

January 14, 2005

F.J. Sonny Maher
Panel Manager
American Chemistry Council
Fatty Nitrogen Derivatives Panel
Nitriles Task Group
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Maher:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Fatty Nitrogen Derived Nitriles Category posted on the ChemRTK HPV Challenge Program Web site on February 23, 2004. I commend the American Chemistry Council Fatty Nitrogen Derivatives Panel Nitriles Task Group 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 Task Group advise the Agency, within 90 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 Donald Rodier, Acting Chief of the HPV Chemicals Branch, at 202-564-7633. 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,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission: Fatty Nitrogen Derived Nitriles Category

Summary of EPA Comments

The sponsors, the Fatty Nitrogen Derivatives Panel Nitriles Task Group of the American Chemistry Council, submitted a test plan and robust summaries to EPA for the fatty nitrogen derived (FND) nitriles category dated December 29, 2003. This category contains 14 sponsored substances. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 23, 2004.

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

1. Category Justification. The grouping of 12 of the 14 nitriles into a single category is generally supported on the basis of structure and the available physicochemical, environmental fate and health effects data. However, additional information is needed to demonstrate that unsaturated elements in the alkyl chains of several category members do not significantly alter toxicity. The test plan does not provide adequate support for inclusion of the two 3-alkylaminopropanenitrile category members.
2. Physicochemical Properties. The submitter needs to provide additional data for melting point, vapor pressure, and water solubility.
3. Environmental Fate. EPA agrees with the submitter that there are sufficient data for category members for photodegradation and stability in water. Additional data are needed for biodegradation. EPA recommends that the submitter estimate the fugacity of representative components of the coco, tallow, and soya nitriles.
4. Health Effects. Adequate data are available for acute toxicity and gene mutations for the category and EPA agrees with the submitter's proposal to conduct testing for chromosome aberrations and reproductive and developmental toxicities. However, the submitted information is inadequate to satisfy the requirements for the classification of these chemicals as closed system intermediates (CSI) eligible for reduced testing in the HPV Challenge Program. Unless additional information is provided to support the CSI claim, the submitter needs to address repeated-dose toxicity for the category. Testing is also needed on a category member having unsaturated alkyl groups.
5. Ecological Effects. EPA agrees with the submitter that, for the alkyl nitriles, adequate data exist for all ecological endpoints for the purposes of the HPV Challenge Program. Data for the two alkylaminonitriles are not adequate.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on the Fnd Nitriles Category Challenge Submission

Category Definition

The Fatty Nitrogen Derived (FND) Nitriles category includes 12 long-chain alkyl nitriles ranging in carbon number from C6 to C22 and two long chain nitriles derived from 3-aminopropanenitrile. Four of the nitriles are single chemicals; the remaining eight are mixtures. The single chemical members with saturated alkyl groups are dodecanenitrile (CAS No. 2437-25-4), hexadecanenitrile (CAS No. 629-79-8), and octadecanenitrile (CAS No. 638-65-3); 9-octadecenenitrile (CAS No. 112-91-4) has one olefinic bond. The eight members that are mixtures contain either saturated alkyl nitriles [hydrogenated tallow nitriles (CAS No. 61790-29-2), C16-18 nitriles (CAS No. 68002-65-3), and C16-22 nitriles (CAS No. 68153-02-6)] or a combination of saturated and unsaturated alkyl nitriles [coco nitriles (CAS No. 61789-53-5), tallow nitriles (CAS No. 61790-28-1), C16 and C18 unsaturated nitriles (CAS No. 68002-64-2),

C14-16 and C16-18 unsaturated nitriles (CAS No. 68513-04-2), and soya nitriles (CAS No. 68514-67-0)]. The unsaturated alkyl nitrile mixtures contain 1 to 3 sites of unsaturation in the hydrocarbon chain. The category also includes derivatives of 3-aminopropanenitrile: 3-[(Z)-9-octadecenylamino]propanenitrile (CAS No. 26351-32-6); and a mixture of N-tallow derivatives of 3-aminopropanenitrile (CAS No. 68784-70-3).

While the CAS number identities of the category members are clearly specified, more information on the carbon number ranges and number of double bonds in the R groups of CAS Nos. 68002-65-3, 68153-02-6, 68002-64-2), and 68513-04-2 would be helpful.

Category Justification

The submitter's rationale for grouping the fourteen fatty nitrogen derived (FND) nitriles into one category is based on structural similarities and the composition of the alkyl portions of category members that result in surfactant-like properties with similar physicochemical properties, environmental fate and toxicities. The submitter states that differences in chain length and degree of unsaturation among category members are expected to have little impact on the fate and effects of these substances. The submitter supports this rationale with data on the single chemical nitriles with hydrocarbon chain lengths of C12 to C18. In addition, the submitter reports that alkyl nitriles derived from natural oils (e.g., coco, tallow and soya) with carbon number ranges of C8-C18 have toxicological properties similar to the single chemical alkyl nitriles. The submitter thus concludes that "there are no significant differences among the chemicals in the category that reasonably can be expected to result in differences in the HPV/Screening Information Data Set (SIDS) endpoints."

