Consumers Union
Comments on Docket No. FDA-2008-D-0394,
"Draft Guidance for Industry: Regulation of genetically engineered animals containing heritable rDNA constructs"

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Introduction

Consumers Union* (CU), the non-profit publisher of *Consumer Reports* magazine, appreciates the opportunity to comment on Docket No. 2004D-0369, "Draft Guidance for Industry: Regulation of genetically engineered animals containing heritable rDNA constructs." We commend FDA for requiring such animals to go through a mandatory safety assessment. However, we believe FDA's decision not to require labeling of milk and meat from such animals denies consumers of their right to choose what they eat, and is contrary to existing law and legal precedents.

Overview

We commend the Food and Drug Administration (FDA) for stating their intent in this Guidance to require environmental and human safety assessments before genetically engineered animals, or food products derived from them, are permitted to be commercialized. This is a step forward from the way FDA regulates genetically engineered plants, which do not have to go through a mandatory human safety assessment. However, we feel the proposal does not go far enough and has some serious deficiencies and ambiguities.

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A major problem with this proposal is that it is simply Guidance for Industry and so is not legally binding: "This draft guidance . . . does not create or confer any rights for on any person and does not operate to bind FDA or the public." We urge the FDA to publish a legally binding regulation for genetically engineered animals, and not just a non-binding "guidance."

A second problem is lack of transparency. FDA has decided to regulate all genetically engineered animals under the New Animal Drug provisions of the Food Drug and Cosmetic Act, arguing that the rDNA construct inserted into the animal's genome is a drug. This is an important and positive step, although we do have specific comments on the kind of safety data that should be required, which we discuss below. However, the down side of using the New Animal Drug provisions of the FDCA is that there is not enough transparency. Virtually all the safety data may remain confidential until after the GE animal is approved. Although we commend FDA for stating that for the first few GE animals that they approve, FDA will have public meetings of their Veterinary Medicine Advisory Committee (VMAC) to get public input on the health and safety data, we believe that, in general, safety and health data should not be considered confidential business information. After the first few approvals, FDA may decide not to hold VMAC meetings for GE animal approvals and so the transparency and chance for the public to comment on GE animal applications will disappear. We urge FDA to release all safety information on GE animals prior to approval so that the public can evaluate these data and make public comment, and to hold VMAC meetings to receive input on all pending approval decisions.

Another problem with this proposal is that GE animals may not receive an appropriate environmental review. FDA is not actually the appropriate agency to assess the potential environmental impacts of GE animals, which can be very serious. With GE fish and shellfish, the potential for release/escape into the environment could be fairly large. This is particularly true with engineered salmon, which would be kept in net pens in the ocean. For example, AquaBounty has a GE salmon engineered with a growth hormone gene to make it grow to adult size faster and to make the adult fish bigger. Since many fish choose mates on the basis of size, research has suggested that the growth hormone trait could, under the right conditions (larger size for the GE males and reduced fitness in the offspring of GE males), lead to potential extinction of a

wild population.[1] GE pigs also have a significant potential to escape and become feral; wild boar are pests in many parts of the US. The National Research Council has ranked taxa of GE animals in terms of their ability to become feral, likelihood of escape from captivity, mobility and historical evidence of environmental disruption. From high to low the NRC ranking consists of insects, shellfish, fish, mice-rats, cat, pig, goat, horse, rabbit, dog, chicken, sheep and cattle.[2] Consequently, we feel that the issue of environmental impacts of GE animals should not be assessed by FDA, but should be assessed by the Environmental Protection Agency (EPA) and other governmental agencies as necessary. FDA should request EPA to seek authority from Congress to do environmental assessments for all GE animals, to ban those animals that pose a significant risk to the environment, and to approve only those that can be shown to present a reasonable certainty of no harm to the environment.

The final problem with the proposed guidance is that the FDA is not requiring labeling of meat and milk products derived from GE animals. We strongly disagree with this FDA decision. For the reasons explained below, we believe that genetic engineering is a material fact that consumers want to know; if food produced from GE animals are not labeled, then we believe that the labels would be false misleading under Secn 403(a) of the Food Drug and Cosmetics Act (FDCA). In October, 2008, the Consumer Reports National Research Center polled over 1,000 people nationwide on various food labeling issues; some that 95% of consumer polled agreed that "food products made from genetically engineered animals should be labeled as such" with 78% strongly agreeing with this statement[3]. This clearly shows consumers overwhelmingly desire food from GE animals to be labeled as such; in other words, whether an animal has been genetically engineered is a material fact that should be displayed on the label. FDA could also require labeling of GE animals as a risk management measure to deal with the scientific uncertainty associated with GE animals and to track any unexpected health effects that may occur.

