

Memorandum

Date . June 16, 1993

From Fred A. Hines, D.V.M., Staff Pathologist Pathology Branch, HFS-716

Subject FLAVR SAVR Tomato (Pathology Review PR-152; FDA Number FMF-000526):
Pathology Branch's Evaluation of Rats with Stomach Lesions From
Three Four-Week Oral (Gavage) Toxicity Studies (IRDC Study Nos.
677-002, 677-004, and 677-005) and an Expert Panel's Report.

Linda Kahl Consumer Safety Officer Office of Premarket Approval Division of Product Policy Biotechnology Policy Branch (HFS-206)

Through: Chief, Pathology Branch, HFS-716

BACKGROUND INFORMATION:

The FLAVR SAVR tomato was developed through transgenic techniques. A "wholesomeness" study was undertaken by the sponsor (Calgene, Inc.) to ensure that this food possesses no unexpected toxicity. Three sequential 28-day studies were done at the International Research Development Corporation (IRDC), Mattawan, Michigan, in which groups of male and female rats were fed via gavage either a transgenic tomato, a non-transgenic tomato, or deionized water. In the first study, no gross or microscopic lesions were reported in the stomach of any rat. The second study included two lines of transgenic tomato that were distinct from the transgenic line that was the subject of the first study. In the second study, gross lesions were described in the stomachs of four out of twenty female rats fed one of the two lines of transgenic tomato. The lesions were reported histologically as gastric necrosis and later identified as gastric erosions, i.e., the two terms are synonymous under the conditions of this study since the "necrotic" or dead cells occurred in the superficial mucosa of the stomach. lesion, gastric erosion, was not reported by IRDC in any other animals from the second study. The IRDC report stated: "[t]he CR3-623 transgenic tomato dosed to females did suggest a possible treatment-related mild, focal necrosis of the glandular stomach in 4 of 20 animals". The third study was described as a "repeat" study and included the single transgenic line that had four of twenty female rats with stomach erosions in the second study, as well as the control line from which that transgenic line originated. In the third study, the tomatoes used were frozen or frozen-lyophilized (concentrated) in contrast to the first two studies in which fresh tomatoes were used. Gross and microscopic

gastric erosions were seen in male and female control rats dosed with deionized water, in male and female rats fed the non-transgenic tomato, and in female rats fed the transgenic tomato. The Sponsor's IRDC report concluded that the "[h]istomorphology and the pattern of incidence of the necrosis and erosion suggested that these lesions were incidental in nature and unrelated to the respective test articles".

An "Expert Panel" was organized by Environ at the request of Calgene, Inc. and according to the Expert Panel Report, they were assembled to review the "data relating to the demonstration of the safety of the FLAVR SAVR tomato". According to the Expert Panel Report, an independent pathology review of the stomach slides "to evaluate the incidence and significance of the observed stomach lesions" was conducted by Pathco, Inc., and a report (the PWG report) was provided to the "Expert Panel".

The Pathology Branch (PB), Division of General Science Support, Office of Scientific Analysis and Support, Center for Food Safety and Applied Nutrition, Food and Drug Administration was requested to review the stomach data and to indicate whether the PB had any concerns about the stomach lesions.

CONCLUSION:

There is considerable disparity in the reported findings of gastric erosions or necrosis lesions from the three studies reported by Calgene, Inc. This disparity has not been adequately addressed or explained by the sponsor or the laboratory (IRDC) where the study was conducted. The Expert Panel report and the PWG report also did not address or explain this disparity. The criteria for qualifying a lesion as incidental were not provided in the Sponsor's report.

Without explanation or other information which was lacking in the submitted data as mentioned in the attached pathology report (the Pathology Branch's Pathology Review PR-152), the Pathology Branch is unable to determine whether or not the gastric erosions or necrosis in these studies are "incidental" findings as reported by the Sponsor.

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Fred A. Hines, D.V.M.

ATTACHMENT: PR-152 Pathology Report (FMF-000526)

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CC:

HFS-003 (Oliver)

HFS-013 (Maryanski)

HFS-016 (Lorentzen)

HFS-200 (Rulis)

HFS-206 (Tarantino)

HFS-225 (Shibko)

HFS-226 (Johnson)

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_378:Disk:172A-6CCB:Initial Draft:4/19/93:

Revised:5/03/93:6/03/93:6/16/93:FT:6/16/93:202-205-4123
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