Overall, the grouping of the twelve alkyl nitrile substances into a single category is supported on the basis of structure and the available physicochemical, environmental fate, health effects and ecological effects data. However, several of the proposed members have unsaturated alkyl elements that may alter toxicity to an unknown degree. The acute toxicity and mutagenicity information supplied are insufficient to support the contention that unsaturation has no effect on the range of health endpoints. Additional toxicity or metabolism data are therefore needed to demonstrate similarity of toxic action between members with and without unsaturated alkyl groups to support the proposed approach.

A serious problem with the proposed category is that two members, 3-[(Z)-9-octadecenyl- amino]-propanenitrile and N-tallow derivatives of 3-aminopropanenitrile, differ structurally from other members. The estimated physicochemical data provided by the submitter suggest that the neutral forms of these alkylaminonitriles have similar properties to the alkyl nitrile members. However, these two nitriles are expected to be protonated at neutral pH and therefore will have a greater hydrophilicity than the alkyl nitrile members. This can result in environmental and toxicological properties that differ significantly from the properties of the alkyl nitriles. No experimental data were submitted for these two members. Consequently, the information provided by the submitter in the test plan is insufficient to support the inclusion of these two members in the FND nitriles category.

Test Plan

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

The data provided by the submitter for boiling point and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Melting Point. For this endpoint, the submitter provided measured data for four chemicals—octadecanenitrile, 9-octadecenitrile, coco nitriles, and tallow nitriles—and estimated data for several other category members. Because of the wide range of measured values (-22 °C to 41 °C), extrapolation to other category members is unreliable. Furthermore, estimated melting point values are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured melting point data

for the remaining category members.

Vapor Pressure. Except for coco nitriles and tallow nitriles, the submitter provided estimated data for the category members. The estimated values provided for C16 and C18 unsaturated nitriles, C16-18 nitriles, and C14-18 and C16-18 unsaturated nitriles are not adequate for the purposes of the HPV Challenge Program because they are greater than the cutoff value of 1×10^{-5} Pa. The submitter needs to provide measured vapor pressure data for these chemicals.

Water Solubility. The submitter reported that octadecanenitrile (CAS No. 638-65-3) and 9-octadecenenitrile are “insoluble” in water, that coco nitriles are “practically insoluble” in water, and that tallow nitriles are “not soluble”. Such qualitative statements unsupported by quantitative data are not adequate for the purposes of the HPV Challenge Program. The estimated data provided by the submitter for seven of the other category members suggest that there are components in these substances with water solubilities above the measured data threshold value of one ppb. Therefore, the use of estimated data is inadequate for defining the water solubilities of these alkyl nitrile mixtures. Instead, locating measured values for chemicals representing the most soluble components of the mixtures and adding the information to the summaries would be adequate for the purposes of the HPV Challenge Program.

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

The data provided by the submitter for photodegradation are adequate for the purposes of the HPV Challenge Program.

Stability in water. EPA agrees with the submitter’s conclusion that these chemicals are generally not hydrolyzable. However, the submitter needs to include in the robust summary a technical discussion of the basis for this conclusion.

Biodegradation. The data provided for n-alkyl nitrile mixtures generally support the conclusion that long chain (here defined as C10 or greater) n-alkyl nitriles are readily biodegradable. However, the submitted data for dodecanenitrile and the coco nitriles mixture, of which C12 is the major component, appear to be inconsistent. According to the submitted data, dodecanenitrile underwent 15 % theoretical oxygen demand (ThOD) in 28 days. However, coco nitrile, which consists of 44-53% C12, in two separate studies underwent 43% and 71% theoretical carbon dioxide demand (ThCO₂D) in 28 days. Substances with alkyl chains shorter than C12 make up a significant mole fraction of the coco nitriles. Because biodegradation rates may be different for these shorter alkyl chains, the submitter needs to submit biodegradation data for one or more of the shorter-chain components (e.g., the C8 nitrile). Additionally, no data were submitted for derivatives of 3-aminopropanenitrile, which differ in structure sufficiently from the other long-chain alkyl nitriles to suggest that their biodegradability may also differ.

Fugacity. The data provided by the submitter are adequate for the purposes of the HPV Challenge Program except for coco, tallow, and soya nitriles and N-tallow derivatives of 3-aminopropane-nitrile. For coco nitriles, the carbon number range of C6-18 is wider than that of the other category members. EPA therefore recommends that the submitter run Level III fugacity estimations for C8, C12 and C18 model compounds as representative chemicals of the coco nitriles. For tallow nitriles, EPA recommends that the submitter run Level III fugacity estimations for C16 and C18 model compounds. For soya nitriles, EPA recommends that the submitter run estimations for C16 and C20 model compounds. For the N-tallow derivatives of 3-aminopropanenitrile, one issue is suitable representative components; another is that the neutral forms of these compounds may partition differently from the protonated forms, which are likely to predominate at environmental pHs. This latter feature of the N-tallow derivatives of 3-aminopropanenitrile also renders their inclusion in the FND Nitriles category questionable.

