June 22, 2009

Jane Staveley
Business Practice Manager
ARCADIS G&M, Inc.
On behalf of BASF Corporation
4915 Prospectus Drive, Suite F
Durham, NC 227713

Dear Ms. Staveley:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for 1,2-dimethyl-4-nitrobenzene posted on the ChemRTK HPV Challenge Program Web site on February 20, 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.

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,

Mark W. Townsend, Chief
HPV Chemicals Branch

Enclosure

cc: O. Hernandez
R. Lee
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
1,2-Dimethyl-4-nitrobenzene

Summary of EPA Comments

The sponsor, BASF Corporation, submitted a test plan and robust summaries to EPA for 1,2-dimethyl-4-nitrobenzene (CAS No. 99-51-4) dated November 29, 2006. EPA posted the submission on the ChemRTK HPV Challenge website on February 20, 2007. The submission included supporting data from four proposed chemical analogs.

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

1. Physical Chemical Properties. Existing data are adequate for these endpoints for the purposes of the HPV Challenge Program.

2. Environmental Fate. Existing data are adequate for these endpoints for the purposes of the HPV Challenge Program. The biodegradation discussion needs enhancement.

3. Health Effects. Existing data are adequate for these endpoints for the purposes of the HPV Challenge Program.

4. Ecological Effects. Submitted data are adequate to address these endpoints for the purposes of the HPV Challenge Program provided the submitter addresses 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 1,2-Dimethyl-4-Nitrobenzene Challenge Submission

Analog Justification

The submitter proposes to use several analogs, 2,4-dimethyl-1-nitrobenzene (4-nitro-m-xylene, CAS No. 89-87-2), 2-nitrotoluene (CAS No. 88-72-2), 3-nitrotoluene (CAS No. 99-08-1), and 4-nitrotoluene (CAS No. 99-99-0), to complete the SIDS dataset for the sponsored chemical by addressing the following endpoints: biodegradation, aquatic toxicity, and most of human health (repeated-dose toxicity, effects on the chromosome, and developmental/reproductive toxicity).

The proposed analogs differ from the sponsored chemical and each other only in the number and/or positions of the methyl substituents. In addition, the submitter provided sufficient test data for the sponsored chemical and proposed analogs to allow some comparison of their physicochemical properties, environmental fate characteristics, aquatic toxicity, and mammalian health effects. EPA agrees that the similarity in their chemical structures and in the existing test data support the use of adequate measured data for the proposed analogs to satisfy the remaining SIDS endpoints for the sponsored chemical, although the appropriateness of each analog varies according to the endpoint type and the data available.

For health effects, EPA agrees that data on 2,4-dimethyl-1-nitrobenzene are appropriate. Among the three monomethyl analogs, EPA considers 3-nitrotoluene and 4-nitrotoluene more appropriate than the 2-nitrotoluene to address the SIDS health endpoints because the two methyl groups on the sponsored chemical are in the 3(meta)- and 4(para)-positions.

For ecological effects, the 2,4-dimethyl analog is the most useful data source.

Test Plan

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

The submitted data are adequate for these endpoints for the purposes of the HPV Challenge Program.

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

With the changes noted below, the submitted data are adequate for these endpoints for the purposes of the HPV Challenge Program.

Biodegradation. The 28-day study in the robust summary for the analog 3-nitrotoluene, showing <10% degradation, addresses the ready biodegradability endpoint. However, the test plan did not reference this study in the text or in the tables. The submitter needs to revise the test plan tables and discussion to reflect this result.

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

Data available for the sponsored chemical were supplemented with data on its isomer, 2,4-dimethyl-1-nitrobenzene (4-nitro-m-xylene), identified in the test plan as "the primary selected analog." The submission also includes additional supporting information from data on three mononitrotoluene isomers.

There are adequate data available with the sponsored chemical for the acute toxicity and genetic toxicity (gene mutation) endpoints, although the data summaries for the latter lack important details (see below). All the other endpoints are adequately addressed by reading across to one or more analogs. Repeated-dose data are available for each of the four analogs. Genetic toxicity (chromosomal effects) data are available with three of the four analogs (including the isomer of the sponsored chemical). Adequate developmental/reproductive toxicity data are available with only one analog (the 4-nitrotoluene).

Although some robust summaries are inadequate (see below), the submission provides sufficient information to satisfy all the health endpoints for the purposes of the US HPV Challenge Program.

Ecological Effects (fish, invertebrates, and algae)

Available data for the sponsored chemical and its isomer, 2,4-dimethyl-1-nitrobenzene, are sufficient to characterize these endpoints for the purposes of the HPV Challenge program. Therefore, EPA did not review in depth the data supplied for the three nitrotoluene isomers.

Acute Toxicity to Fish. Data from a summary of a 96-hour study of 4-nitro-m-xylene are tentatively adequate to satisfy the endpoint pending the receipt of a revised robust summary for the 96-hour study of 4-nitro-m-xylene.

