57

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

DEC 9 1988

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Pyrethrin Data Call-In. Product Chemistry. McLaughlin Gormley King Co.
MRID #s 408363-01, -02, -03. DEB # 4525.

FROM: Michael T. Flood, Ph.D., Chemist
Special Registration Section I
Dietary Exposure Branch
Health Effects Division (TS-769C)

THROUGH: Andrew R. Rathman, Section Head
Special Registration Section I
Dietary Exposure Branch
Health Effects Division (TS-769C)

TO: G. Werdig/F.Rubis, PM Team 50
Special Review and Reregistration Division (TS-767C)

Background

In response to data call-in's for product and residue chemistry, McLaughlin Gormley King Co. (MGK) has submitted product chemistry data.

Originally, we had required analyses of five batches of the 50% refined concentrate from each refinery to set certified limits. The compounds to be quantitated were the active ingredients (6 pyrethrins) and the intentional inerts (R. Loranger, memo of 12/9/85). As a followup to our review of 3/4/87 and as a result of discussions with the registrants, we modified our request for separate analyses for each active ingredient to allow for the use of an AOAC method for pyrethrins in pesticides (R. Loranger, memo of 8/15/88). At that time, we were under the impression that the AOAC method to be used was that given in AOAC Official Methods of Analysis (1984), 6.194-6.198. This AOAC method is a chromatographic method in which a mixture of pyrethrin standards is used. However, based on the present submission, the registrants were referring to an earlier AOAC method, 6.190-6.193. That method, a titration method, does not quantify each of the active ingredients, but determines total pyrethrin I's (three esters of chrysanthemic acid) and total pyrethrin II's (three esters of pyrethric acid). [The method is discussed more fully in Confidential Appendix 2.]

Concerning the analysis of the remainder of the ingredients,

the "nonintentional inerts", we required thorough analyses of one batch of the 50% material from each refinery. Total accountability was to be ≥98% (memo of 12/9/85, memo of telecon, 12/11/85).

We have already reviewed preliminary product chemistry data submitted by the Pyrethrum Task Force (R. Loranger, memo of 3/4/87). For that submission two pyrethrin batches were analyzed by Shrader Analytical and Consulting Laboratories, Inc.: a Kenya pyrethrum batch blend, FEK-39; and the toxicology study blend from each participating refinery, FEK-99. FEK-39 was also analyzed by the Wellcome Foundation. In our review we requested the following additional data:

1. GC/MS response factors. The analytical results were obtained directly from total ion current chromatograms. No standards were used.

2. Percent BHT. BHT and terpene results were combined in the submission.

3. Data confirming that the early eluting alkanes or other hydrocarbons belonged to the solvent.

4. Characterization of fatty acids.

Because MGK's product PYROCIDE 175 contains 20 wt % pyrethrins, the registrant requested that, instead of five batch analyses on the 50% material, analyses be carried out on three normal production batches and three batches of the 50±5% material used as MGK's component of the toxicology blend. The refining process for the three toxicology batches is the same as that for the normal batches, which contain more solvent. We agreed to MGK's request (R. Loranger, memo of 2/27/87).

Conclusions and Recommendations

1. MGK has adequately identified the various components in RPC except for hydrocarbons (solvent) and fatty acids (see Conclusions 2c and 2d).. Product Chemistry Guidelines Series 61 requirements have been satisfied by this and earlier MGK submissions.

2. The registrant has not fully complied with the requirements for analyses of five batches for active ingredients and for a complete analysis of one batch for all ingredients (§62-1):

   a. Quantitative analyses have been carried out for the pyrethrin active ingredients and BHT. However, the analyses, using the AOAC method, for pyrethrins did not quantitate the six esters but rather the two

classes, py I's and py II's. Rather than reanalyze the samples using individual standards, we suggest that the registrant determine relative peak areas from suitable chromatograms (i.e., those in which all six peaks are resolved). Relative concentrations can then be combined with the AOAC results to give good estimates of the concentrations of the individual pyrethrins.

MGK should attempt to explain the discrepancies between the AOAC analyses and submitted HPLC analyses (see discussion in Confidential Appendix 2). The latter yielded generally lower values.

b. "Nonintentional inerts" were not adequately quantitated -- concentrations were calculated from HPLC peak areas only. The registrant should analyze refined pyrethrin concentrate using response factors determined from standards. In those cases where standards are unavailable, or a large group of similar compounds produce one broad peak, approximate response factors can be determined from structurally similar compounds. In that case a rationale should be provided.

c. Data to confirm that early eluting alkanes/hydrocarbons belong to the solvent have not been submitted as requested. The registrant should demonstrate that the observed peaks belong to solvent by injection of solvent into the chromatograph.

d. Triglyceride analyses (also nonintentional inerts) are not yet acceptable:

(1.) Triglyceride residues reported by MGK differ from those reported by Nutrition International Inc. for the same batches [redacted] versus [redacted] MGK should explain the discrepancy.

