September 23, 2002

Has Shah
Panel Manager
American Chemistry Council
Formic Acid and Formates Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Shah:

The Office of Pollution and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Formates Category, posted on the ChemRTK HPV Challenge Program Web site on January 30, 2002. I commend The American Chemistry Council's Formic Acid and Formate 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 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 American Chemistry Council's Formic Acid and Formate Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

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 HPV Challenge Program Web site "Submit Technical Questions" button 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: C. Auer
A. Abramson
M. E. Weber

EPA Comments on Chemical RTK Challenge Submission:
Formates Category

SUMMARY OF EPA COMMENTS

The sponsor, The Formic Acid and Formates Panel of the American Chemistry Council, submitted a test plan and robust summaries to EPA for the Formates Category dated December 21, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 30, 2002. The formates category consists of sodium formate, calcium formate, and methyl formate. Supporting data on formic acid were also submitted.

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

1. Category Justification. The submitter's support for the category is adequate overall, but needs some elaboration.

2. Physicochemical Properties and Environmental Fate. The submitter needs to state why certain endpoint data are not supplied. In addition, the submitter needs to supply more information in the robust summary for stability in water.

3. Health Effects. Adequate data are available for all health endpoints for the purposes of the HPV Challenge Program. No additional testing is necessary, provided developmental toxicity data for formic acid are adequate.

4. Ecological Effects. The studies of acute toxicity in fish and invertebrates for methyl formate are inadequate. The submitter needs to provide water hydrolysis half-life data for this chemical under environmental conditions to support its testing approach.

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

EPA COMMENTS ON THE FORMATES CATEGORY CHALLENGE SUBMISSION

Category Definition

The submitter proposed a category of three formates including the two salts, sodium formate (CAS No. 141-53-7) and calcium formate (CAS No. 544-17-2), and the ester, methyl formate (CAS No. 107-13-3). The submitter also included the parent compound, formic acid (CAS number 64-18-6), as a non-sponsored member to provide supporting data for the category. Formic acid is being sponsored separately as an International Council of Chemical Associations (ICCA) chemical under the OECD/SIDS program.

Category Justification

The submitter supported the category by stating that the physicochemical properties of the members indicate that all category members will dissociate or hydrolyze to form formate ion and concluded that the members have "similar mechanisms of action and metabolic profiles" that "strengthen the coherence of the category." In the case of formic acid, EPA acknowledges that pH effects may be important for acute health effects endpoints, but the effects of the formate ion are expected to dominate at lower exposure levels. EPA agrees that the category is supported by the test plan. However, the submitter needs to

account for the effects of environmental hydrolysis and of methanol formation *in vivo* in the discussion of mechanisms of toxic action.

Test Plan

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

The data provided by the submitter for melting point, vapor pressure, and water solubility for all three chemicals are adequate for the purposes of the HPV Challenge Program.

Boiling Point. The submitter did not provide boiling point data for sodium formate and calcium formate. According to OECD Guideline 103, measured boiling point values are preferred, but boiling points above 300 °C need not be specified. The submitter needs to explain in the robust summary why data were not provided for these two chemicals.

Octanol/water partition coefficient. The submitter did not provide octanol/water partition coefficient data for sodium formate. The submitter needs to provide these data or explain the omission.

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

The data provided by the submitter on photodegradation, biodegradation, and transport and distribution for all three chemicals are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter indicated in the robust summaries that sodium and calcium formates dissociate in water, forming stable ions. Although these two chemicals are not expected to be susceptible to chemical hydrolysis, the submitter should state in the robust summaries of these two chemicals why no testing is required.

The hydrolysis half-life for methyl formate is of special concern because it is important in determining ecological effects testing needs. The submitter needs to consult the original study report to determine whether the study was conducted under environmentally relevant conditions and add the information to the robust summary (the reported rate constant of K_b = 36.6 L/mol-sec for methyl formate was incorrectly stated in the robust summary as 3.66 L/mol-sec and needs to be corrected). If the study was not conducted under appropriate conditions data from a new study may be necessary.

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

Adequate data are available for acute, repeated-dose, and reproductive toxicity, and for gene mutations. Existing data on category members are also adequate for chromosomal aberrations, precluding the need for a proposed chromosomal aberrations test on methyl formate.

Reproductive toxicity. There are typographical errors in the two final bulleted items for formic acid on page 35/44 of the test plan. The concentration that caused no reproductive effects in 13-week rat and mice NTP studies was 128 ppm, not “up to 14-days.”

Developmental toxicity. The study submitted on calcium formate is inadequate because only one dose level was tested and no maternal or fetal toxic effects were observed. Also, the in vitro study on sodium formate is inadequate and no data are available on methyl formate. However, if developmental toxicity data from the ongoing ICCA testing program on formic acid are adequate, these data together with available data on methanol will adequately address the developmental toxicity endpoint for the formate

category members and additional testing will not be necessary for the purposes of the HPV Challenge Program.