Acute Toxicity to Aquatic Invertebrates. Data from summaries of a 48-hour study of the sponsored chemical and a 48-hour study of the analog 4-nitro-m-xylene appear adequate to satisfy the endpoint pending the receipt of revised robust summaries that provide the missing study details.

Toxicity to Algae. Data from a summary of a 96-hour study of the sponsored chemical are adequate to satisfy the endpoint pending the receipt of a revised summary that provides the missing study details.

Specific Comments on the Robust Summaries

Health Effects

The robust summaries for 4-nitro-m-xylene and 2-nitrotoluene were inadequate for the purposes of the HPV Challenge Program, whereas the robust summaries presented for 4-nitrotoluene were exemplary and provided many details. The submitter needs to use the 4-nitrotoluene robust summaries as the standard for enhancing the other summaries. The robust summaries presented for the sponsored

chemical and 3-nitrotoluene were minimally acceptable, with some exceptions noted below. All robust summary information needs to be in English.

Repeated-Dose Toxicity. 4-Nitro-m-xylene: A summary submitted for a 28-day oral repeated dose toxicity study was mostly in German but included a brief "approximate translation" in English, which reported some effects seen at 3000 ppm. The following information should be included (in English) in the summary: year of study, whether it was GLP and/or followed an OECD protocol, and the conversion of ppm in feed to dose in mg/kg/d.

2-Nitrotoluene. Summaries of nine oral studies submitted for mice or rats contained hardly any details and were insufficient. Details missing from most summaries included test substance purity, Klimisch codes, animal strain and/or sex, methodological details, and statistical methods used. Additionally, many summaries appeared to be duplicates of others, and some contained non- English text.

Genetic Toxicity.

Gene Mutation. 1,2-Dimethyl-4-nitrobenzene: Two summaries for bacterial reverse mutation assays with *Salmonella typhimurium* were missing important information, including: whether positive controls were used, concentrations tested, evidence of cytotoxicity, and incubation conditions (temperature, duration, etc.).

4-Nitro-m-xylene: Summaries of 10 *in vitro* gene mutations tests in *S. typhimurium* and/or *Escherichia coli* were missing nearly all study information. Also, it appears that some of the summaries may be duplicates of others.

Chromosomal Aberrations. 4-Nitro-m-xylene: A summary submitted for a reportedly OECD- and GLP-compliant *in vivo* mammalian bone marrow cytogenetic test (no Klimisch code assigned) was duplicated in the robust summary document, and was missing information including control use/data, administration route, test conditions, number of animals tested, statistical methods used, and exposure period. Additionally, the "results" field of the summary reported the result in a language other than English (indicated as "negative" on page 14 of the test plan).

Reproductive Toxicity. 2-Nitrotoluene: Summaries of reproductive organ evaluations from the rat and mouse 13-week National Toxicology Program (NTP) repeated-dose toxicity studies contained hardly any details and were insufficient. Details missing from most summaries included test substance purity, Klimisch codes, animal strain and/or sex, methodological details, and statistical methods used. Additionally, some summaries appeared to be duplicates of others, and some contained non-English text.

Ecological Effects

Fish. 4-Nitro-m-xylene: A summary of an OECD 96-hour acute fish toxicity study with *Brachydanio rerio* was missing nearly all study information including pH, hardness, fish age, and vehicle used. Information missing from one or both summaries included test guideline used, GLP compliance, number of fish per concentration, concentrations tested, test condition data (e.g., dissolved oxygen, temperature, total organic carbon), statistical methods used, loading rate, mortality data, and data on any observed effects, and only reported the test type (static), species, LC_{50}, LC_{100}, and LC_0 values, and year.

Invertebrates. 1,2-Dimethyl-4-nitrobenzene: A summary for a 48-hour static toxicity test in *Daphnia magna* was missing information including number of daphnids per concentration, concentrations tested, test condition data (e.g., dissolved oxygen, photoperiod, temperature, total organic carbon), statistical methods used, loading rate, and immobility/mortality data.

4-Nitro-m-xylene: A summary of the 48-hour acute daphnid toxicity study was missing nearly all study information including number of daphnids per concentration, concentrations tested, test condition data (e.g., dissolved oxygen, photoperiod, temperature, total organic carbon), statistical methods used, loading

rate, and immobility/mortality data, and only reported the exposure duration (24 hours), species, EC_{50}, EC_{100}, and EC_0 values, non-GLP compliance, absence of analytical monitoring, and year.

Algae. 1,2-Dimethyl-4-nitrobenzene: A summary of a 96-hour toxicity test with *Chlorella pyrenoidosa* was missing information including test guideline used, concentrations tested, number of replicates per concentration, test condition information (e.g., dissolved oxygen, lighting, temperature), statistical methods used, initial cell concentration, frequency and method that cell concentrations were quantified, and any observed treatment effects.

Followup Activity

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