(2.) The reported fatty acids constituted only 92% of the total. If the "92%" means 92% of the total fatty acids, then such characterization would be acceptable. If non-triglycerides/fatty acids are present, their percentage should be noted by difference. Because the analytical method for separation of triglycerides -- precipitation of pyrethrins -- probably does not completely separate triglycerides from other inerts, other compounds are expected. Presumably, these other inerts would be separately quantitated in other parts of the total analysis.

Neither the analytical method nor any raw data were submitted for the fatty acid analyses. This information should be reported in future submissions.

3. The registrant has not fully complied with the requirement for certification of ingredient limits (§62-2):

   a. The AOAC analyses, while accurate, do not quantitate individual pyrethrins. Individual pyrethrins may be quantitated in the manner outlined in Conclusion 2a.

   b. Based on the AOAC analyses, the certified limit for pyrethrin II's should be changed from "11.00 to 25.00" to "11.00 to 27.00".

   c. Analyses to set certified limits on BHT and the proposed limits are acceptable.

   d. The registrant should add certified limits for nonintentional inerts, such as: "Plant coextractives (triglycerides, terpenes, high molecular weight hydrocarbons or alcohols)".

4. Product chemistry data requested in Guidelines §§63-2 through 63.21 have been submitted and are acceptable.

Detailed Considerations

The present submission consists of three studies:

1. "Product Identity and Composition of Refined Pyrethrin Concentrate", V.J. Meinen, 9/15/88. (MRID No. 408363-01)

2. "Analysis and Certification of Product Ingredients for Refined Pyrethrin Concentrate", V.J. Meinen, 9/15/88. (MRID No. 408363-02)

3. "Physical and Chemical Properties of Refined Pyrethrin Concentrate", V.J. Meinen, 9/2/88. (MRID No. 408363-03)

Product Identity and Composition of Refined Pyrethrin Concentrate

Two samples were analyzed by GLC-MS, reflecting, respectively, four sources and the major source. Samples of each material were sent to Shrader Labs for GLC-MS analyses. [The same laboratory had analyzed the Pyrethrin Task Force blend (FEK-99)]. Results and a discussion are given in Confidential Appendix 1.

The samples were also sent to Nutritional International Incorporated (NCI) for triglyceride characterization and quantitation. Results also appear in Confidential Appendix 1.

The same volume also includes a review of refined pyrethrin extract components (discussed in our 12/9/85 memo) and a specification sheet for "Odorless Mineral Spirits", the solvent.

Analysis and Certification of Product Ingredients for Refined Pyrethrin Concentrate

Five batches of Refined Pyrethrin Concentrate (RPC) were analyzed for pyrethrins by both the AOAC method and an HPLC method and for BHT (2,6-di-tert-butyl-para-cresol) by an HPLC method. It was our understanding that two sets of three batches each would be analyzed (see above); however, analyses on five batches of RPC are acceptable.

Analyses are discussed in Confidential Appendix 2.

Physical and Chemical Properties of RPC

The data submitted under this report satisfy Product Chemistry Guidelines §63-2 through §63-21. Physical methods are discussed where appropriate. To summarize, RPC is a dark amber viscous liquid at room temperature. It is completely soluble in many nonpolar organic solvents. Solubility in ethylene glycol is less than 0.1%; solubility in water is less than 10 ppm. After room temperature storage for 15 months, the concentration of the active ingredients actually increased slightly (up 2.8% for py I's; up 2.4% for py II's). This small increase could be due to a systematic error in the analyses, but it is more likely the result of gradual loss of petroleum distillate used in the manufacture. Sunlight rapidly degrades RPC when it is exposed as a thin film. Otherwise, the material is stable at temperatures up to 80°C.

cc (without confidential appendixes): Circu.
cc (with confidential appendixes): RF, PMSD/ISB(Eldredge), Mike Flood, Pyrethrin S.F.

RDI:SectionHead:ARRathman:12/7/88:ActingDeputyChief:RALoranger:12/7/88.
TS-769C:DEB:557-4362:MTF:mtf:CM#2:Room810:12/7/88.

CONFIDENTIAL

Pages 6-13 - *Manufacturing process information may be entitled to confidential treatment*