DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date MAY 17 1994

From Consumer Safety Officer, Biotechnology Policy Branch, HFS-206

Subject Summary of consultation with Calgene, Inc., concerning FLAVR SAVR™ tomatoes

To Acting Director, Office of Premarket Approval, HFS-200

In a letter dated August 12, 1991, Calgene, Inc., requested an advisory opinion under 21 CFR 10.85 concerning whether FLAVR SAVR™ tomatoes are food and, therefore, subject to the same regulation as other tomato varieties. In a notice published in the *Federal Register* of May 29, 1992 (57 FR 22984), FDA issued a policy statement (the 1992 policy statement) clarifying the agency's interpretation of the Federal Food, Drug, and Cosmetic Act (the act) with respect to foods derived from new plant varieties. In light of the publication of the 1992 policy statement, we believe that an opinion concerning the status of a particular product such as FLAVR SAVR™ tomatoes is best addressed through a consultation with the agency consistent with the principles outlined in that statement. Therefore, we recommend that the Office of Premarket Approval (OPA) respond to Calgene's request as a consultation in accordance with the 1992 policy statement rather than as an advisory opinion under 21 CFR 10.85. This memorandum summarizes that consultation.

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INTRODUCTION

Background Information

In the development of FLAVR SAVR™ tomatoes, Calgene used recombinant DNA techniques to introduce an antisense polygalacturonase (PG) gene. The sense PG gene, normally present in tomatoes, encodes the enzyme PG, which is associated with the breakdown of pectin (a constituent of the cell wall in tomato fruit). The principle underlying the FLAVR SAVR™ tomato is that the antisense PG gene suppresses the production of the PG enzyme. This suppression of the PG enzyme results in ripe fruit that remains firm for an extended period and allows fresh market tomatoes to remain on the vine longer for enhanced flavor. Thus, FLAVR SAVR™ tomatoes have been modified to contain lower levels of a naturally occurring enzyme, when compared to other varieties of tomatoes.

In addition to the antisense PG gene, FLAVR SAVR™ tomatoes contain the kanamycin resistance gene (the kan^r gene) that encodes the enzyme aminoglycoside-3'-phosphotransferase II (APH(3')II). Calgene used APH(3')II as a selectable marker to identify plant cells carrying the antisense PG gene. In a notice published in the *Federal Register* of May 1, 1991 (56 FR 20004; Docket No. 90A-0416), FDA announced that Calgene had requested an advisory opinion concerning whether the kan^r gene may be used in the production of genetically engineered tomato, cotton, and rapeseed (i.e., oilseed rape) plants intended for human food and animal feed use. Subsequently, Calgene requested that FDA convert the advisory opinion request to a food additive petition. FDA thereafter announced, in the *Federal Register* of July 16, 1993 (58 FR 38429) that Calgene had submitted, and FDA had filed, a food additive petition (FAP 3A4364) proposing that the food additive regulations be amended to provide for the safe use of APH(3')II as a processing aid in the development of new varieties of tomato, oilseed rape, and cotton. FDA's evaluation of the safety of APH(3')II is reflected in the agency's decision on FAP 3A4364.

Following CFSAN's evaluation of the data and information submitted by Calgene, and other relevant material, including public comments on Calgene's advisory opinion request, FDA convened a public meeting[1] of the agency's Food Advisory Committee to undertake a scientific discussion of FDA's approach for evaluating the safety of whole foods derived from a new plant variety developed using recombinant DNA techniques. Calgene's FLAVR SAVR™ tomato served as an example of the agency's approach, and was the focus of the committee's discussion.

The membership of the standing committee was supplemented with temporary members and consultants to the committee representing scientific disciplines appropriate to the evaluation of foods derived from new plant varieties developed using recombinant DNA techniques. At that meeting, committee members expressed their view that the relevant

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[1] The meeting was held on April 6-8, 1994, in Herndon, VA.

scientific issues concerning FLAVR SAVR™ tomatoes had been addressed and that there was no reason, from a safety standpoint, to preclude Calgene from marketing FLAVR SAVR™ tomatoes. A transcript of that meeting (Ref. 1), and a copy of the background information provided to the committee (Ref. 2), is publicly available at Dockets Management Branch.

Approach to the Evaluation of FLAVR SAVR™ Tomatoes

As discussed in the 1992 policy statement, the safety assessment of food derived from a new plant variety may include: (1) an evaluation of the purpose or intended technical effect of the genetic modification; (2) an evaluation of the source, identity, function, and stability of introduced genetic material; (3) analytical studies to determine whether the genetic modification had any effects on the composition of the food (such as the levels of important nutrients and naturally occurring toxicants); and (4) an evaluation of the safety of new or modified substances (i.e., proteins, carbohydrates, and fats or oils) in the food. Also as discussed in that policy statement, animal feeding studies or other toxicological tests are warranted only when the characteristics of the plant or the nature of the modification raise safety concerns that cannot be resolved by analytical methods.[2]

FLAVR SAVR™ tomatoes have been modified by a reduction in the levels of a naturally occurring enzyme that degrades pectin and the addition of a new protein, APH(3')II, encoded by the kan^r gene. Based on these modifications, we believe that a safety evaluation of FLAVR SAVR™ tomatoes is properly addressed by an analysis of the following information: (1) the source, identity, function, and stability of genetic material introduced into FLAVR SAVR™ tomatoes; (2) analytical studies on the composition of FLAVR SAVR™ tomatoes; and (3) the safety of APH(3')II (the protein product of the kan^r gene).

Overall, we evaluated the data and information provided by Calgene to determine whether FLAVR SAVR™ tomatoes have been significantly altered, within the meaning of 21 CFR 170.30(f)(2), when compared to varieties of tomatoes with a history of safe use. In other words, we determined whether FLAVR SAVR™ tomatoes are as safe as other currently consumed tomatoes.

In addition to food safety issues, we evaluated environmental considerations associated with FLAVR SAVR™ tomatoes.

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[2] The agency did not recommend in the 1992 policy statement that toxicological testing be conducted routinely in part because it is well recognized that conventional feeding studies on whole foods have limited sensitivity and are subject to confounding factors unrelated to test article toxicity, such as nutritional or physiologic effects.

Overview of this Memorandum

Calgene initially provided data and information on eight transgenic tomato lines. Calgene subsequently submitted additional information on two other transgenic tomato lines (designated CR3-613 and CR3-623) that the firm currently considers to be more likely candidates for direct commercialization or for further development into commercial varieties (Refs. 3 and 4). This memorandum summarizes the data and information supplied by Calgene concerning FLAVR SAVR™ tomato lines CR3-613 and CR3-623, the conclusions reached by Calgene, and the comments of agency scientists as to whether FLAVR SAVR™ tomatoes have been significantly altered, within the meaning of 21 CFR 170.30(f)(2), when compared to varieties of tomatoes with a history of safe use.

Because neither the characteristics of tomatoes nor the nature of the modification raise safety questions that cannot be resolved by analytical methods, we have determined that animal feeding studies are not necessary to evaluate the safety of FLAVR SAVR™ tomatoes. However, because Calgene submitted to FDA data from animal gavage studies, this memorandum also discusses those studies.

