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The Scientific Advice that FDA Ignored - (A Compilation)

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The United States claims to have the most rigorous regulation for GMOs. But the Bio-Integrity lawsuit against the US Food and Drug Administration (See www.biointegrity.org) uncovered secret memoranda showing how the FDA has ignored all the strongly worded advice given by its own scientists.

New and unique risks from GMOs

- unintended effects due to random insertion of foreign DNA
- rearrangements of foreign DNA
- unexpected activation of metabolic pathways to produce toxins and allergens
- horizontal transfer of antibiotic resistance marker genes

The first GMO to be approved, Calgene's Flavr Savr tomato, failed FDA's toxicological tests, and the question of safety was never resolved by the agency.

The records show that the agency has known all along that chemical analysis is inadequate for proving the safety of GMOs. Furthermore, the potential health hazards posed by the use of antibiotic resistance marker genes was also ignored, despite clear warnings from FDA Public Health Services.

These records make scandalous reading and prove that ISIS and other groups of scientists were not the first to highlight GM food safety issues. US Government needs to resolve these safety issues, raised by its own scientists in the first place, and which remain outstanding to this day.

Scientific Advice given by FDA Scientists 1991-93

October 28 1991 -- Comments made by Dr Edwin J Mathews, FDA Director of Toxicology Review and Evaluation, Dept of Health and Human Services to James Maryanski, Biotechnology Coordinator on the revision of toxicology section of the 'Statement of Policy: Foods Derived from Genetically Modified Plants'.

On the 'Safety of whole food plants transformed by technology methods' he writes;

1. "An analysis of all major toxins that have been identified to occur naturally in the edible part of the plant that has been transformed, or of its close relatives, should be done to show that no change has occurred as compared to the natural parent or relatives."

2. "Results from an appropriately designed 28-day feeding study in swine that show that the edible portion of the transformed plant causes no acute toxicity. End points to be examined include the usual general screen done for 28-day animal studies. These include, but are not limited to effects on 1) weight gain 2) organ function, 3) electrolyte levels, 4) metabolism and 5) gastrointestinal tract. On the 'Analysis of Major Plant Toxins' he writes;

3. "A GE plant may contain an identical profile of expected plant toxicant levels (i.e. expected toxicants) as is normally found in a closely related, natural plant. However, genetically modified plants could also contain unexpected high concentrations of plant toxicants. The presence of high levels of toxicants could be amplified through enhancement of toxicant gene transcription and translation. This might occur as a result of up-stream or down stream promotion of gene activities in the modified plant DNA. In addition, plant toxicant genes, which were normally inactive, could be expressed in the modified plant gene as a result of insertion of the new genetic material (i.e. positional mutagenesis). Thus, the task of analysis of all major toxins in GE plants food include the assessment of both expected toxicants and unexpected toxicants that could occur in the modified plant food. The unexpected toxicant could be closely related chemicals produced by common metabolic pathways in the same plant genus/species; however, unexpected toxicants could also be uniquely different chemicals that are usually expressed in unrelated plants. "

4. "The task of assessing the presence or the absence of expected and unexpected plant toxicants)could be very difficult, because thousands of plant biochemicals have been shown to have toxic effects on animals and microorganisms. While all these plant toxicants could conceivably be harmful to man by direct ingestion of plant food, or indirectly by ingestion of animal by products that had consumed plants containing toxicants, the agency's primary concern is for plant toxicants that could be present in common plants foods."

5. "Analysis of expected and unexpected plant toxicants can be achieved using either chemical/biochemical methods of toxicological bioassays. Chemical/biochemical methods have a high sensitivity for detecting the level of an individual toxicant, but their quantification of toxicant levels require extraction and purification of toxicants

from plant cell homogenates. Unfortunately, purification procedures permit the detection of one toxicant while simultaneously destroying or excluding the detection of additional toxicants. Furthermore current technology has purification procedures for only a fraction of known plant toxicants."

