Animal and " Plant Health Inspection Service Biotechnology, Biologice, and Environmental Protection

APR 2 1992

Dr. James Maryanski Biotechnology Coordinator Food & Drug Administration 200 C Street, SW. Washington, DC 20201

RE: Comments on FDA draft Statement of Policy on foods derived from new plant varieties, including plants derived by recombinant DNA techniques

Dear Dr. Maryanski:

Thank you for the opportunity to review, informally, the draft policy statement. Since it was provided to me informally and under the condition that I not distribute copies outside my office, please consider my comments as unofficial initial comments of this office only. I did not solicit the comments of the Food Safety and Inspection Service and the other appropriate U.S. Department of Agriculture (USDA) Science and Education Agencies. It is anticipated that my Agency and the other appropriate USDA Agencies will have a chance to comment during the formal interagency comment process.

The focus of the draft policy statement is overall very reasonable and the discussion is very comprehensive. However, in the attempt to be comprehensive, especially in the discussion of possible risks, the tone of the document often appears alarmist by discussing theoretical considerations of risk in the absence of specific product reviews or applications. Without specific applications, the potential or theoretical risks must often be given more weight than they would be given in specific case reviews where such factors can often be shown to be irrelevant or not material to the specific review. Therefore, the intent of our comments and suggestions, consistent with the reasonable focus of the draft, is to place discussion of such potential or theoretical risks in context. In our opinion this context should be one of either known risk or reason to believe a particular risk might be presented.

We understand that our previous comments and our subsequent discussion on the NEPA impacts analysis sections are being addressed and we have not raised concerns about those sections in these comments.

For the most part, the document accomplishes its intended function quite well, and does not propose unjustifiable additional regulatory constraints.



## SPECIFICS COMMENTS:

p 10, § 1, the phrase referring to genetically engineered plants used as food, "but the public must be assured that foods developed by now technologies are safe" seems to set a new more stringent standard for these foods. Perhaps it would reflect the current standard better if it wore stated thus: "but the public must be assured that foods developed by the new techniques satisfy the applicable safety standard" [this is consistent with p 26 of the document].

p 11, I continued from previous page, FDA may wish to solicit comments as to whether to address the list of four issues identified in future FEDERAL REGISTER notices.

p 11, T 1, since as stated in Section IX, EPA's policy is yet to be developed, we question the need for the last sentence of the paragraph. However, if it is retained it would be more accurate if it read, "As discussed in Section IX, EPA is responsible for chemical substances which meet the definition of 'pesticide', including those which are added to plants."

p 12, % 1, the discussion on traditional breeding oversimplifies plant breeding and minimises the considerable variability that can result. It could be improved as follows: Nost traditional breeding involves prossing variaties of the same or very closely related species and screening for progeny with desired characteristics. The crosses may be between agronomically viable varieties or cultivars and involve only a few genetic differences. Alternatively, the crosses may be between a developed cultivar and a wild relative with some desired trait such as disease resistance, but with thousands of unwanted traits. In such cases, the resulting progeny are screened for the desired trait and are crossed back to the agronomically adapted parental line. In most cases where the desired gene came from a wild relative, 8 to 12 generations of backcrossing will occur before the resulting progeny are considered to be of sufficient genetic uniformity to be useful as a connercial line or cultivar. At each generation, the progeny will be evaluated in the field or greenhouse not only for the desired trait, but those with undesirable traits will be 'requed out' or destroyed. Continue with a new paragraph, "Breeders have developed . . . "

p 12, the last ¶ does not convey the concept that there is a continuum from crossing agronomic cultivars, to crossing lines with various adaptation, to crossing agronomic cultivars or lines with wild forms of the species, to crossing to wild forms of closely related species, to "wide crosses" which involves crosses to different species or genera to which there is some genetic incompatibility and for which special intervention techniques must be used. This discussion which is carried over onto the next page, in fact, suggests that "wide crosses" are qualitatively different than traditional breeding and must be treated differently; we do not believe this to be the case.

Met charle

not use In

on language

Com

North

المسائد

19518

p 13, T 1, Add a sentence, "Backgrossing, as described above, includes extensive field testing and observation where pleiotropic or unexpected traits can often be identified and those plants carrying . p 14, 1 ine 12, delete "or". a will other Teclip negative traits are eliminated."

p 15, ¶ 1, the Mt delta-endotoxin should be described as, "proteins toxic to pertain insects."

p 16, the text under "A. Unexpected Effects" has a tone that seems alarmist. We suggest a new introductory sentence: "Of course, as noted above, there is always some possibility for any breading technique to have the potential to create unexpected and undesirable effects by carrying undesirable genes with the genes for the desirable traits or on rare occasions genes exhibiting plaintropic effects." It would set the discussion in context to add at the end: "As discussed in Section IV above, plants that have been bred or otherwise genetically manipulated are usually tested at multiple sites for several years. One purpose of such testing is to assure the agronomic quality of the new line or cultivar by ensuring that any unpredicted effects do not occur when the plants are grown in various conditions."