In addition, this memorandum discusses environmental considerations associated with FLAVR SAVR™ tomatoes and requirements for labeling FLAVR SAVR™ tomatoes. It also discusses the public comments on Calgene's advisory opinion request, as well as comments contained in a citizen petition (Docket No. 92P-0222/CP1) filed in accordance with 21 CFR 10.30.

FOOD SAFETY ASSESSMENT CONDUCTED BY CALGENE

Summary of Data Submitted by Calgene

Calgene provided the following data and information in support of the firm's safety assessment of FLAVR SAVR™ tomatoes: (1) Background information on tomatoes, including the level of nutrients and the level of the naturally occurring glycoalkaloid toxicant, tomatine; (2) data and information describing the intended technical effect of the antisense PG gene; (3) background information on the gene transfer system used to deliver and incorporate the kan^r and antisense PG genes into tomatoes; (4) information describing the sources of genetic material transferred to tomatoes; (5) data and information concerning the molecular stability of the inserted kan^r and antisense PG genes; (6) data comparing the levels of nutrients in FLAVR SAVR™ tomatoes to the levels in the parental variety; (7) data comparing the levels of toxicants in FLAVR SAVR™ tomatoes to the levels in other commercial varieties; (8) data and information concerning APH(3')II encoded by the kan^r gene; and (9) results of three 28-day animal studies in which rats were gavaged with water, nontransgenic tomatoes, or FLAVR

SAVR™ tomatoes. This information, including the literature references supplied by Calgene, is on public display at Dockets Management Branch.[3]

Background Information on Tomatoes

Calgene submitted several literature references providing background information on tomatoes (Ref. 5). Most commonly cultivated tomato varieties belong to the species *Lycopersicon esculentum. Lycopersicon* species are members of the *Solanaceae* (nightshade) family. Tomatoes have a long history of safe use as food. Tomatoes are consumed raw or processed and contribute significant amounts of vitamin A and vitamin C to the U.S. diet. Commercial tomatoes generally are picked from the vine at a mature green stage (i.e., before they are fully ripe) and subsequently gassed with exogenous ethylene (a substance that also occurs naturally in tomatoes and promotes ripening) to induce a red color.

A naturally occurring glycoalkaloid toxicant, tomatine, occurs at low levels in domesticated tomato varieties; non-domesticated species generally contain higher concentrations of tomatine than tomatoes that are cultivated for food use. Tomatine is distributed throughout the tomato plant but is most concentrated in leaves and in opening flowers. The tomatine concentration in tomato fruit depends on the degree of ripeness of the fruit, and declines as green fruit ripens to yield red fruit.

The Intended Effect of the Antisense PG gene

FLAVR SAVR™ tomatoes have been modified to contain an antisense PG gene. The sense PG gene, normally present in tomatoes, encodes the enzyme PG, which is

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[3] Calgene submitted information to two Docket Numbers: Docket No. 90A-0416 (request for an advisory opinion on the use of the kan^r gene) and Docket No. 91A-0330 (request for an advisory opinion on FLAVR SAVR™ tomatoes). We have added to Docket No. 91A-0330 literature references that are cited in this document but that originally were submitted by Calgene to Docket No. 90A-0416.

Calgene's original submission to Docket No. 91A-0330 has been on public display at Dockets Management Branch since August 12, 1991. Since that time, Calgene has sent an additional copy of data submitted for FDA evaluation directly to Dockets Management Branch for public display. An informational copy of Calgene's Petition to the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) requesting a determination of the regulatory status of FLAVR SAVR™ tomatoes under 7 CFR 340 has been publicly available at USDA APHIS since July, 1992 and was added to Docket No. 91A-0330 in December, 1993. A copy of Calgene's letter dated September 17, 1992, requesting that FDA review Calgene's voluntary labeling for FLAVR SAVR™ tomatoes, was added to Docket No. 91A-0330 in February, 1993.

associated with the breakdown of pectin (a constituent of the cell wall in tomato fruit). The principle underlying the FLAVR SAVR™ tomato is that the antisense PG gene suppresses the production of the PG enzyme, thereby preventing pectin degradation, which delays the softening of ripe tomato fruits and allows fresh market tomatoes to remain on the vine longer for enhanced flavor.

This intended effect does not raise safety questions, because pectin is widely consumed as a component of many fruits and vegetables and also is a generally recognized as safe (GRAS) substance that is directly added to many food products as a gelling agent (e.g., in marmalade and jelly) or as a stabilizer (e.g., in beverages and ice cream). In addition, as discussed below, the prevention of pectin degradation in FLAVR SAVR™ tomatoes occurs without adversely affecting other characteristics of tomato fruits, such as nutrient and toxicant levels.

Background Information on the Gene Transfer System

Calgene transformed the parental CR3 tomato line using the *Agrobacterium tumefaciens* gene transfer system. Calgene submitted several literature references providing background information on the use of *A. tumefaciens* as a gene transfer vehicle (Ref. 6). The relevant literature is summarized below.

The ability of *A. tumefaciens* to effect the transfer of DNA into plant cells is related to the mechanism by which *A. tumefaciens* causes crown gall tumors (crown galls) in plants. This mechanism is associated with the presence in *A. tumefaciens* of a large plasmid called the Ti (Tumor-inducing) plasmid. Crown gall cells, in contrast to normal plant cells, contain a specific portion of the Ti-plasmid (known as the T-DNA) integrated into the plant genome. The T-DNA contains at least two classes of genes: (1) oncogenes, which are responsible for tumor formation; and (2) genes which are responsible for synthesis of opines in the transformed cells of the crown gall.[4] The Ti plasmid also contains *vir* (virulence) genes, located outside the T-DNA region, which are necessary for both excision of the T-DNA from the Ti plasmid and integration of the T-DNA into the plant genome. Virulence genes do not normally integrate into the plant genome.

Typical procedures for using *Agrobacterium* as a DNA transfer vehicle involve "disarming"[5] the *Agrobacterium* by removing the T-DNA region (and thus the

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[4] Opines are substances that are excreted by tumor cells and serve as an energy source for the infecting *Agrobacterium*.

[5] Such *Agrobacterium* strains are called "disarmed" because they do not cause crown galls.

oncogenes and opine synthesis genes) from the Ti plasmid and subsequently introducing a separate plasmid (called a binary plasmid) that contains a synthetic T-DNA region. During construction of the binary plasmid, the oncogenes and opine synthesis genes are removed from the T-DNA region and replaced with cloning sites into which the gene(s) of interest may be inserted. A binary plasmid is usually designed to be able to replicate in *Agrobacterium* as well as an intermediate host such as *Escherichia coli*. Growing the plasmid in the intermediate host provides plasmid DNA in sufficient quantity to characterize the T-DNA region prior to transfer of the binary plasmid to the disarmed *Agrobacterium* strain that will effect the transfer of the T-DNA to the plant genome.

Sources of DNA Introduced into FLAVR SAVR™ Tomatoes

Calgene created a disarmed *A. tumefaciens* strain containing a binary plasmid with the kan^r and antisense PG genes, accompanied by appropriate regulatory sequences, inserted into the T-DNA region. Calgene transformed CR3 tomato cells using this disarmed *A. tumefaciens* strain and regenerated the transformed tomato cells into mature plants that became the first generation of tomato lines CR3-613 and CR3-623.