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

The data provided by the submitter for acute toxicity and gene mutations are adequate for the purposes of the HPV Challenge Program.

Additional information is needed to demonstrate similarity of health effects among members with and without unsaturated alkyl groups to support the proposed category. Also, it is unknown if the two 3-alkylaminopropanenitriles have toxicities similar to the alkyl nitriles. The 3-alkylaminopropanenitriles are anticipated to be more water soluble than the alkyl nitriles and will likely partition differently in the organism. Therefore, data are needed for the two 3-alkylaminopropanenitriles to support their inclusion in the category.

The submitter claims the FND nitriles are closed system intermediates (CSI) and are eligible for reduced testing in the HPV Challenge Program. The Guidance for Testing Closed System Intermediates for the Challenge Program <http://www.epa.gov/chemrtk/guidocs.htm> allows for a reduced testing protocol provided certain criteria are met. The information required to support a "closed-system intermediate" claim must address the following:

I. Site information

- A. Number of sites.
- B. Basis for "closed process" conclusion at each site.
 - 1) Process description.
 - 2) Monitoring data showing no detection.
 - 3) In the absence of monitoring data, the basis for believing that releases do not occur.
- C. Data on "presence in distributed products."

II. Information on transport (mode, volume, controls, etc)

III. A data search showing that the chemical is not present in other end products.

EPA believes that the submitted information is inadequate to satisfy the requirements for classification of these chemicals as (CSIs) eligible for reduced testing in the HPV Challenge Program for the following reasons:

IA. *Number of sites:*

The CSI claim in the test plan does not cover all U.S. manufacturing sites for the subject chemicals. A review of the TSCA Inventory Update Rule (IUR) information submitted to EPA in 2002 and 1998 identified other producers of the chemicals in this category in addition to members of the Nitriles Task Group.

IB and IC. *Basis for closed process conclusion at each site. Process description. Monitoring data showing no detection. In the absence of monitoring data, the basis for believing that releases do not occur. Data on "presence in distributed products":*

The manufacturing process is not described in sufficient detail. According to the test plan, reaction vessels used to produce FND ether nitriles category chemicals are part of multi-purpose, closed system operations. The process description is not sufficiently detailed to provide a reasonable basis to conclude that the process is closed. In addition, the test plan did not include monitoring data showing no detection of category members or their unidentified downstream products in any media or a statement providing the basis for believing, in the absence of data, that release and exposure to the chemicals in question do not occur. The test plan also states that wastewater generated during periodic equipment cleaning is treated on-site or incinerated, but information on the concentrations of the subject chemicals in wastewater discharges is not provided.

II. *If transport occurs, information on the mode of transport, volume, type of consignment, and*

controls during transport and transfer at dispatching and receiving sites:

Transfer descriptions lacked details. The submitter needs to address handling practices at all sites.

III. *Supporting evidence that the chemical is not present in other end-products.*

Analytical data would help substantiate that the chemical is not present in other end-products. Odor threshold data would also be supportive.

Unless additional information is provided to support the “closed system intermediate” claim, the submitter needs to address repeated-dose and reproductive health effects endpoints for the purposes of the HPV Challenge Program.

EPA agrees with the submitter’s proposal to conduct testing on dodecanenitrile for chromosome aberrations (OECD TG 473) and reproductive/developmental toxicities (OECD TG 421), but recommends a combined repeated-dose and reproductive/developmental toxicity screening test (OECD TG 422) instead of the proposed OECD TG 421. The submitter also needs to conduct these same tests and an *in vitro* gene mutation assay with an appropriately chosen category member having unsaturated alkyl groups, or provide adequate information demonstrating similarity of toxic action between members with and without unsaturated alkyl groups.

Ecological Effects (fish, invertebrates, and algae)

Alkyl nitriles. The data provided by the submitter for the ecological endpoints (i.e., fish, daphnia, and green algae) are adequate for the purposes of the HPV Challenge Program.

3-Alkylaminopropanenitriles. No measured ecotoxicity data were submitted for these two substances that would support their inclusion in the FND nitriles category or their characterization by alkyl nitrile data.

Specific Comments on the Robust Summaries

Generic comments

In general, the robust summaries do not provide sufficient detail. The submitter is encouraged to review the guidance on developing robust summaries (available at: <http://www.epa.gov/chemrtk/robsumgd.htm>) and revise the robust summaries as appropriate.

Health Effects

Acute toxicity. Missing information in the submitted robust summaries includes test substance purity, number and sex of animals per dose, and range or 95% confidence intervals for LD50s.

Genetic toxicity. Although the studies were conducted following OECD guidelines and complied with GLP, omitted information in the robust summaries includes test substance purity, cytotoxic concentration, number of colonies per concentration examined, criteria for positive results, and statistical results.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.