p 17, in the section "B. Matural Toxicants," a useful point would be made in the first sentence by appending the following phrase at the end of the sentence: "which often serve the plant as natural defense compounds against pests or pathogens."

p 17, % 2 needs some clarifying statements, thus: "Hany of these toxicants are present in today's foods at levels that do not cause acute toxicity. Others, such as in cassava and some legumes, although high enough to cause severe illness or death if the foods are not properly prepared, rarely cause a food safety concern because their toxic nature is understood and/or traditional methods of preparation of these foods are adequate to render them safe enough to eat without harm. FDA is concerned that new plant varieties not have significantly higher levels of known toxicants than the range of known levels of toxidents present in other edible varieties of the same species."

p 18, % 1, this paragraph on "activation of silent metabolic pathwaye" is alarmist and speculative. This paragraph adds nothing to the discussion that has not already been said in a more evenhanded way in pravious sections, being another subset of "unexpected effects." This paragraph would only be relevant if FDA were going to suggest a battery of tests for toxins not known to occur in food plants that would be required before marketing for all varieties. It is our understanding that this clearly is not intended. The approach to this subject taken in the guidance section on p 40-41 is more appropriate.

( 19519

p 19, in the Section "E. Allergenicity" [It is our understanding that this section has been changed, therefore the following comments may be no longer valid; they are offered for consideration if still relevant) it is correctly noted that "All allergens that have been characterised have been found to be glycoproteins," but then inexplicably raises concerns about any protein transferred from an allergenic source, rather than focusing concern on transferred glycoproteins. The level of uncertainty about allergenicity is appropriately captured in the statement on p 20: "FDA is unaware of any practical method to predict or assess the potential for changes in allergenicity profile of foods from new plant varieties, and requests comments on this issue." We suggest that all other text on p 20 in the section on allergenicity be deleted. An Agency cannot complete a pre-market review that would result in a finding of non-allargenicity if it is "unaware of any practical method to predict or assess" an effect. Therefore, we have been able to identify three options for FDA with respect to allergenicity: (1) to require labelling for all glycoproteins transferred to new plant varieties, (2) to require allergenicity testing for new plant varieties with new glycoproteins, or (3) to use the post-market surveillance mechanisms to identify problem foods with respect to allergenicity and deal with them appropriately through labelling or other action. If either of the first two are to be used by FDA they would best be instituted through notice-and-comment rulemaking, rather than through a policy notice. We are concerned that the current text would set up a new da facto regulation. We would also note in a general sense that any trait or factor that cannot be predicted or tested for may not be appropriate for premarket review and may be more appropriate for post-market surveillance.

p 22, § 1, this last paragraph of the section on antibiotic resistance departs from the reasoned tone of what precedes and states as fact points open for debate. First, it is suggested that kanamycin is a "clinically useful antibiotic" rather than noting that "kanamycin is rarely used clinically and only for a narrow range of uses." It is not noted that kanamycin resistance is very common among soil microorganisms and very likely, therefore, to be found on foods such as fresh vegetables. Lastly, we are unaware of any evidence which supports the concern raised that a food containing the kanamycin phosphotransferase II enzyme might reduce the therapeutic efficacy of kanamycin.

p 37, f 1, should read, "For example, if a tomato has had a peanut olycoprotein introduced . . ." However, we again question whether FDA should assert that labelling will be required based on a standard that the producer could not prove non-allergenicity, absent any information that the new glycoprotein is implicated in allergenicity except by association with a source food that is allergenic.

revised

and son

06 19520

. .. .. .. ... .. ...



Dr. James Maryanski

p 53 (Fig. 3), the concerns expressed above with regard to allergenicity apply as well to the chart. We are concerned that the answer to the first question would almost invariably be "yes," to the second then in sequence "no" (since most allergens are not specifically identified), and as FDA has noted there are few appropriate tests, so the result could be a ma facto labelling regime for plant varieties from the new techniques.

comp

p 59, last sentence in text. It is not clear why a property such as sweetness or a particular flavor should be considered to impute any particular potentially dangerous characteristic to an organism. Such a trait would have the sole feature of being objectively recognizable to the consumer. Is there a basis that because a particular protein is sweet (or for that matter, tastes like hamburger) that it should a priori constitute a basis for concern? In our opinion the issue that a trait could be easily recognizable should be addressed separately from the fact that a protein with a certain characteristic could become a macrocomponent of the diet.

My

p 69, we offer the following comments on Section "2. Matabolic considerations": When altering biochemical pathways in organisms known to have significant potential for the production of natural toxicants (e.g., potato, tomato), might it not be prudent as a general, rule to examine the levels of significant toxicants, inasmuch as the metabolic signals affecting the expression of biochemical pathways leading to the production of toxicants are unknown?

N

p Si, we would suggest adding the following underlined words to the last sentences of Section IX. "FDA and EPA are agreed that chamical substances that are "posticides" as defined by FIFFA and are added to plants are subject to EPA's regulatory authority. EPA plans to explain how it intends to exercise oversicht over such "pesticidal substances" in a future FEDERAL RECISTER notice."

sincerely,

Terry L. Hedley, J.D. Director

19521