Detailed Comments

[1] Muir, WM and RD Howard. 2001. Fitness components and ecological risk of transgenic release: a model using Japanese medaka (*Oryzias latipes*). *The American Naturalist*, 158: 1-16.
[2] National Research Council (NRC). 2002. *Animal biotechnology: science-based concerns*. Washington, DC, National Academies Press.
[3] At: http://www.greenerchoices.org/pdf/foodpoll2008.pdf

II. Statutory and Regulatory Authority

A. The Regulated Article

The FDA states that this guidance does not cover GE animals containing non-heritable constructs and that they intend to issues another guidance on issues raised by GE animals containing non-heritable constructs. We agree that guidance is needed for safety assessment of foods derived from GE animals containing non-heritable constructs, but we believe that FDA should develop a legally binding regulation for GE animals containing non-heritable constructs.

We strongly agree with FDA that each transformation event is unique and that separate safety assessment (or separate new animal drug evaluations) should be required from animals derived from each transformation event.

III. Investigational Use of GE Animals

C. Investigational Food Use Authorizations

FDA states that it is possible "to introduce investigational animals or animal products into the food or feed supply," as long as the applicant has been granted an Investigational Food Use Authorization. Because of the lack of transparency, at this stage, as well as the fact that the safety assessment is not complete, we believe that FDA should not grant any Investigational Food Use Authorizations for any GE animal. Rather, such GE animals or products derived from them should only be allowed into the food supply *after* FDA has made a decision to approve and the VMAC has held a public meeting.

IV. FDA Approval of GE Animals

B. New Animal Drug Application Requirements

3. Labeling (21 CFR 514.1(b)(3))

The FDA maintains that "the fact that the animal from which a food was obtained was genetically engineered would not be material information with respect to labeling." We strongly disagree.

Consumers Union believes that <u>all</u> genetically engineered food, particularly GE animal products should be labeled, for several reasons. First, at least two different labeling provisions of the FDCA--the ingredients labeling provision (Sec. 403(i)) and the provision prohibiting "false or misleading" labeling (Sec. 403(a))--would seem to require it.

Sec. 403(i) of the FDCA requires that any food made from two or more ingredients must have a label with the common or usual name of each ingredient. The law defines an ingredient broadly as all "those substances that have been used to manufacture a food." Included in this definition would be all added substances. Added substances are all those substances present in food with the exception of those that are an "inherent natural constituent" but not intrinsically part of the food. Since there is some grey area here, a federal court has ruled that the law distinguishes between substances that are present in the food due to "acts of man" and those present due to "acts of nature;" the former are considered added and therefore subject to labeling while the latter are not (U.S. v. Anderson Seafoods, Inc. 447 F. Supp. 1151, [ND Fla 1978]). This distinction is important because the law requires a higher safety standard for substances present by reason of "acts of man." As the court pointed out, "[I]f a coffee processor subjects coffee to a process in which the naturally occurring caffeine is removed and later replaced with an equal amount of identical caffeine, it seems clear that Congress would have the stricter health standard apply" (Anderson).

Given this logic, we feel all genetic material moved into an animal via genetic engineering techniques, and any expression products from the genes, should be considered added and therefore, treated as an ingredient. Take the Enviro pig that is engineered to reduce the amount of phosphate in the pig's manure, thereby reducing phosphate pollution, for example[4]. The genetic construct transferred includes a gene for phytase (which is an enzyme that can digest the phosphorous in phytate, the most abundant source of phosphorous in the pig diet, which comes from *E. coli)*, a promoter (which comes from mice) and a selectable marker gene. This genetic construct was added to the pig by an "act of man," as the gene does not exist in nature. Obviously, the process whereby these different genetic materials were spliced together to form a single stretch of DNA was an act of man. Even though some might argue that the phytase protein from *E. coli* is "natural," the process by which it is added to pigs renders it an "act of man" in the same way that the caffeine artificially added to a coffee bean is considered added, while the naturally occurring caffeine is not.

In our view, the added genetic material, as well as the expression products, should be considered as ingredients. In a commonsensical consumer understanding of the word ingredient, something that contains genetic material from at least two dissimilar sources contains at least two ingredients. By "dissimilar sources" we mean simply sources such as pigs, mice, and *E. coli*, that have a breeding barrier between them that is not already breached by traditional breeding.

[4] Goloban, S.P., Meidinger, RG, Ajakaiye, A, Cottrill, M, Wiederkehr, MZ, Barney, DJ, Plante, C, Pollard, JW, Fan, MZ, Hayes, MA, Laursen, J, Hjorth, JP, Hacker, RR, Phillips, P and CW Forsberg. 2001. Pigs expressing salivary phytase produce low-phosphorous manure. *Nature Biotechnology* 19: 741-745.