6. "Alternatively, toxicological bioassays could be used to simultaneously detect both expected and unexpected toxicants. Based on our current knowledge)these toxicants should elicit toxic effects in two types of assays).First, a portion of the plant toxicants would)be mutagenic in *Salmonella typhlmurium* reverse mutagenesis assay)Second, rats and swine would be expected to be sensitive to the toxicological effects of most plant glycoside-,alkaloid-,protein and phenolic-toxicants).Furthermore, the 28-day study should be optimised to detect hepatotoxicity, toxicity to certain sensitive organs (i.e. gastrointestinal tract, pancreas, spleen and thyroid), anti-nutritive effects (e.g. growth retardation), and specific clinical chemistry tests (anemia, electrolytes etc). "

November 1st 1991 -- Comments from the Division of Food Chemistry and Technology and Division of Contaminants Chemistry on the points to consider for safety evaluation of GM foods, to James Maryanski, Biotechnology Coordinator.

1. "All the above marker genes produce proteins that are new with respect to plants) They should be considered to be new proteins in the human diet and be subjected to safety evaluation. Because the marker genes are inserted randomly in the plant genome, each insert behaves essentially as a separate gene. As a result, subsequent crosses between two independently obtained transformants may lead to the amplification of a marker gene in the progeny. This possibility should be taken into account in the projections of exposure to any protein, especially however, to proteins produced by the marker genes because they are used repeatedly within the same species."

2. "The insertion of any DNA into the plant genome may result in various phenotypic changes (desirable or undesirable) referred to as pleiotropic effects. Undesirable phenotypes may include, for example, poor growth, reduced levels of nutrients, increased levels of natural toxicants etc. Pleiotropic effects occur in GE plants obtained with Agrobacterium-mediated transformation at frequencies up to 30%).Some undesirable effects such as increased levels of known naturally occurring toxicants, appearance of new, not previously identified toxicants; increased capability for concentrating toxic substances from the environment e.g. pesticides or heavy metals and undesirable alterations in the levels of nutrients may escape breeders attention unless GE plants are evaluated specifically for these changes. Such evaluations should be performed on a case-by-case basis, i.e. every transformant should be evaluated before it enters the marketplace. [A similar approach was recommended by the International Food Biotechnology Council]."

3. "Toxicological evaluation of the edible plant tissue may be more appropriate than using chemical identification and quantitative procedures."

Jan 3 1992 -- Dr Linda Kahl writes to Dr James Maryanski, the FDA Biotechnology Coordinator and comments on the Federal Register document "Statement of Policy: Foods from genetically modified plants".

1. "The current document (particularly the section on scientific issues and the appendix) is very schizophrenic in regard to the objective. The June 1986 Coordinated Framework does not seem to be so concerned with traditional methods and makes no apologies for discussing only biotechnology).It notes that the framework seeks to distinguish those organisms that need review and those that do not)So why can't that current appendix deal only with new biotechnology? Why try to make it appear that we are discussing all modified crops?"

2. "I believe that there are at least two situations, relative to this document, in which it (FDA) is trying to fit a square peg into a round hole. The first square peg in the round hole is that the document is trying to force an ultimate conclusion that there is no difference between foods modified by GE and food modified by traditional breeding practices."

3. "The processes of GE and traditional breeding are different, and according to the technical experts in the agency, they lead to different risks."

4. "The 'Points to consider' for products of GE must be different than the " points to consider" for products of traditional breeding. How can you expect a traditional breeder to have the most basic molecular data (e.g. DNA sequences of the inserted material), when he has no idea of the molecular identity of the genetic material being introduced? Are we to insinuate that practitioners of GE do not need to adhere to the most basic level of good laboratory techniques simple because the traditional breeding community cannot also provide that data?"

5. "The second square peg in a round hole is that the approach, of at least part of the document, to use a scientific analysis of the issues involved to develop the policy statement. In the first place, are we asking the scientific experts to generate the basis for this policy statement in the absence of any data?)It's an exercise in hypothesis forced on individuals whose jobs and training ordinarily deal with facts".

