approach.

Test Plan

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

Adequate data are available for melting point, boiling point, log Kow, and water solubility for the purposes of the HPV Challenge Program.

Vapor Pressure. The submitter provided an estimated vapor pressure value of 3.0x10-6 hPa (2.3x10-6 mm Hg). According to Challenge Program guidelines, only calculated values <10-5 Pa (<7.5x10-8 mm Hg) at 25°C are acceptable in lieu of measured values. The calculated data are not below the HPV cut-off and the submitter needs to provide adequate measured data for this endpoint.

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

Adequate data are available for stability in air and stability in water for the purposes of the HPV Challenge Program.

Biodegradation. EPA reserves judgment on this endpoint. The submitter states that in an OECD TG 301 D study the substance was not readily biodegradable, but the robust summary lacks any key information for this study. Additional experimental information such as conditions, percent degradation, and duration of study are needed in order to evaluate this endpoint. Without adequate details, the study cannot be considered adequate and an adequate OECD TG 301 study on the sponsored chemical will be needed. (Although the test plan cited information from an inherent biodegradability study for 2-amino-2-methyl-1,3-propanediol, inherent biodegradation tests are generally not adequate for this endpoint.)

Fugacity. (1) The fugacity summaries are confusingly presented, with model levels I and III not clearly distinguished. (2) Although the submitter noted elsewhere that the substance was not readily biodegradable, the fugacity results state that biodegradation is expected in water and soil. (3) Although it is true that, as stated, the substance has "high water solubility, a low vapor pressure, and low log Kow", these properties may not result in "a low potential for adsorption to soil or sediments" because some amines have an increased ability for soil and sediment binding compared to neutral compounds. This is not explicitly accounted for in the model and should be noted in the discussion. (4) The results of level III fugacity modeling are significantly impacted by the environmental compartment a chemical is released to. The submitter's level III fugacity modeling assumed, for chemical process reasons, that all releases were to water. In its approach to HPV Challenge submission reviews, EPA uses a default assumption of equal releases to all media because information identifying which media receive releases is not generally available. This assumption also allows comparability of model results among HPV Challenge Program chemicals. In this case, while the submitter states that 100% of the compound will distribute into water, EPA found that the EPIWIN level III model predicts distribution into water of 45% and soil of 54%. Inclusion of both results would be useful. The submitter needs to make appropriate revisions to the robust summary to reflect comments 1-3 above.

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

EPA believes the available data are likely adequate for the health effects endpoints. However, most of the robust summaries need enhancement, and EPA has identified data that need to be added to the submission (see below).

Adequate data are available for the acute toxicity endpoint. EPA agrees that the submitter should continue its attempt to obtain useful toxicity data on TRIS AMINO from FDA files. The submitter needs to

submit any such data to the HPV Challenge program in robust summary format. If such data do not exist or cannot be obtained and made public, EPA will consider the AMP OECD TG 421 and TG 414 data adequate to satisfy the reproductive/developmental toxicity endpoints for TRIS AMINO for the purposes of the HPV Challenge program. As stated earlier , EPA believes that AMP is a reasonable worst-case analog for TRIS AMINO for the reproductive/developmental endpoints.

Repeated-Dose Toxicity. All data presented for the sponsored chemical are via the intravenous route of administration. These data, likely generated to support the stated pharmaceutical uses of TRIS AMINO, are difficult to interpret in the context of exposure routes and levels generally considered under the Toxic Substances Control Act. However, because TRIS AMINO is injected into humans as a pharmaceutical agent/buffer (doses used not provided in submission) the need to interpret the intravenous data is less important.

Oral toxicity data for the analog AMP are presented in the submission (90-day rat study: inadequate robust summary lacks specifics; and one-year dog study). However, EPA is aware of more AMP data because the submitter is preparing US-sponsored AMP dossiers (through the ICCA) for the OECD HPV Program and several additional studies are identified in that draft submission (see Goldenthal, 1976a, b; and Pittz 1977). The Pittz study specifically should be added to this TRIS AMINO HPV Challenge submission because it is a 90-day study in rats that includes two study groups (one at pH 7 and the other at pH 11) and for which the draft IUCLID robust summary is adequately detailed.

