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May 29, 2003

Via US Mail and E-mail

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency (EPA)
P.O. Box 1473
Merrifield, VA 22116

Re: Formic Acid and Formates Panel, Consortium No.
HPV Chemical Challenge Program Submission
Formates Category Justification and Testing Rationale
Response to EPA's Comments of September 12, 2002 on ACC Panel's Original Submission of December 21, 2001

Dear Administrator Whitman:

The Formic Acid and Formates Panel of the American Chemistry Council is pleased to submit the attached response to EPA's comments of September 12, 2002 on our initial test plan submission of December 21, 2001 for a category covering three chemicals (methyl formate, sodium formate and calcium formate). The attached response is provided on behalf of the following companies who are members of the Formic Acid and Formates Panel: BASF Corporation, Bayer Corporation, Celanese, GEO Specialty Chemicals and Hercules Inc.

This submission includes following documents:

- Item by Item Response to EPA's Comments of September 12, 2002 on ACC Panel's Original Submission of December 21, 2001;
- Revised Test Plan for the Formates Category, May 27, 2003;
- Formic acid robust data summaries in IUCLID format, updated May 24, 2000;
- Sodium formate robust data summaries in IUCLID format, updated March 2, 2003;
- Calcium formate robust data summaries in IUCLID format, updated March 2, 2003; and
- Methyl formate robust data summaries in IUCLID format, updated March 2, 2003.

Data on formic acid are used to support the conclusions reached for the formates category.

This submission is also being sent electronically to the following e-mail addresses:

Oppt.ncic@epa.gov
Chem.rtk@epa.gov

I also want to inform you that the Formic Acid and Formates Panel now has decided to switch commitment from the HPV Chemical Challenge Program to the ICCA Initiative. EPA has agreed for the U.S. to be the sponsoring country. BASF AG will be the lead company and Has Shah will be the Panel contact under the ICCA Initiative.

If you require additional information, please contact Has Shah, Formic Acid and Formates Panel Manager at (703) 741-5637 or has_shah@americanchemistry.com.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Attachments

cc: C. Auer, EPA (w/o attachments)
R. Hefter, EPA (w/o attachments)
O. Hernandez, EPA (w/o attachments)
B. Leczynski, EPA (w/o attachments)
L. Scott, EPA
Formic Acid and Formates Panel Members

AMERICAN CHEMISTRY COUNCIL
Formic Acid and Formates Panel
Consortium Number
May 29, 2003

Item by Item Response to EPA's Comments of September 12, 2002 on ACC Panel's Original Submission of December 21, 2001

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.

> Response: These have been added. There is an extensive discussion of hydrolysis and aquatic toxicity and the *in vivo* hydrolysis has been taken into consideration for the repeated dose, reproductive and developmental hazard characterization of methyl formate.

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.

> Response: The boiling point for these is > 300 ° C. Information about the decomposition of Sodium formate was added and the boiling point for Calcium formate has been added as > 300° C with a notation that boiling points > 300° C need not be specified according to the SIDS Manuel.

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.

> Response: A KOWIN estimate has been added for Sodium formate as this program recognizes sodium salts.

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.

> Response: Information as to why no testing is required was added to these robust summaries.

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.

> Response: The decimal point error was corrected. An additional higher-confidence reference was added (work of Hammett) which gives a similar result for the K_b. This new value was used to calculate a half-life under typical environmental conditions. A reference was added that substantiates the relevance of this laboratory-condition study to typical environmental conditions. The conditions of the Hammett studies are considered appropriate for this determination and are provided in the new robust summary.

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

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.

> Response: We are in agreement that this test is not necessary; it has been removed from the plan.

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."

> Response: Thank you. These have been corrected.

**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.

> Response: The developmental toxicity study has been placed in a laboratory and is scheduled to start in 2003.

*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).

> Response: Methanol developmental toxicity studies have been included in an Appendix to the test plan.

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.

Response: Available additional information has been added.

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.

Response: The original and a supplemental reference have been obtained that gives the laboratory conditions used to determine the hydrolytic rate constant. Supplemental information has been found that establishes the relevance of these determinations to actual environmental conditions. Both have been added to the Methyl formate water stability robust summary.

Relative to the aquatic toxicity testing, QSAR determinations have been used and justified as the primary means of estimating the aquatic toxicity of Methyl formate. Data for the hydrolysis products has been used to estimate long-term environmental hazard of Methyl formate. An appendix has been added that provided an in-depth discussion of issues involved in aquatic toxicity studies of Methyl formate and how they relate to the practical hazard. It is believed that the current data, supplemented with QSAR information and a through discussion of the hydrolytic process and toxicity of the hydrolytic products is adequate for the purposes of and HPV hazard assessment.