6. "I do not think that the scientific analysis as presented is complete. The scientific issues section of the document talks of the "possibility of unintended, accidental changes in GE plants" but I believe that in most cases the word "risk" is avoided."

7. "Surely the following series of events must all occur in order to present a danger to the public health: (1) The accidental change must activate a pathway for production of a toxin that was unanticipated, or for which there is no suitable analytical method. (2) This unanticipated toxin must be expressed at a high enough level to exert an effect. (3) This toxin must have serious adverse consequences to humans and or animals that consume it. (4) The presence of this dangerous unanticipated toxin in amounts sufficient to cause a public health problem must not manifest itself in any other way, so that the first and only clue will be the "body count" so to speak."

8. "I wonder if part of the problems associated with this approach (using scientific issues to set the stage for the policy statement (are due to the fact that the scope of the technical experts assigned to the project did not include any whose usual job is risk analysis."

9. "Are there any alternatives to toxicology testing that could tip the scales to a level where the modified food can meet a safety standard of reasonable no harm? My impression is that the limitation of the number of insertion sites to one is not sufficient (what does that actually tell you about safety?"

Jan 8th 1992 -- Points made by Dr Mitchell Smith, FDA Department of Health and Human Services to James Maryanski, biotechnology coordinator. Re; Comments of draft Federal Register Notice on Food Biotechnology (Draft 12th Dec 1991).

1. "My general conclusion is that the issue turns the conventional connotation of 'Food Additive' on its head. It also conveys that the public need not know when it is being exposed to 'new food additives', for lack of a better descriptor."

2. "The statement 'organisms modified by modern molecular and cellular methods are governed by the same physical and biological laws as are organisms produced by classical methods' is somewhat erroneous because in the former, natural biological barriers to breeding have been breached."

3. "The statement "to the extent that it is known" begs the question as to what degree of identification and toxicological evaluation is sought or prudent. In this instance ignorance is not bliss."

Jan 31 1992 -- Comments by Dr Samuel I Shibko, Director of Toxicological Review and Evaluation, Dept of Health and Human Services (FDA), to Dr James Maryanski (the biotechnology coordinator, on the Draft document -- Revision of Toxicology Section of the Statement of policy: foods derived from GM plants.

1. "At this time it is unlikely that molecular and compositional analysis can reasonably detect or predict all possible changes in toxicant levels or the development of new toxic metabolites as a result of GM. FDA believes that, until sufficient time and experience with the new techniques of gene transfer have accumulated, the possibility of unexpected, accidental changes in GE plants justifies a limited traditional toxicological study. This study would provide the basis for assuring the absence of any new highly toxic materials that are not present in the parental plant variety, and would establish the wholesomeness of the food for subsequent limited studies in humans. Addition assurance of safety would be provided by *in vitro* genotoxicity and digestion studies with the food or appropriate extracts."

Feb 5th 1992 -- Points made by Dr Gerald B. Guest, Director, Centre of Veterinary Medicine FDA to Jame Maryanski on the regulation of transgenic plants (FDA draft Federal Notice on Food Biotechnology.

1. "It has always been our position that the sponsor needs to generate the appropriate scientific information to demonstrate product safety to humans, animals and the environment .) Generally, I would urge you to eliminate statements that suggest that the lack of information can be used as evidence for no regulatory concern."

2. "We believe that animal feeds derived from GM plants present unique animal and food safety concerns."

3. "Unlike the human diet, a single plant product may constitute a significant portion of the animal diet. For instance, 50-75% of the diet of most domestic animals consists of field corn. Therefore a change in nutrient or toxicant composition that is considered insignificant for human consumption may be a very significant change in the animal diet."

4. "Animals consume plants, plant parts and plant byproducts that are not consumed by humans. For example, animals consume whole cotton seed meal, whereas humans consume only small amount of cottonseed oil. Gossypol, a natural toxicant, is concentrated in the cotton seed meal during the production of cotton seed oil. Since plant byproducts represent an important food source for animals, it is important to determine if significant concentrations of harmful plant constitutes or toxicants are present in the transgenic plant byproducts."