EPA believes that the combination of the use of TRIS AMINO as a buffering agent in humans and the available conventional toxicity data with AMP as a reasonable worst-case analog are sufficient to describe the repeated-dose toxicity of TRIS AMINO for the purposes of the HPV Challenge Program.

Genetic Toxicity (Gene Mutation and Chromosomal Aberration). The data presented for the sponsored chemical are inadequate because both the in vitro gene mutation data and the single micronucleus assay provided are labeled as “unassignable” quality (Klimisch code 4) in the robust summaries (pp. 39 and 40). However, the aforementioned draft AMP OECD submission contains adequate robust summaries for both the gene and chromosomal endpoints (see Gudi, 1998; San and Clark, 1997; and Wagner, 1996). This information needs to be added to this TRIS AMINO HPV Challenge submission.

Ecological Effects (fish, invertebrates, and algae)

Although most studies were conducted following OECD guidelines and GLPs, some relevant information and method details for each of these studies need to be included in the robust summaries. In general the data provided on acute fish and invertebrates testing as a whole will be sufficient for the purposes of the HPV Challenge Program once all missing critical elements have been submitted. In the case of the single algal study, an NOEC test concentration of 100 was reported as ug/L in the IUCLID and mg/L in the test plan. The submitter needs to address this discrepancy. If the test concentration was only 100 ug/L then algae testing needs to be conducted up to at least 100 mg/L.

Specific Comments on the Robust Summaries

Health Effects

Repeated-Dose Toxicity. The Parekh (1981) study inadequately summarized on p. 34 of the robust summaries is adequately detailed in the AMP OECD HPV Submission but is considered invalid because of methodological deficiencies and a high viral infection rate in the test animals (pp. 52-55 of IUCLID summary dated 11/30/2006). This summary should be deleted from the TRIS AMINO US HPV Challenge robust summary document and replaced with other summaries per comments above.

Ecological Effects

Fish. Details missing from the summaries include test substance purity, concentrations tested, measurement of test concentrations (nominal/measured), statistical methods used and confidence limits, photoperiod, water chemistry parameters (temperature, pH, hardness, dissolved oxygen, TOC), loading rate, number of animals per concentration, number of replicates per concentration, control use and response, mean length and weight, and specific mortality results at each dose level.

Invertebrates. Details missing from the summaries include GLP compliance, controls and control response, age of the daphnids, test substance purity, test guideline used, concentrations tested, number of replicates and daphnids per replicate, statistical methods, confidence limits, photoperiod, and water parameters (pH, temperature, dissolved oxygen, TOC).

Algae. The summary of the 4-day EC50 study lacks results at each measurement interval, initial cell concentrations, lighting conditions, purity, control response, GLP status, and pH values. The summary consists of only the NOEC - not an EC50 value. The original study needs to be located and full study details need to be assessed by the sponsor to determine why an EC50 was not calculated.

Followup Activity

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

References

Goldenthal, E. (1976a) Eight Week Tolerance Study in Rats. The Dow Chemical Company Report No: DR-0309-4391-022, Unpublished.

Goldenthal, E. (1976b) Eight Week Tolerance Study in Mice. The Dow Chemical Company Report No: DR-0309-4391-018, Unpublished.

Gudi, R. (1998) Mammalian Erythrocyte Micronucleus Test (2-amino-2-methyl-1-propanol). Laboratory Study Number G97CG03.123 of MA Bioservices, INC., Rockville, MD. Sponsored by Angus Chemical Company, Buffalo Grove, IL.

Pittz, E. (1977) A 90-Day Safety Evaluation Study of 2-Amino-2-methyl-1-propanol (AMP) in Rats. The Institute of Comparative and Human Toxicology, Albany Medical College, Albany, NY. The Dow Chemical Company Report No: DR-0309-4391-023.

San, R. and Clark, J. (1997) In Vitro Mammalian Cell Gene Mutation Test with an Independent Repeat Assay. Microbiological Associates, INC. The Dow Chemical Company Report No: DR-0309-4391-005.

Wagner, V. (1996) Salmonella/Escherichia Coli Plate Incorporation Mutagenicity Assay with a Confirmatory Assay. Study Number G95BU17.502001 of Microbiological Associates, INC., Rockville, MD.