Calgene provided information on the source and nucleotide sequence of genetic material present in the T-DNA region that was introduced into FLAVR SAVR™ tomato lines CR3-613 and CR3-623. The genetic material present in the T-DNA region was derived from *A. tumefaciens*, *E. coli*, Cauliflower Mosaic Virus, and tomato. Calgene described the full length kan^r and antisense PG genes, as well as incomplete genes present in the T-DNA region. Calgene concluded that the potential for the expression of the incomplete genes introduced into FLAVR SAVR™ tomatoes is very low.

Calgene also designed an experiment (using the Southern blot technique) intended to demonstrate that the genome of CR3-613 FLAVR SAVR™ tomatoes did not incorporate sequences from the binary plasmid other than those located within the T-DNA region, and concluded that only sequences located within the T-DNA of the binary plasmid had been transferred to tomato line CR3-613. Calgene did not provide similar experimental evidence for CR3-623 FLAVR SAVR™ tomatoes. The firm did state that they had implemented a procedure to screen newly transformed tomato lines, as part of an overall quality assurance program, for the presence of DNA located outside the T-DNA region. Calgene further stated that they would not commercialize FLAVR SAVR™ tomato lines containing DNA from outside the T-DNA region unless they first evaluated the safety of the transferred sequences (Ref. 3).

CFSAN scientists commented on the information provided by Calgene, and the conclusions reached by Calgene, concerning the sources of genetic information in FLAVR SAVR™ tomatoes, as follows: The information supplied by Calgene satisfactorily characterizes the genetic composition of the T-DNA region introduced into FLAVR SAVR™ tomatoes. The T-DNA region does not appear to contain full length

genes that would encode any protein known to be harmful. The use of adequately controlled Southern blots is acceptable as a screening procedure to detect DNA sequences derived from the sequences of a binary plasmid located outside the T-DNA.

Genetic Stability

Calgene provided data on the genetic stability of the transferred DNA in successive generations of CR3-613 FLAVR SAVR™ tomatoes. Calgene analyzed the ability of the CR3-613 line to maintain a specific DNA fragment consisting of a border between the inserted T-DNA region and the tomato DNA, and concluded that the inserted DNA containing the kan^r and antisense PG genes remained stably incorporated in the tomato genome over the course of five generations. Calgene did not submit similar data for CR3-623 FLAVR SAVR™ tomatoes.

CFSAN scientists commented on the information provided by Calgene, and the conclusions reached by Calgene, concerning the genetic stability of FLAVR SAVR™ tomato line CR3-613, as follows: The information supplied by Calgene establishes that the inserted T-DNA is stably integrated into FLAVR SAVR™ tomato line CR3-613 and that the structure of the inserted T-DNA in FLAVR SAVR™ tomato line CR3-613 remains unchanged over five generations. As a practical matter, stable integration of a trait in a commercial plant variety is inherent in the development of the plant and any instability would likely be discovered in quality control tests routinely conducted by plant breeders when maintaining production varieties.

Nutrients in FLAVR SAVR™ Tomatoes

Calgene compared the nutritional profile of FLAVR SAVR™ tomato lines CR3-613 and CR3-623 to the nutritional profile of the parental (CR3) variety over a period of time corresponding to the expected shelf life of vine-ripened fresh market tomatoes (i.e., tomatoes picked pink) and gassed green tomatoes (i.e., tomatoes picked at a mature green stage and gassed with ethylene). Mature green and pink fruits from both the FLAVR SAVR™ and parental lines were harvested on the same day, and the green fruits were gassed with ethylene. Representative fruits were analyzed periodically for vitamin A and vitamin C levels during storage under conditions expected for commercial tomatoes. The last analysis was performed at the end of the shelf life (i.e., after 25 days for tomatoes picked mature green and after 18 days for tomatoes picked pink). Calgene reported that, during the course of their evaluation, mean values obtained for levels of vitamin A and vitamin C in fruits obtained from both the FLAVR SAVR™ and parental lines were all within the range reported in the literature. Calgene concluded that no significant differences exist between the FLAVR SAVR™ tomato lines and the control parental tomato line with respect to levels of vitamin A and vitamin C.

CFSAN scientists commented on the information provided by Calgene, and the conclusions reached by Calgene, concerning levels of vitamin A and vitamin C in FLAVR SAVR™ tomatoes, as follows: The levels of both nutrients varied among FLAVR SAVR™ fruits as well as among control fruits. Such variability could reflect differences in field conditions, weather, post-harvest treatment, as well as other factors. Considering this overall variability, agency scientists noted no significant differences in nutrient levels between FLAVR SAVR™ tomatoes and control tomatoes, and considered that all levels reported for vitamin A and vitamin C were within the range regarded as normal (as reflected in literature data).[6]

Glycoalkaloid Toxicants in FLAVR SAVR™ Tomatoes

Calgene compared the tomatine levels in mature green and red ripe FLAVR SAVR™ tomato lines CR3-613 and CR3-623 to the tomatine levels in mature green and red ripe commercial tomato varieties. Calgene reported that tomatine levels in green FLAVR SAVR™ tomatoes were comparable to tomatine levels in one commercial tomato variety, but somewhat higher than tomatine levels in a second commercial tomato variety. Calgene detected tomatine (at a limit of detection of 2.5 ppm) in only one out of 38 red ripe FLAVR SAVR™ fruits and four out of 60 red ripe commercial fruits. Calgene concluded that, as expected, tomatine levels decreased during tomato ripening in both FLAVR SAVR™ and commercial tomato lines and that tomatine levels in red ripe fruit (i.e., tomatoes as they will be presented to consumers) of FLAVR SAVR™ tomato lines are comparable to tomatine levels in red ripe fruit of commercial tomato varieties.

Calgene used a high performance liquid chromatography (HPLC) method to measure tomatine levels. Calgene analyzed the unidentified peaks having elution times within the range expected for glycoalkaloids by comparing their elution times and ultraviolet spectra to those of major glycoalkaloids that occur in potatoes. Based on these analyses, Calgene determined that the unidentified peaks do not represent glycoalkaloids and concluded that no significant differences in the content of glycoalkaloids were observed between FLAVR SAVR™ and commercial tomato varieties.

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[6] Calgene provided data on nutrients other than vitamin A and vitamin C, and CFSAN scientists commented on such additional data. However, this memorandum focuses on vitamin A and vitamin C because tomatoes contribute significant amounts of these vitamins to the U.S. diet. In their discussions, the Food Advisory Committee (Ref. 1) noted that some substances that occur naturally in tomatoes and currently are uncharacterized may be nutritionally important. We note that, as knowledge concerning the identity and level of important nutrients in foods such as tomatoes changes, we would expect developers to conduct appropriate testing accordingly.

CFSAN scientists commented on the information provided by Calgene, and the conclusions reached by Calgene, concerning levels of tomatine and other glycoalkaloids in FLAVR SAVR™ tomatoes, as follows: The information supplied by Calgene supports Calgene's observation that the tomatine levels in vine-ripened FLAVR SAVR™ tomatoes are comparable to the tomatine levels in commercial tomato varieties. Calgene's data also provide evidence that neither FLAVR SAVR™ tomatoes nor commercial control tomato varieties contain other glycoalkaloids at levels measurable with the HPLC method used.