5. "The use of antibiotic-resistance genes as selectable markers in transgenic plants must be reviewed to determine the effect on animal therapeutics. For example, the enzyme product of the kanamycin resistance gene) inactivates the antibiotic neomycin, which is used in feed and drinking water of animals."

6. "Nutrient composition and availability of nutrients in feed are extremely important to the animal industry and animal health. If GM makes a higher percentage of a nutrient unavailable)for example, if an unintended effect of modification of soybeans was increased content of phytin, the amount of phosphorus available could be greatly reduced. Animal health problems could result unless the diet were supplemented with phosphorus. "

7. "Residues of plant constituents or toxicants in meat and milk products may pose human food safety problems."

   On Toxicology (Target animal safety feeding study

8. "Sponsors with products to be incorporated into animals feeds should conduct appropriately controlled feeding studies in the target animal comparing the new plant variety to the conventional plant. The study should be of sufficient size and duration to provide adequate statistical power to detect adverse effects should they occur."

27 Feb 1992 -- Comments on FDA ‘Biotechnology Draft Document’ by Dr Louis J. Pribyl.

1. "What has happened to the scientific elements of this document?. Without a sound scientific base to rest on, this becomes a broad, general ‘what do I have to do to avoid trouble -- type document. The examples do not supply the scientific rational that is needed. A scientific document is needed, because there is very little (even when things are called scientific) scientific information supplied. If the FDA wants to have a document based upon scientific principles these principles must be included, otherwise it will look like and probably be just a political document."

2. "It reads very pro-industry, especially in the area of unintended effects".

3. "There is a profound difference between the types of unexpected effects from traditional breeding and genetic engineering, which is just glanced over in this document."

4. "The flow charts are just a version of a Redbook, hoops through which industry must jump, and are not scientific considerations. Industry will do what it HAS to do to satisfy the FDA "requirements" and not do the tests that they would normally do because they are not on the FDA's list".

5. "How many "first" examples will have to be examined? First examples of what (new genes; new types of modifications: genes from organisms from other kingdoms: first submissions. Also in order not to be sued by the "first" group of submitting biotech companies, who will be required to submit data when others later on will not. What will they receive for being the guinea pigs? (After all even those who do not submit will also have the implicit seal of approval from the FDA if they "follow " the code of practice.)) "First" examples again, who decides when enough is enough? Industry? FDA? Congress? Safety? The president? The council for Competitiveness? "

6. "If there is no difference between traditional foods and genetically engineered foods, then why would that FDA even bother to challenge them: unless it is really saying that they are in fact different."

7. "Is it really feasible to think that breeders would freely (without some sort of urging) back-cross to get only one chromosomal location, unless there was interference with the desired outcome. And besides multiple copies inserted at one site could become potential sites for rearrangements, especially if used in future gene transfer experiments, and as such may be more hazardous."

8. "Unexpected effects -- This is industries pet idea, namely that there are no unintended effects that will raise the FDA's level of concern. But time and time again there is no data to back up this contention, while the scientific literature does contain many examples of naturally pleiotropic effects. When the introduction of genes into plant's genome randomly occurs, as is the case with the current technology (but not traditional breeding), it seems apparent that many pleiotrophic effects will occur. Many of these effects might not be seen by the breeder because of the more or less similar growing conditions, in the limited trials that are performed. Until more of these experimental plants have a wider environmental distribution, it would be premature for the FDA to summarily dismiss pleiotropy as it has done here."

9. "The potential for activating cryptic pathways has NOT "been effectively managed in the past by sound agricultural practices", because the breeders have not had to face the issue of new, powerful regulatory elements being randomly inserted into the genome. So there is no certainty that they will be able to pick up effects that might not be obvious, such as cryptic pathway activation. This situation IS different than that experienced by traditional breeding techniques."

