

June 13, 2001

LuAnn Maloney
FMC Corporation
Agricultural Products Group
1735 Market Street
Philadelphia, PA 19103

Dear Ms. Maloney:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on FMC's submission to the RTK HPV Challenge Program of the robust summaries and test plans for two single chemicals, 3-chloro-2-methylpropene (Methallyl chloride, CAS No. 563473) and 2,3-dihydro-2,2-dimethyl-7-benzofuranol (CAS No. 1563388), posted on EPA's ChemRTK Web site on February 13, 2001. I commend FMC 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 Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

Methallyl chloride comments

As outlined in the Comments, we suggest that special procedures be followed for the planned ecotoxicity testing and that the assumption and data inputs to the fugacity model be included with the report for that endpoint. FMC also needs to supply information missing from certain health robust summaries.

FMC summarized an acute oral toxicity study conducted with a 10% solution of the test material. Aspects of the study are unclear. The Company needs to explain why the diluted substance was tested and how the results can be applied to the undiluted material.

Finally, because 13-week repeated-dose rat and mouse studies are available for methallyl chloride, EPA recommends that FMC consider conducting the planned reproduction/developmental toxicity study according to OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test instead of Guideline 422: Repeated dose/Reproductive/Developmental Toxicity study,.

Because FMC proposes to perform reproduction/developmental toxicity testing, I emphasize that, as pointed out in my letter to FMC dated March 7, 2001, in order to conform to the intent of EPA's October 14, 1999, letter (<http://www.epa.gov/chemrtk/ceoltr2.htm>), animal testing for SIDS endpoints on individual chemicals shall be deferred until November, 2001.

2,3-Dihydro-2,2-dimethyl-7-benzofuranol comments

As explained in the comments, the submitted test data summaries for ecological effects could not be adequately evaluated because many required robust summary data elements are missing; this information needs to be supplied. The Company also needs to better define the chemical identity of test substances.

The proposed acute dermal toxicity test is not necessary because acute dermal toxicity testing is not an element of the U.S. HPV Challenge Program. There also appear to be existing data on repeat dose toxicity and developmental toxicity not identified in the submission that, depending on the adequacy of the studies, might alter the proposed test plan.

FMC proposes to perform an *in vivo* study for chromosomal effects. In order to conform to the intent of EPA's October 14, 1999, letter to sponsors, which encourages the use of *in vitro* genotoxicity tests unless known chemical properties preclude their use, we ask FMC to elaborate why it considers *in vivo* testing necessary in this case. As stated above for methallyl chloride, animal testing for SIDS endpoints for individual chemicals shall be deferred until November, 2001.

As with other submissions where the available data are either inadequate or insufficiently documented, these cases will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that FMC advise the Agency, within 60 days of the posting on the Chemical RTK website, 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 202-260-3470. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment 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 tsc-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

Attachment

cc: W. Sanders
C. Auer
M. E. Weber
A. Abramson

EPA Comments on Chemical RTK HPV Challenge Submission: 2,3-Dihydro-2,2-dimethyl-7-benzofuranol

SUMMARY OF EPA COMMENTS

The sponsor, FMC Corporation, submitted a Test Plan and Robust Summaries to EPA, dated December 28, 2000, for 2,3-Dihydro-2,2-dimethyl-7-benzofuranol (CAS No. 1563-38-8). EPA posted the submission on the ChemRTK HPV Challenge Web site on February 13, 2001. FMC later supplied clarifications to the test plan, which have replaced the original posting.

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

1. Physicochemical and Environmental Fate Data. The sponsor's approach is acceptable for all endpoints except vapor pressure (see Robust Summary Comments below).
2. Health Endpoints: (1) Acute dermal toxicity testing is not an element of the U.S. HPV Challenge Program; (2) the sponsor is encouraged to conduct an *in vitro* chromosomal mutation study instead of an *in vivo* study unless the properties of the chemical indicate otherwise; and (3) there appear to be existing data on repeat dose toxicity and developmental toxicity not identified in the submission that, depending on the adequacy of the studies, might alter the proposed test plan.
3. Ecotoxicity. The submitted test data summaries for fish, daphnia, and green algae could not be adequately evaluated because many required robust summary data elements are missing. The sponsor needs to supply the missing information and better define the chemical identity of test substances (see Robust Summary section).

EPA is requesting that the Sponsor advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE 2,3-DIHYDRO-2,2-DIMETHYL-7-BENZOFURANOL CHALLENGE SUBMISSION

Test Plan

The test plan consists of a table that lists the availability of studies and identified those tests required under the SIDS program.

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

The sponsor's approach is acceptable for these endpoints, except that the data submitted for vapor pressure were not adequate (see comments on Robust Summaries) and measured data need to be supplied.

Fate (photodegradation, stability in water, biodegradation, and transport/distribution).

Adequate data are available for stability in water. The sponsor's plan for addressing the remaining endpoints is acceptable.