New Proteins Introduced into FLAVR SAVR™ Tomatoes

As noted above, in developing FLAVR SAVR™ tomatoes, Calgene used APH(3')II as a selectable marker to identify plant cells carrying the antisense PG gene. Calgene provided data and information addressing the safety of APH(3')II, including the direct effects of ingestion as well as effects associated with the biological activity of APH(3')II (i.e., the effect of the enzyme on the therapeutic efficacy of orally administered antibiotics). FDA has evaluated the safety of APH(3')II in the context of a food additive petition (FAP 3A4364) and has concluded that APH(3')II is safe for use as a processing aid in the development of, among other plants, tomatoes.

Animal Gavage Studies

Introduction

When Calgene approached FDA in 1991, while the agency was developing the 1992 policy statement, the firm indicated that they wished to provide additional assurance that all possible tests to establish the safety of this first example of a food derived from a new plant variety developed using recombinant DNA techniques had been performed. One question raised was whether toxicological studies could help to determine whether unexpected toxicants might be present in FLAVR SAVR™ tomatoes. Although there are no well established toxicological approaches to testing the safety of whole foods, Calgene accepted an agency suggestion (Refs. 7 and 8) that the firm conduct a short-term feeding study in rodents. The firm then designed and conducted three rat gavage studies.

Results

Calgene submitted data from three short-term (28-day) gavage studies, conducted at the International Research and Development Corporation (IRDC), in which groups of male and female rats were given (by gavage) deionized water, control (nontransgenic) tomatoes, or FLAVR SAVR™ tomatoes. IRDC identified no biologically significant changes in body weight, organ weight, food consumption, hematologic parameters or clinical chemistry findings in any of the three studies. In addition, in the first study, IRDC identified no adverse findings that could be related to consumption of FLAVR SAVR™ tomatoes following complete gross and microscopic examination of a comprehensive selection of tissues. In the second and third studies, however, IRDC

noted gastric erosions in some animals. These findings on the gastric erosions are discussed below.

Gastric Erosions

In the first study, groups of male and female rats were given by gavage either (1) deionized water; (2) homogenized FLAVR SAVR™ tomatoes obtained from a noncommercial tomato line; or (3) homogenized nontransgenic tomatoes. IRDC reported no gastric erosions in rats from any group. (See Table 1.)

In the second study, groups of male and female rats were given by gavage either (1) deionized water; (2) homogenized nontransgenic CR3 tomatoes; (3) homogenized FLAVR SAVR™ tomatoes obtained from the CR3-613 tomato line; or (4) homogenized FLAVR SAVR™ tomatoes obtained from the CR3-623 tomato line. In this second study, IRDC reported gastric erosions in four of twenty female rats given CR3-623 FLAVR SAVR™ tomatoes, but not in rats in any other group. (See Table 1.)

In the third study (which was designed in an attempt to clarify the results of the second study), groups of male and female rats were given by gavage either (1) deionized water; (2) homogenized nontransgenic CR3 tomatoes; (3) lyophilized nontransgenic CR3 tomatoes;[7] (4) homogenized CR3-623 FLAVR SAVR™ tomatoes; (5) lyophilized CR3-623 FLAVR SAVR™ tomatoes grown in one geographical location; or (6) lyophilized CR3-623 FLAVR SAVR™ tomatoes grown in a second geographical location (females only). In this third study, IRDC reported gastric erosions in eight of eleven groups. (See Table 1.)

At the request of Calgene, PATHCO, Inc., assembled a panel of pathologists (the Pathology Working Group or PWG), who conducted a review of coded microscopic slides containing stomach sections from all three studies to evaluate the incidence and significance of the observed gastric erosions. (See Table 1.) Also at the request of Calgene, ENVIRON Corporation prepared a summary of Calgene's overall safety assessment of FLAVR SAVR™ tomatoes and assembled an expert panel to review that summary. The PWG concluded, and the expert panel concurred, that the gastric erosions observed were incidental and not test article related. Calgene submitted to CFSAN the original data from the IRDC studies, the PWG report on the three gavage studies, and the conclusions of the expert panel.

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[7] The amount of homogenized tomatoes administered to the rats in each study was equivalent to a human consumption of approximately 10 large or 40 small (e.g., plum) tomatoes per day. The use of tomatoes that were lyophilized and reconstituted to 50% of the original volume doubled the dose of tomatoes (i.e., approximately 20 large or 80 small tomatoes) compared to the dose that could be achieved using homogenized tomatoes.

TABLE 1
Incidence of Rats with Gastric Erosions

Treatment Group	Sex	Incidence of Rats with Gastric Erosions[8]					
		Study 1		Study 2		Study 3	
		IRDC[9]	PWG[10]	IRDC	PWG	IRDC	PWG
Water	M	0/20	0/20	0/20	0/20	3/20	4/20
	F	0/20	0/20	0/20	0/20	1/20	1/20
Nontransgenic (Vickie Male) control tomatoes (fresh)	M	0/20	0/20	-	-	-	-
	F	0/20	0/20	-	-	-	-
FLAVR SAVR™ tomato line 501-1001-15 (fresh)	M	0/20	1/20	-	-	-	-
	F	0/20	0/20	-	-	-	-
Nontransgenic CR3 control tomatoes (frozen) (Dixon)[11]	M	-	-	0/19	0/19	3/20	3/20
	F	-	-	0/20	0/20	2/20	2/20
Nontransgenic CR3 control tomatoes (lyophilized) (Indio)	M	-	-	-	-	1/20	1/20
	F	-	-	-	-	0/19	0/20
FLAVR SAVR™ tomato line CR3-613 (frozen)	M	-	-	0/20	1/20	-	-
	F	-	-	0/20	1/20	-	-
FLAVR SAVR™ tomato line CR3-623 (frozen) (Dixon)	M	-	-	0/20	1/20	0/20	0/20
	F	-	-	4/20	7/20	3/20	1/20
FLAVR SAVR™ tomato line CR3-623 (lyophilized)	M[12]	-	-	-	-	0/20	0/20
	F[13]	-	-	-	-	1/20	0/20
	F[14]	-	-	-	-	2/15	2/15

[8] The symbol "-" indicates that the treatment group was not included in that study.

[9] As reported by IRDC.

[10] As reported by PWG following review of coded microscopic slides.

[11] In Study 3, Calgene reported the geographic source (Dixon or Indio) of tomatoes for each group.

[12] Geographic source: Dixon.

[13] Geographic source: Dixon.

[14] Geographic source: Indio.

Calgene subsequently submitted additional data and information on the gastric erosions, including a Pathology Consensus Report (prepared by the pathologists from IRDC and PWG), historical control data, and selected photomicrographs of the gastric erosions from Calgene's gavage studies. The Pathology Consensus Report described the gastric erosions as being minimal to mild in severity; stated that the morphology and severity of gastric erosions were similar in rats that received transgenic tomatoes, non-transgenic tomatoes, or deionized water; and pointed out that no dose-response relationship was observed when the dose of tomatoes was doubled. The report also noted that gastric erosions seen in these studies "... are not unique lesions since they can also be caused by physiologic factors such as stress or fasting as well as by a wide variety of agents including drugs, chemicals, and natural toxins such as tomatine." In the judgment of PWG and IRDC pathologists, the lesions were of short duration and would likely be completely resolved in a short time. Calgene's Pathology Consensus Report stated that "[a]ll of the pathologists involved in the review of the studies on the transgenic tomatoes concluded that there were no effects observed in the glandular stomach which were related to the administration of transgenic tomatoes to Sprague-Dawley rats by gavage."

