May 27, 2009

Rod Gerwe, Ph.D.
Technical Contact for BASF Corporation
PCA Services, Inc.
2704 Trail Wood Drive
Durham, NC 27705

Dear Dr. Gerwe:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 3-Hydroxy-2,2-Dimethylpropanoic acid, 3-hydroxy-2,2-dimethylpropyl ester, posted on the ChemRTK HPV Challenge Program Web site on January 19, 2007. I commend BASF Corporation 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 BASF 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:
3-Hydroxy-2,2-dimethylpropanoic Acid, 3-Hydroxy-2,2-dimethylpropyl Ester

Summary of EPA Comments

The sponsor, BASF Corporation, submitted a test plan and robust summaries to EPA for 3-hydroxy-2,2-dimethylpropanoic acid, 3-hydroxy-2,2-dimethylpropyl ester (HPHP, CAS No. 1115-20-4) dated November 28, 2006. EPA posted the submission on the Chem RTK HPV Challenge Web site on January 19, 2007. The robust summary for HPHP was submitted December 28, 2006, and posted on April 27, 2009. The initial submission also included data for two proposed supporting compounds, isobutyl isobutyrate (IBIB, CAS No. 97-85-8) and neopentyl glycol (NPG, CAS No. 126-30-7).

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

1. Physicochemical Data. Adequate data are available for these endpoints for the purposes of the HPV Challenge Program.

2. Environmental Fate and Pathways. Adequate data are available for these endpoints for the purposes of the HPV Challenge Program. EPA-located data for biodegradation need to be added to the submission.

3. Health Effects. Adequate data are available for the acute toxicity and gene mutation endpoints. EPA does not find the support for the proposed analogs sufficient to characterize the remaining health effects endpoints under the HPV Challenge Program. Specifically, the use of neopentyl glycol (NPG) as an analog for HPHP lacks supporting information, and the use of IBIB as an analog for health effects does not appear reasonable.

4. Ecological Effects. Adequate data are available for these endpoints for the purposes of the HPV Challenge Program.

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

EPA Comments on the 3-Hydroxy-2,2-Dimethylpropanoic Acid, 3-Hydroxy-2,2-Dimethylpropyl Ester Challenge Submission

Analog Justification

Health Effects. The submitter proposes to satisfy most of the health effects endpoints with data on two analogs: isobutyl isobutyrate (IBIB, CAS No. 97-85-8), a less sterically hindered version of HPHP, and neopentyl glycol (NPG, CAS No. 126-30-7), the alcohol hydrolysis product of HPHP. There are several significant weaknesses in the case for using these analogs.

Postulated rapid enzymatic hydrolysis to support the use of NPG data. Data in the submission show that IBIB hydrolyzes rapidly *in vivo* (half-life in seconds) to isobutanol and isobutyric acid. While the test plan states, reasonably, that hydrolysis of HPHP will yield NPG and hydroxypivalic acid, no experimental data are provided to show whether enzymatic hydrolysis occurs or is rapid.

The test plan does not address whether increased steric crowding in HPHP is likely to significantly affect the rate of enzymatic hydrolysis relative to that of the less heavily substituted IBIB. A further possible complication is the role of the two hydroxyl groups in HPHP in its metabolic fate. Intramolecular hydrogen bonding involving the β-hydroxyl group of HPHP could result in a favored conformation that could affect enzymatic binding and thus the rate of enzymatic hydrolysis of HPHP. In the absence of experimental data, it is unclear whether such effects will occur. The sponsor needs to better support the potential for rapid enzymatic hydrolysis of HPHP to NPG in order to justify use of NPG as an analog. Published examples of steric effects on enzymatic ester hydrolysis rates could be helpful.

The use of IBIB health effects data. The justification for using IBIB health effects data is inadequate as presented. There are three major structural differences between HPHP and IBIB, any one of which would normally tend to disqualify a substance as a suitable analog: (1) the presence of quaternary carbon atoms in HPHP but not IBIB; (2) a higher degree of steric crowding in HPHP than in IBIB; (3) two hydroxy groups in HPHP but none in IBIB. While the test plan mentions the presence of hydroxy groups, nothing further is said about them, and the other two points are essentially ignored.

The use of isobutanol health effects data. Although the test plan proposes only the two analogs IBIB and NPG to provide data for health effects endpoints, the test plan later cites isobutanol data for certain of these endpoints without an explicit justification for doing so or an explanation of why health effects data for isobutanol would apply to HPHP.

In summary, EPA believes that the test plan does not make an adequate case for the proposed analogs.

Non-Health Effects. The test plan did not propose analogs for physical-chemical and fate properties or for ecological effects.

Test Plan

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

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

Melting Point. The submitter provided a measured melting point range of 48-54.9°C, and other values around 50°C. EPA located values ranging from 51 to 64°C (Beilstein 2007, CERIJ 2007). EPA suggests that the submitter include the higher reported values.

Boiling Point. The submitter reported a measured boiling point of 283.2°C at 760 mm Hg from unpublished company documents and an estimated boiling point of 303.7°C at 760 mm Hg from EPIWIN. EPA obtained literature reduced-pressure boiling point values that could be normalized to values of 270-323°C. The data are adequate for this endpoint.

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

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

Biodegradation. The submitted adequate OECD TG 301A test data indicated ready biodegradability. EPA located data from a OECD TG 301C test that indicated the sponsored compound was not readily biodegradable (CERIJ 2007). Because of the differing results in different tests, the submitter needs to add the 301C data to the submission in order to fully characterize the endpoint.

Stability in Water. The submitter provided an estimated hydrolysis half-life of 113 years at pH 7. For this sterically hindered molecule, hydrolysis across the environmental pH range is expected to be slow. In this case the estimated data for this endpoint are adequate.

Health Effects

Adequate data are available for the acute toxicity and gene mutation endpoints for the purposes of the HPV Challenge Program. EPA reserves judgment on the use of NPG data for the remaining endpoints (repeated-dose, reproduction/developmental toxicity, and chromosomal effects) pending the receipt of better information about the *in vivo* enzymatic hydrolysis of HPHP, of other data supporting the use of NPG as a health effects analog, or of additional health effects data on HPHP.

Ecological Effects

Adequate data are available for acute fish, invertebrates and algal toxicity endpoints for the purposes of the HPV Challenge Program.

Specific Comments on the Robust Summaries.

Physical-Chemical Properties

For water solubility, the test plan cites BASF 1999 in the text, but lists no corresponding reference. The discrepancy needs to be corrected.

Followup Activity

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

References

Beilstein On-line Search, May 1, 2007.

CERIJ (Chemicals Evaluation and Research Institute, Japan); Search at query page by CAS registry number, available at: http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.