10. "All plants produce toxicants)at their native dose range, they might be benign, but if they are increased by unintended effects, their effect(s) are unknown. So to just say "No problem" would be premature and potentially unsafe."

11. "Is there clear evidence that allergens have not been transfer to host? Since there are very few allergens that have been identified at the protein or gene level, this question can only be answered "No" when the gene comes from a plant which produced allergies. So the companies are going to have to consult FDA on tomatoes, peanuts, wheat and every other plant which produce allergic reactions. Also the only definitive test for allergies is human consumption by affected peoples, which can have ethical considerations."

12. "Newly introduced proteins present in the plant?', this does not take into account, nor does the document as a whole, those introduced proteins (enzymes), that while acting on one specific substrate, intended substrate to produce the desired effect, will also affect other cellular molecules. Either as substrates, or by swapping the plants regulatory/metabolic systems and depriving the plant of resources needed for other things."

13. "The toxicity section is going to be a problem. Industry will say it is too much and the environmental/consumer groups will say it is not enough. A more complete presentation of the scientific concerns), as well as a more forceful show of reliance on the usefulness of molecular biology would have reduced this problem by spelling out the need for toxicity tests, in limited circumstances. Better yet, a separate (Federal Register) presentation of the scientific concerns with an analysis of comments before ever producing flow charts of guidelines (as currently presented) would produce better understood guidelines."

14. "A recent report in the Feb 8;1992 issue of new Scientists (pg 40-44) By C. Heron, implies that plants can form hybrid chains that include plants that are not often considered capable of making such hybrids. There are many things about hybridization that are not known that could cause the transfer of introduced genes into unintended species. This possibility should not be written off so easily."

March 10th 1992- Points made by Dr Steven Gindel, Chief, Biotechnology Section, Food Engineering Branch, FDA Dept of Health and Human Services, to Dr James Maryanski, Biotech coordinator.

1. "Regarding silent metabolic pathways. I would like to see this paragraph include a mention of the fact that a 'silent pathway' can become 'activated' due to an increased concentration of some metabolic intermediate, allowing mass flow into a low affinity pathway. This apparent activation of a silent pathway can occur without direct mutational change in the pathway involved, and might result in the production of a toxicant."

March 18th 1992 Dr Louis J Pribyl comments on the March 1992 version of the Biotechnology Document.

"I can see many ways that a protein (enzyme) could modify a plant without the protein being toxic; e.g. a protein could modify secondary substrates (non-primary, intended substrates) such that they change the nutritional value of the food. There is also the potential for the newly introduced gene (or gene product) to swamp the plants resources, be they proteins binding to regulatory regions, thereby shutting down other genes (as has occurred when two separate T-DNA have been introduced separately [at different times] into the same plant, Matzke, et al (1990) Dev Genetics 11:214-223). "

1st Aug 1992 -- Points made by Dr Carl B Johnson on the draft 'Statement of Policy for Biotechnology'.

1. "Unintended effects. The nature of unintended effects on gene expression may vary depending on; the site of integration in the genome of the host plant; the number of integration sites; the number of copies of the introduced DNA at each integration site; the source and nucleotide sequence of all introduced DNA."

2. "Line 9-7 appear to provide a justification for the use of toxicological studies in safety assessment, citing as an example the inability of analytical or molecular methods to detect the presence of an unknown toxin produced by activation of a previously cryptic gene. However, lines B-end of paragraph says that toxicological studies will not be needed if DNA insertion is limited to only a single site of known genomic location. This discussion implies that pleiotropy (i.e. the production of an unknown toxin due to activation of a previously cryptic gene) will disappear or be negligible if gene insertions are limited to a single copy at a known genomic location. Evidence should be provided to support this position."

3. "What if the inserted DNA is from a non-food source and encodes a protein that is toxic to certain organisms (e.g. Bt toxin)? Wouldn't knowledge of the toxicity of this protein product be necessary to ensure safety?"

