

October 2, 2007

Nancy Sandrof
Manager, FND Panel
American Chemistry Council
1300 Wilson Boulevard,
Arlington, VA 22209

Dear Ms. Sandrof:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the revised test plan and robust summaries for the Fatty Nitrogen Derived (FND) Imidazoline Derivatives dated September 16, 2004. EPA posted the submission on the ChemRTK HPV Challenge Program Web site on October 18, 2004. The submission is one of five revisions in response to EPA comments dated June 27, 2002 on the original submission dated December 19, 2001. The other four revisions--FND Amides, FND Amphoterics, and two single chemicals—are being reviewed separately. I commend the FND Panel 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 a chemical for further work.

EPA will post this letter on the HPV Challenge Web site within the next few days. We ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send 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 tsc hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-s-

Mark Townsend, Chief
HPV Chemicals Branch

cc: O. Hernandez
R. Lee
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:

FND Imidazoline Derivatives

Summary of EPA Comments

The sponsor, the American Chemistry Council's Fatty Nitrogen Derivatives Panel Amides Task Group, submitted a test plan and robust summaries to EPA for fatty nitrogen-derived amides (FND amides) dated September 16, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on October 18, 2004. The submission is a revision in response to EPA comments dated June 27, 2002, on the original submission dated December 19, 2001. The revised submission covers three new categories: FND amides, FND imidazoline derivatives and FND amphoteric (N-carboxymethyl substituted) that were created within the original category. This review covers the FND imidazoline derivatives category, which consists of five sponsored substances. The other new categories are reviewed separately.

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

1. Category Definition. The category definition is clear.
2. Category Justification. There is inadequate support for the grouping of the sponsored substances into one category owing to significant variations among the substituents on the imidazoline rings and a lack of data to demonstrate similarity. The submitter needs to explain and support with data how the specific properties of the category members directly influence the proposed uniformity of behavior.
3. Analog Justification. The use of the analog to characterize more than one or two substances needs to be supported by data and a convincing discussion.
4. Physicochemical Properties. The submitter needs to indicate the physical state of these substances at 25 °C and provide decomposition values for the sponsored substances, vapor pressure values for representative structures for all five substances and dispersibility data at pH 7 for CAS Nos 61791-39-7, 72623-72-4 and 65817-50-7.
5. Environmental Fate. The submitter needs to provide estimated photodegradation and fugacity data for representative structures of all the sponsored substances. The submitter needs to provide measured hydrolysis data for most of the substances and measured ready biodegradation data for all the sponsored substances.
6. Health Effects. Adequate data were submitted for the two amides for all SIDS endpoints for the purposes of the HPV Challenge Program. The submitter needs to provide data to support the inclusion of the alcohol and primary amines in the category for the purposes of the HPV Challenge Program. The submitter needs to clarify what impact, if any, the use of isopropyl alcohol as a diluent had on the toxicity data submitted for the test substance.
7. Ecological Effects. EPA believes that additional testing is necessary to characterize these chemicals, as the large differences in molecular weights and size and type of hydrophilic groups suggest toxicities will vary among members of the category.

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

EPA Comments on the FND Imidazoline Derivatives Challenge Submission

General

Although the organization of the present submission is an improvement over the previous submission, the overall category structure for the FND Amides as defined by the submitter is complex, unclear, and ultimately unworkable. The FND Amides category is complex because it is divided into three categories, some of which are further divided into subcategories, suggesting that the definition of the FND Amides category is too broad, and the different categories and subcategories should have been separate submissions. In addition, the test plan is frequently unclear, especially when the discussion includes the word "category", since this could refer to either the entire submission or to one of the separate categories; clarity in associating information with a specific category/subcategory is critical to assessing its overall support.

For purposes of clarity and organization, EPA is reviewing separately the three categories identified for the FND Amides: Category I, FND Amides; Category II, FND Imidazoline Derivatives; and Category III, FND Amphoterics. The present comments focus on Category II – the FND Imidazoline Derivatives.