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.

Response: Added in as much detail as available in the report.

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.

Response: The source of this information is the ECB IUCLID 2000. The data are from Huels and attempts to obtain the original report have been unsuccessful. Continued efforts to obtain the detailed information will be made as the work on the Formates Category continues. The lack of details for this particular study is not viewed as a serious gap in the necessary HPV information for Sodium formate. In addition, more data on the short-term effects of Sodium formate will be generated in the planned developmental toxicity study.

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}.

> Response: There are four acute oral toxicity studies for this material. The critical study (Bayer data) has information concerning the details of the study conduct. A notation has been added to other studies that no details are available and they are included only as supporting data.

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.

> Response: The findings for surviving animals and the method for estimation of the LD50 were added to the appropriate robust summary.

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.

> The purity of the material was 95% with water as the only significant impurity and this has been added to the robust summary.
>
> Test material generation procedure and characterization has been added. Absolute and relative organs weights of affected organs, with level of significance, have been added to the robust summary as a table.

****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.

> Response: The first entry is an abstract from a meeting, it has been obtained but contains no relevant information
>
> The second entry (Calcium formate) has been updated to include the missing information.
>
> The third entry is the NTP Ames test. The published data were obtained and added to the robust summary along with the other requested information.
>
> Information about the SCE assay in CHO cells was obtained from the original literature (Basler et al. Arch Toxicol 58:10-13, 1985) and experimental details were added.
>
> Information about the SCE assay in human lymphocytes was obtained from the original literature (Sipi et al. Mutation Research 279:72-82, 1992) and available experimental details were added as requested.
>
> Details of the SOS chromotest procedure were obtained from the original publication and were added to the robust summary for that study.

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.

Response: The number of replicates and the source of the metabolic activation system was added. The other requested information was not available in the laboratory report. As this is only one of several relevant studies the lack of some details is not viewed as a significant shortcoming of the document.

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.

Response: The number of replicates was added; however, in this abbreviated report, the use of colchicine was not stated nor was 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.

Response: Both the number of replicates and the chemical used for liver-enzyme induction have been added to the robust summary.

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.

Response: The noted information has been added to the robust summary that is in the repeated-dose section of the summary document.

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

Response: This lack of maternal toxicity deficiency was pointed out in the original robust summary as a deficiency. The dietary level produced a dose of about 200 mg/kg-day calcium. Although there are no data to indicate that this dose produced hypercelcemia, it is known that significant hypercalcemia induces fetotoxicity (Liebgott B, Srebrolow G. Fetal toxicity caused by excessive maternal dietary calcium. J Can Dent Assoc 1989 Feb;55(2):129-33.). The mechanism is postulated to be suppression of para-thyroid hormone in the conceptus. Therefore, high levels of calcium formate will not serve as a robust model for formate developmental toxicity due to the disturbance of fetal calcium levels.

In addition a developmental toxicity study of sodium formate is proposed for the category. It is thought that the use of the sodium salt will provide a more robust test of formate developmental toxicity than the use of the calcium salt as excess calcium is indicated in the literature as fetotoxic.

<u>Ecotoxicity (fish, invertebrates, and algae)</u>.

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.

Response: The test concentrations were reported as requested in all summaries. For the formate salts, evaluation at less than the recommended 96 hours for fish and 48 hours for invertebrates can provide useful information as these materials have no tendency to accumulate in the organisms.

Sodium Formate

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

Response: The temperature and dissolved oxygen content were added to the robust summary. A statement was also added that the purity is unknown.

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

Response: The temperature and dissolved oxygen content were added to the robust summary. A statement was also added that the purity is unknown.

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

Response: The pH information was added, it was also added that reverse osmosis water was used to prepare algal media, the dissolved oxygen not was not reported and it is stated that the purity in unknown

Calcium Formate

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

Response: There was no SAR in the robust summary and a the statement was added "Water parameters were not available"

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

Response: This was added to the robust summary.

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

Response: This was added to the robust summary.

Methyl Formate

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

Response: As the medium was synthetic and prepared according to formula the water hardness is not a reported variable. The other information has not yet become available. It has been requested and will be added to the robust summaries as the Category moves into the ICCA program.

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.

Response: Requested information was available for one of the two studies and was added. The result was changed to > 100 mg/L at neutral pH.

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

Response: Requested information was added to first daphnid study.

Requested information was added to the second and third algal inhibition entries. The original reference for the first entry was reviewed and it was determined that this study was conducted under more strongly buffered conditions, which is consistent with the findings. This was added to the robust summaries.

References

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

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