Conclusions

Given the nature of the modification to FLAVR SAVR™ tomatoes (i.e., the suppression of the production of the naturally occurring PG enzyme and the addition of APH(3')II encoded by the kan^r gene), CFSAN believes, as noted above, that a safety evaluation of FLAVR SAVR™ tomatoes is properly addressed by an analysis of the following information: (1) the source, identity, function, and stability of genetic material introduced into FLAVR SAVR™ tomatoes; (2) analytical studies on the composition of FLAVR SAVR™ tomatoes; and (3) the safety of APH(3')II encoded by the kan^r gene. As discussed above, Calgene has provided such information, which has served as the basis of the firm's evaluation. In light of this information, CFSAN has determined that data from animal gavage studies are not necessary to an evaluation of whether FLAVR SAVR™ tomatoes are significantly altered, when compared to other tomatoes with a history of safe food use.

However, Calgene did conduct animal gavage studies and submit them to the agency for evaluation. CFSAN scientists did comment on the information provided by Calgene, and the conclusions reached by Calgene, concerning these studies, as follows: The three studies consistently demonstrated no biologically significant changes in body weight, organ weight, food consumption, hematologic parameters and clinical chemistry findings. There was disparity among the three studies regarding the incidence of rats with gastric erosions. Data and information supplied by Calgene fail to clarify or explain the factors responsible for this disparity. Based on the information Calgene has provided, no definitive conclusions can be drawn regarding the etiology(ies) of the gastric erosions. Regardless of the etiology(ies), however, the gastric erosions as described by Calgene are no more severe in transgenic tomatoes than in nontransgenic tomatoes.

STATUS OF FLAVR SAVR™ TOMATOES

In sum:

1. The intended effect of the antisense polygalacturonase RNA in FLAVR SAVR™ tomatoes does not raise safety questions.

2. The T-DNA transferred to FLAVR SAVR™ tomatoes does not appear to contain full length genes that would encode any protein known to be harmful.

3. The information supplied by Calgene establishes that the inserted T-DNA is stably integrated into FLAVR SAVR™ tomato line CR3-613 and that the structure of the inserted T-DNA in FLAVR SAVR™ tomato line CR3-613 remains unchanged over five generations.

4. The levels of vitamin A and vitamin C in FLAVR SAVR™ tomato lines CR3-613 and CR3-623 are comparable to the levels of these same nutrients in control (parental) tomatoes. All levels reported for these nutrients were within the range considered normal, as reflected in literature data.

5. Tomatine levels in vine-ripened FLAVR SAVR™ tomato lines CR3-613 and CR3-623 are comparable to tomatine levels in commercial tomato varieties. Calgene's data provide evidence that neither FLAVR SAVR™ tomatoes nor commercial control tomato varieties contain other glycoalkaloids at levels measurable with an HPLC method.

6. The safety of a new protein in FLAVR SAVR™ tomatoes, APH(3')II, is the subject of FAP 3A4364. In that rulemaking, a fair evaluation of the data available to FDA establishes that APH(3')II is safe for use as a processing aid in the development of, among other plants, new varieties of tomatoes.

7. Additional information submitted by Calgene (i.e., the data from the 28-day rat gavage studies) are not necessary to our determination of whether FLAVR SAVR™ tomatoes are as safe as other currently consumed tomatoes. Nevertheless, the three studies consistently demonstrated no biologically significant changes in body weight, organ weight, food consumption, hematologic parameters and clinical chemistry findings. There was disparity among the three studies regarding the incidence of rats with gastric erosions. Based on the information Calgene has provided, no definitive conclusions can be drawn regarding the etiology(ies) of the gastric erosions. Regardless of the etiology(ies), however, the gastric erosions as described by Calgene are no more severe in transgenic tomatoes than in nontransgenic tomatoes.

Based on the information Calgene submitted concerning FLAVR SAVR™ tomatoes, we have determined that this new variety, the FLAVR SAVR™ tomato, has not been

significantly altered within the meaning of 21 CFR 170.30(f)(2), when compared to varieties of tomatoes with a history of safe use. In other words, the FLAVR SAVR™ tomato is as safe as other commonly consumed tomatoes.

ENVIRONMENTAL CONSIDERATIONS

As set forth in the 1992 policy statement (57 FR 22984 at 23005), a consultation, such as the consultation between Calgene and FDA on FLAVR SAVR™ tomatoes, is not an agency action under the National Environmental Policy Act (NEPA). Therefore, neither an environmental assessment (21 CFR 25.22) nor a claim for a categorical exclusion (21 CFR 25.23 and 21 CFR 25.24) is required.[15]

Calgene petitioned the U.S. Department of Agriculture Animal and Plant Health Inspection Service (APHIS) and requested a determination of the regulatory status of FLAVR SAVR™ tomatoes under the Plant Pest Act. APHIS determined that FLAVR SAVR™ tomatoes: (1) exhibit no plant pathogenic properties; (2) are no more likely to become a weed than non-engineered parental varieties; (3) are unlikely to increase the weediness potential for any other cultivated plant or native wild species with which the organism can interbreed; (4) do not cause damage to processed agricultural commodities; and (5) are unlikely to harm other organisms that are beneficial to agriculture. Because FLAVR SAVR™ tomatoes do not present a plant pest risk and are not otherwise deleterious to the environment, APHIS determined that FLAVR SAVR™ tomatoes, previously field tested under permit, would no longer be considered regulated articles (57 FR 47608; October 19, 1992).

However, Calgene submitted to FDA a copy of the firm's petition to APHIS. CFSAN scientists reviewed the information provided by Calgene and concur with APHIS' conclusions regarding the environmental safety of FLAVR SAVR™ tomatoes.

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[15] The approval of a food additive petition, or the affirmation of a food ingredient as generally recognized as safe, unlike a consultation with a food producer on the status of a food product or food safety issues, is an agency action that requires environmental consideration under NEPA. In the notice announcing Calgene's request for an advisory opinion on the status of FLAVR SAVR™ tomatoes, FDA summarized Calgene's arguments in favor of the firm's claim that FLAVR SAVR™ tomatoes are food that is subject to a categorical exclusion (57 FR 22772 at 22773). At that time, FDA stated that the decision as to whether Calgene must file an environmental assessment might depend upon the regulatory status of FLAVR SAVR™ tomatoes and, thus, the agency deferred a statement of its position until the agency responded to Calgene's request. Because, as a result of the consultation between Calgene and FDA, the agency is not requesting that Calgene file a food additive petition or GRAS affirmation petition for FLAVR SAVR™ tomatoes, there is no further need to consider whether FLAVR SAVR™ tomatoes would warrant a categorical exclusion.

LABELING

Statutory and Regulatory Requirements for Labeling

Section 403 of the act governs the labeling of food. Under section 403(a)(1), a food is misbranded if its labeling is false or misleading. Under section 201(n) of the act, labeling is misleading if it fails to reveal all facts that are "material in light of * * * representations [made or suggested in the labeling] or material with respect to consequences which may result from the use of the article to which the labeling * * * relates under the conditions of use prescribed in the labeling * * * or under such conditions of use as are customary or usual."

