

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date

. December 10, 1993

From

Fred A. Hines, D.V.M., Staff Toxicologic Pathologist Pathology Branch (HFS-716)

Subject

FLAVR SAVR Tomato (Pathology Review PR-152; Food Master File FMF 000526): Pathology Branch's Remarks to Calgene Inc.'s Response to FDA Letter of June 29, 1993

To

Linda Kahl, Ph.D. Biotechnology Policy Branch (HFS-206)

Through: Chief, Pathology Branch, HFS-716 (MW. Mr. Leader, Diagnostic Pathology Section, HFS-716

REFERENCES:

Letter dated June 29, 1993 from Linda Kahl, Ph.D., Biotechnology Policy Branch, HFS-206, Division of Product Policy, Center for Food Safety and Applied Nutrition addressed to Mr. Donald Emlay, Director, Regulatory Affairs, Calgene, Inc; subject: Docket No. 91A-0330, FMF #526. Two attachments:

a) Attachment 1 (a review and summary of IRDC Studies 677-002, 677-004, and 677-005 by FDA toxicologists and pathologists).

- b) Attachment 2 (nineteen comments from FDA reviewers; the first fourteen comments specifically compiled by the Pathology Branch of FDA/CFSAN).
- 2) Letter dated September 2, 1993 from Keith Redenbaugh, Ph.D., Manager, Regulatory Affairs, Calgene Fresh addressed to Dr. Laura Tarantino, Biotechnology Policy Branch, HFS-206, Center for Food Safety and Applied Nutrition, Food and Drug Administration; subject: Docket No. 91A-0330; Response to FDA Letter of 6/29/93. Three attachments:

a) "Response to FDA Letter of June 29, 1993 - Overview and Detailed Answers, Volume 1 of 3, September 2, 1993."

b) "Response to FDA Letter of June 29, 1993 - Pathology Consensus Report, Volume 2 of 3, September 2, 1993."

c) "Response to FDA Letter of June 29, 1993 - References, Volume 3 of 3, September 2, 1993."

The attached report evaluates the response by Calgene, Inc. (abovecited reference 2) to the comments raised specifically by the Pathology Branch (above-cited reference 1).

SUMMARY:

Although Calgene's response clarified some procedural details in the feeding studies conducted for them by the International Research and Development Corporation (IRDC) with the transgenic tomato, Calgene failed to adequately address in their response some of the major issues raised by the Pathology Branch (PB) relating to the conduct and interpretation of the studies. Some of those major issues included:

- 1) the disparity among the three studies in the incidence of rats with gastric erosions reported by TRDC. The pattern of the incidence of rats with gastric erosions among the three studies is, in our opinion, unusual considering that the factors which usually tend to cause variation among studies were minimized, i.e., the studies were done at the same laboratory, employing the same procedures and personnel. Yet in the first study, no rats with gastric erosions were reported by IRDC; in the second study, gastric erosions were reported only in the female rats fed transgenic tomato; and in the third study, gastric erosions were reported in essentially all groups of animals. Calgene's response provided no explanation for this disparity among the studies.
- 2) a comment, made in the IRDC report of the second study, of "a possible treatment-related mild, focal necrosis [gastric erosions] of the glandular stomach in 4 of 20 animals". The explanation by Calgene that the comment was made in isolation and out-of-context seems implausible since the results of the third study were already available to IRDC before the second study report was completed. It is unclear why the comment was made by IRDC at the time when the results of the follow-up study were available to them.
- 3) a seeming discrepancy in the diagnosis of gastritis among the three studies. Although the incidence of rats with gastritis was not considered by the PB to be a test-material related lesion, the PB raised this issue since there was a disparity in the reported incidence of rats with gastritis among the three studies. Not a single rat with gastritis was reported in the first study but a random distribution of rats with gastritis was reported in the second and third studies (up to an incidence of 45%). It is unclear why Calgene did not attempt to re-assess gastritis in response to our comment, i.e., confirm whether the lesion was overlooked or not present in the stomach sections from the first study.

In the absence of adequate explanations by Calgene, the issues raised by the Pathology Branch, including those listed above, remain and leave doubts as to the validity of any scientific conclusion(s) which may be drawn from the studies' findings.

Fred A. Hines, D.V.M.

ATTACHMENT: PR-152 Pathology Report (FMF-000526): Remarks to Calgene's Response to the FDA Letter of June 29, 1993.

cc: HFS-003 (Oliver) HFS-013 (Maryanski) HFS-016 (Lorentzen) HFS-200 (Rulis) HFS-206 (Tarantino) HFS-225 (Shibko) HFS-226 (Biddle) HFS-227 (Edwards, Jonnson) HFS-247 (Olempska-Beer) HFS-500 (Scheuplein) HFS-700 (Falci) HFS-705 (Springer) HFS-706 (Ruggles) HFS-715 (Corneliussen) HFS-716 (Moch, Dua, Hines, Central File)

HFS-716: FAHines:fah:Doc_401:Disk:172A-6CCB:Initial Draft:11/05/93; Redrafted:11/17/93,11/19/93,11/22/93;11/30/93;12/8/93;FT:12/10/93; 202-205-4123