The submitter needs to provide robust summaries on methanol for developmental toxicity, discussed on page 37 of 44 of the test plan. A number of developmental toxicity studies of methanol, including a primate study, have been reported (Ref.1).

Ecological effects (fish, invertebrates, and algae).

Adequate data are available for all ecotoxicity endpoints on calcium formate and sodium formate for the purposes of the HPV Challenge Program. However, the submitter needs to provide additional details in all the robust summaries.

The underlying studies of acute toxicity in fish, invertebrates, and algae on methyl formate are inadequate because the chemical's volatility was not considered, as evidenced by the use of nominal concentrations and open test systems. The submitter needs to provide additional information on the stability of methyl formate in water under standard test conditions (see remarks above under *Stability in water*). If the half-life of methyl formate under environmental conditions is >1 hour and < 5 days, the submitter needs to test methyl formate or provide analog/SAR information to satisfy the ecotoxicity testing requirements. Tests should be done using measured concentrations in flow-through closed systems, no head space, with the chemical administered to the organisms within 10 minutes of sample preparation. If testing of the ester itself is not indicated, adequate studies on formic acid may be used to assess the ecotoxicity of methyl formate hydrolysis products.

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. A robust summary for an OECD guideline (401) study on formic acid omitted the effects (mortality, clinical signs, body weight, necropsy results) by dose and sex.

The robust summaries for acute oral toxicity of sodium formate did not provide any details of methods or results beyond the LD_{50} and species.

Information omitted in the robust summaries for acute oral toxicity studies on calcium formate included: tested concentrations, gavage vehicle, length of the observation period, mortality and necropsy data by dose/sex, and method for calculating the LD_{50}.

A robust summary for acute oral toxicity on methyl formate was complete except for the method of calculating the LD_{50} and necropsy data for animals that survived the 14-day observation period.

Repeated-Dose Toxicity. The robust summaries for the 13-week NTP inhalation bioassays of formic acid in rats and mice did not report the purity of the test material, the method of generating the test atmosphere, the characteristics of the test atmosphere, or the size of the observed organ weight changes.

Genetic Toxicity. Information omitted in the robust summaries for genetic toxicity assays on formic acid included: the tested compound, the substance purity, the number of replicates, details of exposure, the number of cells scored, the criteria for scoring, the positive controls, cytotoxic concentration, and the source of the metabolic activation system.

Information missing in the robust summary for a reverse mutation assay in bacteria for sodium formate included: the tested and cytotoxic concentrations, the method of exposure, the number of replicates, the positive controls, the criteria for scoring, and the source of the metabolic activation system. A robust

summary for a chromosomal aberration assay for sodium formate omitted the number of replicates, the use of colchicine, and the criteria for scoring.

A robust summary for a reverse mutation assay in bacteria exposed to calcium formate did not provide the number of replicates and the chemical used to induce rats for S9 preparation.

Reproductive Toxicity. Robust summaries for the studies in rats and mice exposed to formic acid vapor in 13-week NTP bioassays did not report the method for generating the test atmosphere or characteristics of the test atmosphere.

Developmental Toxicity. A 2- to 5-generation drinking water assay of calcium formate in rats did not include a maternally toxic dose.

Ecotoxicity (fish, invertebrates, and algae).

Only test durations of 96-hours for fish, 48-hours for aquatic invertebrates and 72- to 96-hours for algae were reviewed to determine data adequacy. Test concentrations should be expressed as measured or nominal in all tests and the test method reported.

Sodium Formate

Fish. Missing are water temperature, chemical purity and dissolved oxygen.

Invertebrates. Missing are dissolved oxygen, chemical purity, and water temperature.

Algae. Missing are pH, water hardness, dissolved oxygen, and chemical purity.

Calcium Formate

Fish. Missing are chemical purity and water temperature. Missing from the SAR robust summary is log Kow input value.

Invertebrates. Missing from the SAR robust summary is log Kow input value.

Algae. Missing detail from the SAR robust summary is log Kow input value.

Methyl Formate

Algae. Missing are pH, water hardness, water temperature, dissolved oxygen, and chemical purity.

Formic Acid

Fish. Missing are pH, water hardness, water temperature, dissolved oxygen, and chemical purity. LC_{50} endpoint should be reported as > 100 mg/L after pH adjustment.

Invertebrates and algae. Missing are pH, water hardness, water temperature, dissolved oxygen, and chemical purity.

Followup Activity

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

References

1. HPV Challenge Program Test Plan for Methanol. Posted at http://www.epa.gov/chemrtk/volchall.htm on August 3. 2001.