Section 403(i) of the act and regulations promulgated thereunder (21 CFR 101.3) require that a food product be described by its common or usual name or, in the absence thereof, an appropriately descriptive term. Section 403(i) of the act also requires that, in the case of foods fabricated from two or more ingredients, a food product bear on the label the common or usual name of each ingredient.

Labeling Foods Derived from New Plant Varieties

The 1992 policy statement described situations in which a developer of a new plant variety should consult FDA to determine whether special labeling would be required for the food. Examples potentially relevant to FLAVR SAVR™ tomatoes include (1) the alteration of levels of important nutrients to levels not within the range ordinarily seen in the host species; and (2) the existence of a safety or usage concern, such as the introduction into the food of a protein derived from a commonly allergenic food if there is insufficient information to demonstrate that the allergenic determinant has not been transferred.

In the 1992 policy statement, FDA also stated that the agency does not believe that the method of development of a new plant variety (including the use of new techniques such as recombinant DNA) is normally material information within the meaning of section 201(n) and would not usually be required to be disclosed in labeling. In light of comments received to the 1992 policy statement, FDA published a notice (the 1993 labeling notice) requesting data and information on several issues relating to the labeling of genetically engineered foods, including whether all genetically engineered foods should be labeled to reveal that fact to consumers (58 FR 25837; April 28, 1993). We are in the process of evaluating the comments received in response to that notice. To date, we have encountered no factual information in the comments that would provide the basis to alter FDA's current interpretation of the act, under which special labeling for the class of genetically engineered foods is not required.

Requirements for Labeling FLAVR SAVR™ Tomatoes

We have reviewed the information submitted by Calgene concerning FLAVR SAVR™ tomatoes in light of (1) the statutory provisions for labeling and existing agency regulations and policy implementing those statutory provisions and (2) the opinions of the agency scientists who evaluated the information submitted by Calgene. We believe that the correct common or usual name for the FLAVR SAVR™ tomato is "tomato", because the FLAVR SAVR™ tomato has not been significantly altered when compared to the range of commercial varieties referred to by "tomato." We also find no safety or usage concern to which consumers of FLAVR SAVR™ tomatoes must be alerted by special labeling. (The labeling issues relating to the presence of APH(3')II in foods, such as FLAVR SAVR™ tomatoes, are discussed in the agency's evaluation of FAP 3A4364.)

EVALUATION OF COMMENTS

Overview

FDA received 20 comments to the notice announcing Calgene's request for an advisory opinion on the status of FLAVR SAVR™ tomatoes. Comments were received from manufacturers, trade organizations, universities, consumer organizations, individual consumers and one state government. In addition, a citizen petition relating to FLAVR SAVR™ tomatoes was filed in accordance with 21 CFR 10.30. We address below those issues raised in the citizen petition relevant to FLAVR SAVR™ tomatoes, and have prepared a separate reply that responds to the actions requested in the citizen petition.

All of the comments from manufacturers, trade organizations, universities, the state government, and one comment from an individual consumer expressed support for the marketing of FLAVR SAVR™ tomatoes. Several of these comments stated that Calgene's FLAVR SAVR™ tomato is identical to other tomatoes, has been extensively evaluated and field tested, and poses no food or environmental safety problems. Several comments stated that Calgene's FLAVR SAVR™ tomato would serve to introduce the public to the value of genetically engineered foods and instill public confidence in FDA's science-based safety assessment. Other comments stated that FLAVR SAVR™ tomatoes could answer consumer demands for tomatoes with more flavor than tomatoes that are currently marketed. Two comments specifically responded to and supported Calgene's claim that FLAVR SAVR™ tomatoes are food subject to a categorical exclusion from NEPA. We see no need to further discuss these comments supporting the marketing of FLAVR SAVR™ tomatoes.

Comments from the Environmental Defense Fund, the Foundation on Economic Trends, and three individual consumers, as well as comments contained in a citizen petition filed by the Foundation on Economic Trends, opposed the marketing of FLAVR SAVR™ tomatoes. These comments raised a variety of issues, which we discuss in detail below.

Regulatory Issues Raised in the Comments

Premarket notification

The citizen petition and one comment requested that FDA require that producers of genetically engineered foods analyze the composition of these foods and notify FDA of the results of these analyses at least 90 days before the foods are introduced or delivered for introduction into interstate commerce. To the extent that these comments suggest that FDA require mandatory premarket notification for foods other than FLAVR SAVR™ tomatoes, the comments do not require a response in the context of FDA's consultation concerning FLAVR SAVR™ tomatoes. Further, as discussed in detail above, Calgene has submitted to FDA analytical data on the composition of FLAVR SAVR™ tomatoes and thus has effectively given FDA premarket notification more than 90 days in advance of their intent to commercialize FLAVR SAVR™ tomatoes. Accordingly, we believe that the comments regarding premarket notification require no further response.

Premarket approval

One comment asserted that FDA should not approve Calgene's tomato, but should let consumer acceptance serve as the approval. Calgene's consultation with FDA will not result in an approval per se of FLAVR SAVR™ tomatoes. Rather, as a result of the consultation, we have determined that FLAVR SAVR™ tomatoes have not been significantly altered within the meaning of 170.30(f)(2), when compared to varieties of tomatoes with a history of safe use. Thus, consumer acceptance will still play a role in the marketing of FLAVR SAVR™ tomatoes.

FDA regulations concerning advisory opinions

One comment provided three arguments in support of its contention that FDA should deny Calgene's request for an advisory opinion because that request violated the letter and spirit of FDA regulations governing advisory opinions (21 CFR 10.85). These regulations give the Commissioner of Food and Drugs the discretion to deny a request for an advisory opinion if "[t]he request covers a particular product * * * and does not raise a policy issue of broad applicability" (21 CFR 10.85(a)(2)(iv)) or if "[t]he request contains incomplete information on which to base an informed advisory opinion" (21 CFR 10.85(a)(2)(i)). First, the comment stated that Calgene's request covers a particular product. Second, the comment asserted that Calgene's request does not raise any issues of broad applicability that were not raised independently in the 1992 policy statement, and that any policy issues not adequately addressed in the 1992 policy statement should properly be addressed through the comments to that statement. Third, the comment declared that Calgene's request contained incomplete information because the safety of the kan^r gene for use as a selectable marker in genetically engineered whole foods was still under review.

Because we have recommended that FDA not provide an advisory opinion under 21 CFR 10.85, we believe that this comment requires no further response. That is, we agree that an advisory opinion under 21 CFR 10.85 concerning the status of a specific food product

derived from a new plant variety is no longer appropriate in light of the publication of the 1992 policy statement. However, because Calgene submitted its request before FDA issued the 1992 policy statement, we do not agree that Calgene's request is inconsistent with 21 CFR 10.85.[16]

The status of new substances introduced into FLAVR SAVR™ tomatoes

Comments asserting that the kan^r gene and its expression product (i.e., APH(3')II) are food additives subject to premarket approval are addressed by the agency's determination in FAP 3A4364 and do not require a response in this memorandum. (In fact, such comments are essentially moot in that Calgene filed, and the agency has evaluated, a food additive petition for APH(3')II.)