When developing the fugacity model, the sponsor needs to provide the assumption and data inputs to the model (see Guidance for Robust Summary preparation).

Furthermore, in order to develop the fugacity model, EPA recommends using the EQC Level III model from the Canadian Environment Modeling Centre at Trent University, which allows full control of data inputs. This model can be found at the following Web address:
<http://www.trentu.ca/academic/aminss/envmodel/>.

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

The sponsor proposes to conduct an acute dermal toxicity study, an *in vivo* genotoxicity study and a combined repeat dose/reproductive/developmental toxicity study.

Acute Toxicity. Acute dermal testing is not an element of the Challenge program. Although the acute inhalation toxicity study is considered inadequate (see below), the existence of an adequate acute oral toxicity study is sufficient for this endpoint for the purposes of the U.S. HPV Challenge Program.

Genotoxicity. EPA encourages conducting an *in vitro* genotoxicity study rather than an *in vivo* study unless the properties of the chemical indicate otherwise. In this case, the study would assess chromosomal genotoxicity because adequate gene mutation data exist.

Repeat Dose Toxicity and Developmental Toxicity. EPA brings to the sponsor's attention the following studies: (1) TSCA Section 8(e) notice of a pilot developmental toxicity study (8EHQ-0299-14384) submitted to EPA in 1999; and (2) a toxicology review dated 1984 submitted to EPA in May of 2001 (8EHQ-0501-14384 Supplement) (unpublished report by Reyna, 1972, as cited in "Toxicological Evaluation of 2,3-Dihydro-2,2-dimethyl-7-benzofuranol ("7-Hydroxy")", unpublished report by Env. Tox. Int'l., Inc., Seattle, dated May 12, 1994) in which a repeat dose toxicity study is summarized.

Ecological Effects (fish, invertebrate and algal toxicity).

The sponsor provided data generated according to EPA FIFRA guidelines on fish, daphnid, and algae. The sponsor needs to better characterize the test substance for each endpoint, such as percent purity, and, if a pesticide formulation, what other substances were included. In addition, required data elements clearly describing how the test was conducted were missing from the robust summaries and need to be provided before data adequacy can be determined.

SPECIFIC COMMENTS ON ROBUST SUMMARIES

Chemistry

Vapor pressure. The submitter provided a value of 0.204 torr at 20 °C (27.2 Pascals at 20 °C), determined by extrapolation from a value at a higher temperature. A measured value for comparison was not located. Therefore, EPA estimated values of 2×10^{-3} torr at 25 °C using EPIWIN v. 3.05, and 3×10^{-2} torr at 25 °C from the submitter's reported boiling point (76 °C at 1 torr) using a vapor-pressure-temperature nomograph.

Because of the lack of agreement among the submitted value and other estimated values, EPA recommends that the submitter provide measured data for this endpoint.

Health Effects

Six robust summaries were reviewed. The following comments pertain to two of the summaries:

Acute oral toxicity. The robust summary should include, if available in the full report, a description of clinical signs or symptoms observed and whether the data indicated any target organ effects.

Acute inhalation toxicity. This summary is considered inadequate for the purposes of the U.S. HPV Challenge Program because of the following: (1) only one concentration was tested; (2) there is no indication whether the tested concentration was the maximum attainable concentration (OECD Test Guideline 403 states the highest concentration to be tested should not exceed 5 mg/L; this test reportedly used 0.03 mg/L).

Ecotoxicity Studies

Robust Summaries are available for acute effects on rainbow trout (96-hour), algae *Selenastrum capricornutum* (120-hour) to include brief reporting of the 72- and 96-hour values, and daphnia (48-hour). All tests were conducted according to FIFRA guidelines: acute fish toxicity according to guideline 72-1(c), acute invertebrate toxicity according to guideline 72-2, and algal toxicity according to FIFRA Subdivision J, 123-2. Therefore, the information missing from the summaries is likely to be in the underlying studies.

The Robust Summaries contained insufficient information to determine data adequacy; insufficiencies are detailed below for each summary. Test substance definition was poor in all cases. Substances were identified only by trade names; percent purity or product formulation (e.g., presence and amount of inert ingredients or vehicle) could not be determined. The sponsor needs to supply the indicated information before data adequacy can be determined.

Fish. Required data missing from the robust summary are dissolved oxygen, pH, age of fish, percent purity, test substance description, stock solution content (vehicle, solvent, inert ingredient), TOC, and TSS.

Invertebrates. Required data missing from the robust summary are dissolved oxygen, pH, TOC, percent purity, TSS, stock solution content (vehicle, solvent, inert ingredient), and test substance description.

Algae. Required data missing from the robust summary are dissolved oxygen, TSS, EDTA, salinity, stock solution preparations (vehicle, inert ingredient, solvent), percent below the growth curve, test substance description, percent purity, and TOC were not reported in the robust summary.

Followup Activity

EPA is requesting that the Sponsor advise the Agency within 60 days of any modifications to its submission.