4. "It is my understanding that pleiotropic effects are unpredictable, and may be triggered by gene insertion at a single site, as well as at multiply sites, in the plant genome. Restriction of foreign DNA insertion to a single site in the plant genome would reduce, but not eliminate the chance that the insertion event might trigger pleiotropic effects. The document does not present evidence that pleiotropic effects (e.g. alterations in biosynthesis of unknown toxicants) can be controlled by restriction of foreign DNA insertion to a single site in the plant genome. If such evidence exists, it should be summarized in this document."

Dec 17th 1992 -- Dr Murray Lumpkin, Director, Anti-infective Drug Products comments to Dr Bruce Burlington.

1. "The Division comes down fairly squarely against the use of the Kanamycin resistance gene marker in the GM tomatoes (Calgene's Flavr Savr (the first GM food approved in the US). I know this could have serious ramifications."
   Taken from 'The Medical Officer's summary of final comments':

2. "The Division representatives expressed that their main concern focussed on the gene

itself. Concern was expressed that the endogenous bacterial population could be transformed by the insertion of the kanamycin resistance gene)The presence of these genes in commensal intestinal bacteria could have far-reaching implications with respect to antimicrobial treatment of patients and in particular, the immunosuppressed patient. "

3. "Dr Flamm and Maryanski stated that the gene transfer from the eucaryotic tomato plant genome to the procaryotic bacterial genome was improbably. Even if the gene transfer were successful, in order to have expression of the gene product i.e. the enzyme; the bacterial genome would require a procaryotic promoter region. The Kanamycin resistance gene originates in a prokaryotic system, i.e. a plasmid; can it be assumed that the prokaryotic promoter region is not available?"

4. "By ingesting the GM foodstuffs and thus increasing the background exposure of the kanamycin resistant gene many fold, are we creating a selective pressure to induce natural transformation of bacteria?"

5. "The author of the sponsor's document presents clinical assumptions, which are not entirely valid)namely the model that addresses that potential uptake and expression of the Kanamycin resistance gene in humans consuming GE fresh tomatoes. In addition the sponsor reports that the human intestinal microflora already has a substantial population of organisms with kanamycin resistance) However, it is not clear from this statement whether the sponsor clarified that the mechanism of kanamycin resistance was the same as that which occurs with the kanamycin resistance gene."

6. "The major issue of concern from a clinical standpoint is the introduction of the kanamycin resistance gene into significant numbers of microorganisms in the general population of human microflora. IT WOULD BE A SERIOUS HEALTH HAZARD TO INTRODUCE A GENE THAT CODES FOR ANTIBIOTIC RESISTANCE INTO THE NORMAL FLORA OF THE GENERAL POPULATION. "

7. "The sponsor should consider a brief controlled animal study designed to determine the rate of transformation in the intestinal microflora after a dietary challenge of gene modified food."

8. "The sponsor should address the presence or absence of a bacterial promoter region for Kanamycin resistance in the T-DNA region."

9. "The sponsor should also consider implementing a program of post-marketing surveillance, similar to a phase IV drug safety surveillance, to monitor for increases in frequency in the kanamycin resistance gene."

10. "Finally, the sponsor should seek an alternative gene marker, one that does not involve antibiotics used in human therapy. Although there is, at present, no proof that the introduction of the Kanamycin gene in the tomato genome will result in widespread bacterial incorporation of the resistance gene, the potential risk of this happening would have enormous implications."

March 30th 1993 -- Points made by Dr Albert Sheldon, FDA Department of Human Health Services, Public Health Services, and FDA Centre for Drug Evaluation and Research, to Dr James Maryanski, Biotechnology Coordinator on the use of Kanamycin Resistance Markers in Tomatoes.

1. "The sponsor contends that resistance to Kanamycin already exists in microorganisms colonizing the gastrointestinal tract and utilization of the Kanamycin marker in transgenic tomatoes (Calgene's Flavr Savr) will not increase the genetic burden in that environment.) A review of their citation) reveals that the b

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