One comment maintained that Calgene deliberately added the antisense PG RNA to achieve specific technical effects in the tomato and that therefore the antisense PG RNA is a food additive unless it is GRAS. The comment argued that there may not be an adequate basis to conclude that the antisense PG RNA is GRAS if FDA does not find that sufficient scientific studies have been published demonstrating the safety of the antisense PG RNA under the intended conditions of use. The comment argued that, although Calgene submitted to FDA a large number of published studies concerning

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[16] Our reasons for believing that Calgene's request for an advisory opinion on the status of FLAVR SAVR™ tomatoes is consistent with 21 CFR 10.85 are as follows. First, these regulations do not require that a request be denied if the request covers a particular product. We believe that, at the time Calgene filed its request, an advisory opinion under 21 CFR 10.85 was an appropriate mechanism to obtain an agency opinion on the status of a whole food such as FLAVR SAVR™ tomatoes because, in the absence of an announced FDA policy on the status of foods derived from new plant varieties, FLAVR SAVR™ tomatoes raised policy issues of broad applicability.

Second, we disagree that Calgene's request for an advisory opinion violated 21 CFR 10.85(a)(2)(i) because the safety of the kan^r gene for use as a selectable marker in genetically engineered whole foods was still under review. Prior to the request for an advisory opinion concerning the status of FLAVR SAVR™ tomatoes, Calgene requested an advisory opinion concerning whether the kan^r gene can be used in the production of genetically engineered tomato, cotton, and oilseed rape plants intended for human food and animal feed use. The safety of the kan^r gene for use as a selectable marker in genetically engineered whole foods was therefore already under consideration and we see no reason to believe that the agency would have disregarded Calgene's request for an advisory opinion on the kan^r gene when responding to Calgene's request for an advisory opinion concerning FLAVR SAVR™ tomatoes.

Third, the regulations in 21 CFR 10.85 do not prohibit any interested person from making a request for an advisory opinion, nor do they prohibit FDA from responding to that request if FDA considers a response to be in the public interest. We believe that, because of the issues raised by Calgene's request, it was in the public interest for FDA to consider Calgene's request. The notice announcing Calgene's request provided the public an opportunity to comment on those issues.

tomato biology and genetic engineering techniques, Calgene had not submitted a published scientific study addressing the toxicology and nutritional value of FLAVR SAVR™ tomatoes.

We believe that the issues raised in these comments were addressed in the 1992 policy statement. Specifically, in that statement FDA explained that the agency did not anticipate that transferred genetic material would itself be subject to food additive regulation, because nucleic acids are present in the cells of every plant used for food by humans or animals and do not raise a safety concern as a component of food (57 FR 22984 at 22990). Moreover, we note that nucleic acids are efficiently digested (Ref. 9).

FDA also explained in the 1992 policy statement that the introduction of a gene encoding an antisense RNA would not raise concerns about either the gene or the antisense RNA, and that any safety considerations associated with antisense RNA would focus on the intended effects of the antisense RNA (57 FR 22984 at 23004). As discussed above, this intended effect does not raise safety questions.

Furthermore, we note that published studies ordinarily are required in the context of a GRAS affirmation petition.[17] Here, however, Calgene did not submit a GRAS affirmation petition and, thus, FDA has not been asked to affirm a substance, such as the antisense PG RNA, as GRAS. Therefore, we believe that it is not necessary to require Calgene to submit published studies.

The scope of FDA's response

One comment maintained that FDA should deny ruling on Calgene's request because the scope of any such ruling would be unclear. The comment questioned whether FDA's response would encompass FLAVR SAVR™ tomatoes, all genetically engineered tomatoes, or all genetically engineered foods; whether FDA's response would encompass any other whole foods containing the kan^r gene, or all whole foods containing the kan^r gene; and whether FDA's response would encompass genetically engineered foods containing multiple copies of the kan^r gene.

We note that our evaluation, conducted in the context of a consultation with Calgene, is specific to FLAVR SAVR™ tomatoes and does not address any other variety of genetically engineered tomato or any other genetically engineered whole food. The comments concerning the scope of FDA's decision with respect to the kan^r gene need not be addressed in this memorandum because the scope of FDA's decision concerning the kan^r gene is discussed in the agency's decision on FAP 3A4364.

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[17] We are not aware of any published studies demonstrating the safety of any specific RNA that is present in the cells of any food crop, nor would we expect such publication because, as discussed above, nucleic acids are present in the cells of every plant used for food, are efficiently digested, and do not themselves raise a safety concern as a component of food.

Labeling

Several comments requested that genetically engineered foods such as FLAVR SAVR™ tomatoes be labeled to reveal that fact to consumers. We have discussed above the reasons why FLAVR SAVR™ tomatoes are not subject to any special labeling. Moreover, we note that Calgene has announced an intention to provide voluntarily to consumers labeling that explains that FLAVR SAVR™ tomatoes were developed using genetic engineering techniques (Ref. 10).

Other comments requested that APH(3')II be labeled as an ingredient of FLAVR SAVR™ tomatoes and of any food containing FLAVR SAVR™ tomatoes. As discussed in the agency's decision concerning FAP 3A4364, FDA's authority over food labeling is based on section 403 of the act (21 U.S.C. 343). Section 403(i) of the act requires that, in the case of foods fabricated from two or more ingredients, a food product bear on the label the common or usual name of each ingredient, unless compliance with the requirement for labeling is impracticable or results in deception or unfair competition. FDA considers an "ingredient" to be a substance used to fabricate (i.e., manufacture or produce) a food. FDA does not consider those substances that are inherent components of a food to be ingredients that must be disclosed on the food's label.

A genetic substance introduced into a plant by breeding becomes an inherent part of the plant as well as of all foods derived from the plant. Consistent with FDA's general approach on ingredient labeling, the agency has not treated as an ingredient a new constituent of a plant introduced by breeding, regardless of the method used to develop the variety. The comments provide no basis for FDA to deviate from its current practice in the case of APH(3')II.[18] Accordingly, as discussed in the agency's decision on FAP 3A4364, FDA has determined that neither the kan^r gene nor APH(3')II is an ingredient that, under section 403(i) of the act, must be individually identified in labels of foods containing them.

The Nutritional Value of FLAVR SAVR™ Tomatoes

One comment argued that Calgene's analysis of the nutritional composition of FLAVR SAVR™ tomatoes was inadequate for two reasons. First, the comment asserted that Calgene did not state how long after harvest the tomato analyses were performed. The comment argued that Calgene should compare the nutritional value of fresh market FLAVR SAVR™ tomatoes to the nutritional value of nontransformed fresh market tomatoes after a period of time that corresponds to their respective shelf lives, because

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[18] Furthermore, APH(3')II satisfies the definition of "processing aid" in 21 CFR 101.100(a)(3)(ii)(c), and will be regulated as such following the agency's decision on FAP 3A4364. As the comment acknowledges, FDA's labeling regulations exempt processing aids like APH(3')II from the labeling requirements of section 403(i)(2) of the act. Thus, even if APH(3')II were properly considered an ingredient, its presence in a food would not be required to be disclosed in the food's labeling.

Calgene's tomatoes are engineered to have a longer shelf life and some nutrients may degrade over time. In addition, the comment argued that Calgene should obtain nutritional data appropriate to processing tomatoes (i.e., soon after harvest). Second, the comment asserted that Calgene did not use formal statistical hypothesis testing when designing the firm's experiments comparing nutritional data for FLAVR SAVR™ tomatoes and parental varieties, and noted that Calgene did not have even close to a 50 percent chance of detecting a 20 percent difference in nutritional value between FLAVR SAVR™ tomatoes and the parental variety. The comment cited a 1974 presentation by an FDA official at an annual meeting of a trade organization in which the official indicated that the agency would consider a 20% difference in nutritional content to be a significant change in the nutritional value of food derived from a crop plant (Ref. 11).

