

August 12, 2003

Ken Nitschke
Technical Contact
The Dow Chemical Company
1691 North Swede
Midland, MI 48674

Dear Dr. Nitschke:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Nitroalcohol Category posted on the ChemRTK HPV Challenge Program Web site on April 3, 2003. 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 The Dow Chemical Company 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 addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. 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-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission: Nitro Alcohol Category

Summary of EPA Comments

The sponsor, The Dow Chemical Company, submitted a test plan and robust summaries to EPA for the nitro alcohol category dated March 20, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on April 3, 2003. The category consists of two compounds: 2-methyl-2-nitropropanol (MNP, CAS No. 76-39-1) and 2-(hydroxymethyl)-2-nitro-1,3-propanediol (TN, CAS No. 126-11-4).

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

1. Category Justification. The category is adequately justified for physicochemical properties, environmental fate, and ecotoxicity but not for health effects.
2. Physicochemical Properties. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.
3. Environmental Fate. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program. However, the submitter needs to correct some errors in its biodegradation robust summaries.
4. Health Effects. EPA reserves judgment on the adequacy of the submitted data pending submission of (1) information on the major exposure route for both chemicals; (2) substantiation of the closed-system intermediate status; and (3) critical information lacking in the robust summaries.
5. Ecological Effects. EPA agrees with the submitter that adequate data are available for TN with the exception of data elements missing from the robust summaries. EPA agrees with the use of TN as an analog for MNP.

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

EPA Comments on the Nitro Alcohols Challenge Submission

Category Definition

The submitter proposed a category to cover two 2-nitro alcohols, 2-methyl-2-nitro-1-propanol (MNP) and 2-(hydroxymethyl)-2-nitro-1,3-propanediol (TN). The category definition is clear and unambiguous.

Category Justification

Structurally, these compounds are 2-nitro derivatives of branched, four-carbon alcohols, that differ in the number of alcohol functions. Although not directly stated in the test plan, the submitter appears to justify the nitro alcohol category on the basis of the structural similarities of the two compounds and their production and decomposition chemistries; such arguments need to be more explicit.

Some differences exist in the physicochemical data for the two compounds; however, their environmentally important physicochemical properties are similar from the standpoint of low vapor pressures, high water solubilities, and negative partition coefficient values.

Differences in estimated photodegradation rates for the two compounds are small (approximately 3-fold). No data were given for hydrolysis of MNP, but this compound is expected to resemble TN with respect to instability at basic pH. No biodegradation data were given for MNP, but similarities in structure suggest similar biodegradation rates for the two nitro alcohols. The differences in the modeled distribution of the compounds in the environment were not significant.

The acute oral toxicities and lack of mutagenic effects (Ames test) have been shown to be similar for MNP and TN, although MNP is a severe eye irritant, whereas TN was classified as nonirritating to eyes. No data were provided to support using TN data to fill repeated-dose and reproductive/developmental data gaps for MNP. Although the common functional groups and decomposition products (formaldehyde and nitroparaffins) suggest the possibility of similar toxicity profiles, additional information (such as similarities in metabolism) is needed to justify the category for the human health endpoints, especially because the data on MNP are so limited.

Acute ecotoxicity data were provided for TN, but none for MNP to allow a comparison; however, given the similarities in chemical functions, decomposition products, and reasonably similar log K_{ow} values, similar acute fish, invertebrate, and algal aquatic toxicities are expected for both nitro alcohols.

Test Plan

The submitter notes that MNP is used as a “closed system intermediate” in the production of two alkanolamines.¹ If the submitter wishes to claim the chemicals are closed system intermediates, more supporting information is needed in the test plan. The submitter should consult EPA’s Feb 8, 1999 “Guidance for Testing Closed System Intermediates for the HPV Challenge Program” (available at <http://www.epa.gov/opptintr/chemrtk/guidocs.htm>) for the types of information needed to support a “closed system intermediate” claim.

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

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program. While the test plan states that MNP decomposes near its melting point, this information does not appear in the robust summary, and the discrepancy should be resolved..

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

The data provided by the submitter for photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program.

Biodegradation. The biodegradation data provided by the submitter for TN are adequate for the purposes of the HPV Challenge Program. However, the robust summary incorrectly states that this chemical is “inherently biodegradable.” The entry needs to show that this chemical is “not readily biodegradable.”

The submitter provides no biodegradation data for MNP, stating that it is an analog of TN. Since the submitter reports that TN undergoes 13.4 % biodegradation in 28 days in a ready test, then the robust summary for MNP needs to indicate that on the basis of the analog data it is not readily biodegradable.