Category Definition

The FND Imidazoline Derivatives were grouped as a separate category within the larger Fatty Nitrogen Derived (FND) Amides category submission. These substances are formed by the reaction of fatty acids with ethylenediamine derivatives (diethylenetriamine, N-(2-hydroxyethyl)-ethylenediamine, and tetraethylenepentamine), yielding amides which are subsequently dehydrated to form imidazolines (*all three* of the structures in the illustrative reaction scheme, and thus also the scheme itself, are incorrect). The FND imidazoline derivatives category consists of five sponsored substances:

CAS No. 72749-55-4	Imidazolium compounds, 2-(C17 & C17-unsat. alkyl) -1[2-(C18 & C18-unsat. amido)ethyl]-4,5-dihydro-1-methyl-, methyl sulfates,
CAS No. 61791-39-7	1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-nortall oil alkyl derivatives,
CAS No. 68442-97-7	1H-Imidazole-1-ethanamine, 4,5-dihydro-, 2-nortall oil alkyl derivatives,
CAS No. 72623-72-4	Amides, C14-18, N-[2-(C13-17-alkyl-4,5-dihydro-1H-imidazol-1-yl)ethyl]- , and
CAS No. 65817-50-7	1,2-Ethanediamine, N-(2-aminoethyl)-N'-[2-(8Z)-8-heptadecenyl-4,5-dihydro-1H- imidazol-1-yl]ethyl.

One additional chemical is included to provide support for the category: imidazolium compounds, 4,5-dihydro-1-methyl-2-nortallow alkyl-1-(2-tallow amidoethyl)-, methyl sulfate (CAS No. 68122-86-1).

The Test Plan states "Note that in the naming convention used for the FND Amides chemicals, the carbon in the carbonyl group is one of the carbons in the alkyl chain when R or R' is used to designate the alkyl chain (e.g., when R=C18 with a carbonyl group, the structure is C17-C=O)." The R' s in two structures are thus incorrect and should be "C17 & C17 unsaturated" for CAS No. 72749-55-4 and "C13 & C17 alkyl" for CAS No. 72623-72-4.

Category Justification

The submitter has not provided adequate support for the grouping of the sponsored substances into one category. The grouping is not supported owing to variations among the substituents on the imidazoline rings and a lack of data to demonstrate similar behavior. Differences in the structures and functional groups impact the physical and chemical properties of the sponsored chemicals in ways that may affect their abilities to be absorbed by living organisms, the pathways by which they are metabolized and cleared from the body, and their toxicities. For example, CAS No. 61791-39-7 is an alcohol, and CAS Nos 68442-97-7 and 65817-50-7 are primary amines, whereas the remaining two are amides, one of which has a permanent positive charge.

At many points throughout the test plan, but principally in the sections on the physicochemical, environmental fate, and ecological effects endpoints, the submitter discusses the importance of the surfactant character of the category members. In general, these sections discuss experimental difficulties with surfactants (e.g., physicochemical properties) and how surfactant properties dominate the anticipated behavior of the category members (e.g., ecological effects). However, the submitter does not link any of the expected experimental difficulties or anticipated behavior with data specific to the surfactant properties of the category members. The submitter needs to expand this discussion by indicating how these properties will influence the interpretation of the available data, with specific reference to the chemical functionality of category members. This is particularly important for a proposed category such as this one, which has structurally dissimilar members and spans a molecular weight range of 350 to 644.

Analog Justification

On a structural similarity basis, the analog seems appropriate for one or possibly two of the category members. However, because of the structural differences already discussed, the use of the analog data to characterize the remaining substances needs to be supported by data and a convincing discussion.

Test Plan

Physicochemical Properties

Melting point. The submitter indicates that these chemicals are mixtures and therefore a determination of this endpoint is not applicable. EPA agrees with this reasoning for this endpoint. However, the submitter needs to indicate the physical state of these chemicals at 25 °C.

Boiling point. The submitter states that determination of this endpoint is not applicable because these chemicals are expected to degrade at temperatures well below their expected boiling points. Determination of an exact boiling point may not be possible; however, to substantiate the statement, the submitter needs to provide decomposition temperature ranges for all five sponsored substances. Temperatures above 300 °C may be estimated.

Vapor pressure. The submitter indicates that determination of this endpoint is not applicable. EPA disagrees; the submitter needs to provide vapor pressure values for representative structures of all five sponsored substances. Vapor pressures below 1×10^{-5} Pa may be estimated.

Partition coefficient. EPA agrees with the submitter's reasoning for not providing data for this endpoint.

Water solubility. In table 5b, the submitter indicates that "this material is a mixture and has no single value for water solubility. Determination of this endpoint is not applicable." EPA agrees in that a discrete water solubility value may not be obtainable. However, measured dispersibility values are needed for the purposes of the HPV Challenge Program. The submitter needs to provide dispersibility information at pH 7 for CAS Nos. 61791-39-7, 72623-72-4, and 65817-50-7 for ecotoxicological testing purposes.