Calgene originally provided limited nutrient composition data in support of their safety assessment of eight FLAVR SAVR™ tomato lines that the firm is not currently evaluating for direct commercialization. Although the nutrient composition of these FLAVR SAVR™ tomato lines was similar to the nutrient composition of the parental varieties and is within the range of values for tomatoes reported in the literature, most of the nutrient composition data was based on the analysis of single samples (due to a limited amount of available tomato fruits).

However, in a subsequent submission, Calgene included additional data on the two FLAVR SAVR™ tomato lines (CR3-613 and CR3-623) that the firm currently is evaluating for commercialization. As discussed above, Calgene compared the nutrient composition of these two FLAVR SAVR™ tomato lines to the nutrient composition of the parental variety, and conducted the comparative study over a period of time corresponding to the expected shelf life of fresh market tomatoes. We believe that the design of these experiments addresses the specific comments concerning the timing (relative to harvest) of Calgene's analytical measurements, and therefore are relevant to processing as well as fresh market FLAVR SAVR™ tomatoes. Further, we find that these data refute the comment's assertion that FLAVR SAVR™ tomatoes might exhibit a different nutritional profile than tomatoes derived from the parental variety because, as discussed above, the levels of vitamin A and vitamin C in FLAVR SAVR™ tomatoes are comparable to the levels of these same nutrients in control (parental) tomatoes.

With respect to the comment's assertion that an FDA official had previously indicated (nearly 20 years ago) that the agency would consider a 20% difference in nutritional value to be a significant change in the nutritional value of food derived from a crop plant, we note that although this concept was the subject of informal discussion, FDA ultimately did not incorporate a definition of "significant change" into the agency's regulations regarding the GRAS status of substances of natural biological origin (21 CFR 170.30(f)(2)). We also note that the concentration of principal nutrients in foods derived from existing plant varieties frequently varies by more than 20%. Because the agency's regulations establish no limits on the variability in the levels of nutrients, and in light of the known variability in nutrient levels in existing plant varieties, we believe there is no reason to request from Calgene a statistical evaluation to demonstrate compliance with a

20% limit on the difference between the nutrient composition of FLAVR SAVR™ tomatoes and the parental variety.

In summary, we find that Calgene has adequately addressed whether nutrients in FLAVR SAVR™ tomatoes are comparable to nutrients in the parental variety.

The Safety of FLAVR SAVR™ Tomatoes

One comment maintained that the safety assessment of a new plant variety such as FLAVR SAVR™ tomatoes should not be left to the developer. The citizen petition expressed concern that foods such as FLAVR SAVR™ tomatoes will be allowed to enter commerce without premarket safety testing.

As noted in the 1992 policy statement, developers of new foods have an obligation under the act to ensure that the foods they offer to consumers are safe and in compliance with all requirements of the act (57 FR 22984 at 22985), and ultimately, it is the food producer who is responsible for food safety (57 FR 22984 at 22991). Therefore, if premarket testing is needed to establish the safety of a food, the food producer does have the responsibility to perform the appropriate testing.

Moreover, we note that Calgene requested consultation with FDA concerning their safety assessment. We evaluated the safety assessment conducted by Calgene and reached the conclusion that FLAVR SAVR™ tomatoes have not been significantly altered within the meaning of 21 CFR 170.30(f)(2), when compared to varieties of tomatoes with a history of safe use. Moreover, we believe that the testing conducted by Calgene is consistent with guidance set out in the 1992 policy statement concerning the safety testing of foods derived from new plant varieties.

One comment argued that Calgene's data on levels of the naturally occurring plant toxicant tomatine provided relatively little statistical power. Because tomatine levels decrease as tomatoes ripen, Calgene could not detect tomatine in 97% of the samples of ripe FLAVR SAVR™ tomatoes tested. Moreover, tomatine levels in the 3% of fruits that contained detectable levels were comparable to tomatine levels in samples of ripe commercial tomato varieties. In light of these findings, we believe that a statistical analysis of Calgene's data on tomatine levels is not essential to the safety assessment of FLAVR SAVR™ tomatoes.

Economic Harm Resulting from Decreased Consumption of Tomatoes

The citizen petition maintained that there is a substantial risk of consumer confusion because current FDA regulations would not distinguish tomatoes developed using traditional breeding techniques from novel foods such as FLAVR SAVR™ tomatoes and that consumers therefore may choose to reduce their purchase of tomatoes. The citizen petition argued that farmers who derive a significant part of their income from the production of tomatoes developed using traditional breeding will suffer serious economic

injury if their products are confused with genetically engineered products such as FLAVR SAVR™ tomatoes.

The citizen petition did not provide data or other information to support the assertion that, in the absence of labeling distinguishing genetically engineered tomatoes from tomatoes developed using traditional breeding, consumer confusion will result in reduced purchase of tomatoes and cause farmers to suffer serious economic injury. In addition, as discussed above, we have reviewed the information submitted by Calgene concerning FLAVR SAVR™ tomatoes in light of (1) the statutory provisions for labeling and existing agency regulations and policy implementing those statutory provisions and (2) the opinions of the agency scientists who evaluated the information submitted by Calgene. We have concluded that FLAVR SAVR™ tomatoes do not require special labeling to comply with the act. The authority provided to FDA by the act does not permit FDA to prevent a company from legally marketing a product that is in compliance with the act because of potential economic consequences for competitors.

Moreover, as discussed above, we note that Calgene has announced its intention to provide voluntarily to consumers labeling that explains that FLAVR SAVR™ tomatoes were developed using genetic engineering techniques. Thus, in this particular case, there would appear to be no risk that the alleged economic consequences would occur.

CONCLUSIONS

1. We considered the information provided by Calgene as well as the information provided in the comments and other relevant material. We believe that this information supports a conclusion that FLAVR SAVR™ tomatoes have not been significantly altered within the meaning of 21 CFR 170.30(f)(2), when compared to varieties of tomatoes with a history of safe use. In other words, the FLAVR SAVR™ tomato is as safe as other commonly consumed tomatoes.

2. We recommend that OPA provide Calgene with the opinion, that FLAVR SAVR™ tomatoes have not been significantly altered within the meaning of 21 CFR 170.30(f)(2), when compared to varieties of tomatoes with a history of safe use, by letter from OPA rather than as an advisory opinion under 21 CFR 10.85.

3. We have concluded that the consultation between Calgene and FDA, and any letter or other communication from FDA that may result, is not an agency action under NEPA.

4. We believe that the correct common or usual name for the FLAVR SAVR™ tomato is "tomato", because the FLAVR SAVR™ tomato is not significantly different from the range of commercial varieties referred to by that name. We also have determined that there is no safety or usage concern to which consumers of FLAVR SAVR™ tomatoes must be alerted by special labeling.

5. We believe that the safety assessment conducted by Calgene is consistent with the applicable provisions of the act, as reflected in FDA's guidance to industry, set out in the 1992 policy statement, on scientific considerations for evaluating foods derived from new plant varieties.

Linda S. Kahl

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