¹The submitter notes that TN is used as a biocide and is expected to present the potential for occupational exposures; however, this use is regulated under FIFRA and therefore, is not considered in this review.

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

The submitted data for the acute, repeated-dose, genetic, reproductive, and developmental toxicity endpoints are tentatively acceptable pending (1) verification that the chemicals are either closed-system intermediates or that the only exposure is via the dermal route and (2) receipt of revised robust summaries.

If the submitter substantiates the claim that the chemicals are closed-system intermediates and that exposures (excluding the biocidal use of TN) are limited to the dermal route, the reproductive and repeated-dose toxicity data are acceptable.² The submitter did not claim that the primary exposure for MNP would be via the dermal route; therefore, more information is needed to determine that the dermal route is the main exposure route for this compound. Also, more information on the cross-linking process for plywood is needed to verify that exposures are limited to the dermal route.

Genetic Toxicity. The adequacy of the bacterial mutagenesis study on MNP cannot be determined from the data provided; the submitter needs to provide a revised summary.

Reproductive Toxicity. The submitter needs to provide a separate reproductive toxicity robust summary for the study used for the reproductive toxicity endpoint, documenting the reproductive organs examined and the effects on these organs.

Developmental Toxicity. The developmental toxicity data on TN are tentatively acceptable pending receipt of revised robust summaries.

Ecological Effects (fish, invertebrates, and algae)

EPA agrees with the submitter that adequate data are available for TN. EPA agrees with the use of TN as an analog for MNP based on the information provided in the test plan and therefore the TN data can be extrapolated to MNP.

Specific Comments on the Robust Summaries

Generic comments

Some robust summaries did not provide enough detail. The submitter should consult EPA guidance documents for the preparation of robust summaries (<http://www.epa.gov/opptintr/chemrtk/guidocs.htm>).

Each summary should clearly identify the test substance by the chemical name rather than as "other TS" or its commercial name. In addition, the purity should be stated where available.

Health Effects

Repeated-Dose Toxicity. The submitter should include the number of animals per sex per dose. The EPA OPP Guideline number should be 82-3 (90-day dermal), not 82-2 (21-28 day dermal).

²If inhalation or oral exposures occur, the dermal repeated-dose study (also used for the reproductive toxicity endpoint) are not adequate because it appears that TN and MNP may not be absorbed via the dermal route based on reviewing the submitted acute and repeated-dose data. The acute data showed an oral LD50 of less than 1500 mg/kg/day for both compounds (and also shows several systemic effects for MNP). In addition, acute inhalation toxicity of TN resulted in deaths and some systemic effects. However, by the dermal route, no deaths or systemic effects were observed for MNP and TN at doses of 2000 and 5000 mg/kg/day, respectively. Finally, the 13-week repeated-dose dermal test of TN also showed no systemic toxicity.

Genetic Toxicity. Limited information was provided for the MNP and TN studies of bacterial mutagenesis. The robust summaries should include the following information if the methods differ from those specified by OECD Guideline 471: number of replicates, frequency of dosing, use of positive and negative control groups, criteria for evaluating results, and the precipitation concentration (if applicable).

A robust summary for a negative *in vitro* chromosomal aberration assay on TN was conducted under GLP and EPA OTS 798.5375, which is equivalent to OECD Guideline 473. However, the submitter should include the following information if the methods differ from those specified by OECD Guideline: number of replicates, frequency of dosing, use of positive and negative control groups, criteria for evaluating results, and the precipitation concentration (if applicable).

Developmental Toxicity. The first robust summary, for a developmental toxicity study in rats exposed by gavage to "TRIS NITRO," was missing information on the vehicle used and the number of rats per sex per dose. It would be useful if both the rat and rabbit developmental robust summaries (first and second summaries) included additional details regarding incidence of effects at each dose as well as the incidence of effects in the concurrent and historical control groups.

Ecological Effects

Fish. Missing data elements include pH, hardness, and dissolved oxygen for the *Cyprinodon variegatus* and *Pimephales promelas* studies.

Invertebrate. Missing data elements are pH, hardness, and dissolved oxygen for the *Daphnia magna*, *Mysidopsis bahia*, and *Crassostrea virginica* studies.

Algae. Missing data elements are pH and hardness. The submitter needs to check whether the substance purity should be 96.9 % rather than the 9.69 % reported.

Followup Activity

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