Environmental Fate

For the environmental fate endpoints, the submitter proposes to obtain data using a read-across approach. This approach is not adequate for the purposes of the HPV Challenge Program because, as indicated above under category justification, the grouping of these five substances is not supported for the environmental fate endpoints owing to structural variations among the imidazoline ring substituents and the lack of data on which to base a determination of similar behavior.

Photodegradation and fugacity. In table 6b of the test plan, the submitter indicates that all photodegradation and fugacity data will be obtained using a read-across approach as described on page 14. This approach for these two endpoints is inadequate for the purposes of the HPV Challenge Program for reasons mentioned above. The submitter needs to provide estimated photodegradation and fugacity data (following a level III model) for representative structures of the sponsored substances.

Stability in water. The submitter in its test plan proposes to test CAS No. 72749-55-4 following OECD TG 111 and use these data to characterize all five substances. This approach is inadequate for purposes of the HPV Challenge Program for reasons mentioned above and specifically because no experimental support is presented for the implied proposition that imidazoline ring hydrolysis will be unaffected by structural variation. Furthermore, the selected chemical is the only one with a permanent positive charge, which could lead to atypical results. The submitter needs to provide hydrolysis data, according to OECD TG 111, for enough members to characterize all the structure types among the five substances.

Biodegradation. In table 6b of the test plan, the submitter proposes to provide measured biodegradation data for CAS No. 72749-55-4, and use these data to characterize the other four substances in the category. This approach is inadequate for the reasons mentioned above. Differences in the structures of substituents impact the physical and chemical properties of the sponsored substances, which may affect their rate of biodegradation. The submitter needs to provide measured ready biodegradation data according to OECD TG 301 for each sponsored substance.

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

A Re-registration Eligibility Decision (RED) document exists for 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-nortall oil alkyl derivatives (CAS No. 61791-39-7). This document can be found at the following website: (http://www.epa.gov/oppad001/reds_list_ad.htm). The submitter should review the RED to determine what studies are available to add to this submission.

Adequate studies were submitted for the two amides for all SIDS endpoints for the purposes of the HPV Challenge Program. The submitter needs to provide data to support the inclusion of the alcohol and primary amines in the category.

General. Except for acute toxicity, all data submitted for the Health Effects endpoints were for the test substance suspended in isopropyl alcohol. Because isopropyl alcohol has its own inherent toxicity, the submitter needs to provide data and/or a technical discussion demonstrating that the toxicity data provided represent the test substance. Further, there is no indication in the robust summaries that the values obtained have been adjusted for the percentage of the test substance present.

Reproductive Toxicity. The submitter stated that this endpoint is satisfied by the histological evaluation of reproductive organs in the 13-week repeated dose toxicity study in dogs for the analog, CAS No. 68122-86-1. The submitter needs to extract this information from the study data and prepare a robust summary for this endpoint. Also, for the 13-week rat study, the submitter needs to extract the relevant reproductive toxicity data and prepare a robust summary.

Ecological Effects (fish, invertebrates, and algae)

Invertebrates. EPA reserves judgment on the adequacy of the test on CAS No. 61791-39-7 because critical data elements (especially total organic carbon (TOC) and dissolved oxygen (DO) content) were not reported in the robust summaries.

The submitter proposes testing CAS No. 61791-39-7 in fish and algae to provide data for the other category members. Because the five substances have widely varying molecular weights and different functional groups of varying hydrophilicity and reactivity on the imidazoline ring, EPA considers that testing two additional chemicals (CAS Nos. 65817-50-7 and 72623-72-4) in fish, invertebrates and algae using OECD TGs 201, 202, and 203, respectively, is necessary to adequately characterize the FND imidazolines. All tests should be conducted at or below the chemicals' dispersibility limit, with TOC of < 2 mg/L, mean measured concentrations, and water hardness of < 150 mg/L CaCO₃.

Specific Comments on the Robust Summaries

Health Effects

Genetic Toxicity. The summaries of the reverse mutation assay and the chromosomal aberrations assay on the analog, CAS No. 68122-86-1, need to include a description of the control responses.

Ecological Effects

Invertebrates. TOC and DO content need to be reported for the test on CAS No. 61791-39-7.

Followup Activity

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