Sec. 403(a) of the FDCA prohibits "false and misleading" labels. The ingredients labeling provisions of the law provide for labeling an ingredient if it is a "material fact" (21 U.S.C. 321 (n)). A material fact, in FDA's view, is information that consumers view as important. If such information is not on the label, then the label is considered to be misleading. FDA articulated this position in a final rule that required labeling of irradiated foods (51 FR 13376-88, [1986]), even though the FDA had ruled that irradiated foods were safe. FDA has stated in this final rule on food irradiation (April 18, 1986, 51 FR 13376 at 13380) that the large number of respondents who asked for labeling of retail products was *one* factor indicative of the materiality of food irradiation: "Whether information is material under section 201(n) of the act depends not on the abstract worth of the information but on whether consumers view such information as important and whether the omission of label information may mislead a consumer. *The large number of consumer comments requesting retail labeling attest to the significance placed on such labeling by consumers"* (italics ours). In October, 2008, the Consumer Reports National Research Center polled over 1,000 people nationwide on various food labeling issues; some that 95% of consumer polled believed that "food products made from genetically engineered animals should be labeled as such" with 78% strongly agreeing with this statement[5]. This clearly shows consumers overwhelmingly desire food from GE animals to be labeled; in other words, whether an animal has been genetically engineered is a material fact that should be displayed on the label.

FDA has used the material fact rationale to require source labeling for protein hydrolysates. Labeling the source of protein hydrolysates was required because of the concern of vegetarians and observant Jews and Muslims. As the FDA stated, "the food source of a protein hydrolysate is information of material importance for a person who desires to avoid certain foods for religious or cultural reasons" (56 FR 28592 [1991]).

Food derived from genetically engineered animals should be labeled to address religious, moral, and ethical concerns, as well. People are very concerned about genetically engineering animals, because of a range of ethical issues. Indeed, the National Research Council's 2002 publication, *Animal Biotechnology: Science Based Concerns*, has a chapter that deals, in part, with socioeconomic, cultural, religious, and ethical factors raised by rDNA animals, which contains a box on labeling. As the NRC report noted, "Some religious, spiritual, ethnic, or cultural groups prescribe dietary norms or rules that include foods that are to be avoided. These norms or religious traditions might be violated by genetic engineering of animals used as food."[6] The NRC has realized that the labeling issue is very important to consumers as they point out "that there reasons--beyond safety or nutrition--for a consumer to want labeling of food derived from genetically plants or animals, including religious, ethical, right-to-know,

[5] At: http://www.greenerchoices.org/pdf/foodpoll2008.pdf

[6] pg 118 in National Research Council. 2002. *Animal Biotechnology: Science Based Concerns.* National Academy Press, Washington, D.C.

or simple preference reasons. It could be argued that in the current climate surrounding biotechnology, the fact of genetic engineering is an aspect of the identity of a food derived from a genetically engineered organism. The committee notes, however, that while any one or all of these reasons might provide a legitimate basis in public policy for requiring labeling of biotechnology-derived foods . . . whether they justify labeling is beyond the committee's charge."[7] However, we believe that FDA could use the material fact criterion to require labeling of food derived from genetically engineered animals.

Another reason for requiring labeling of GE animals is that without such labeling, such animals could inadvertantly become part of the food supply and pose problems for organic producers and those producers raising non-GE meat. GE traits are likely to be patented, so that initial purchasers will likely know if they are buying a GE animal. However, if the company producing the GE animal goes out of business, patents may no longer be enforced and the GE animals could be bought and sold as regular animals. Organic producers and those who are producing for the non-GE animal/meat market (this could be a sizeable market) could be adversely economically impacted as it would be very, very hard to determine at an auction, for example, if the animals they buy have GE traits or not.

We also believe that FDA should require labeling for food derived from GE animals as a risk management measure to deal with scientific uncertainty and to track any potential unexpected adverse health effects associated with consumption of GE animals. This would be consistent with the recommendations developed by the Codex Alimentarius Ad Hoc Intergovernmental Task Force on Foods Derived from Modern Biotechnology and adopted by the Codex Alimentarius Commission in 2003. The *Principles for the Risk Analysis of Foods Derived from Modern Biotechnology* (CAC/GL 44-2003)[8] clearly state that labeling can be used as a risk management option to deal with scientific uncertainties associated with the risk assessment of GE foods: "18. Risk managers should take into account the uncertainties in the risk assessment and implement appropriate measures to manage these uncertainties. 19. Risk management measures may include, as appropriate, food labeling, conditions for market approval and post-market monitoring" (pars 18, 19 in CAC/GL 44-2003).

Significant scientific uncertainty exists in the risk analysis of foods derived from GE/GM, and this is recognized in the Codex. In fact, the *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals*[9]

[7] Pg 118, IBID
[8] Available at: http://www.codexalimentarius.net/web/standard_list.do?lang=en
[9] Available at: http://www.codexalimentarius.net/web/standard_list.do?lang=en

has a whole section on unintended effects which clearly states that they can have an unintended effect on human health: *"Unintended effects due to genetic modification may be subdivided into two groups: those that are "predictable" and those that are "unexpected" . . . A variety of data and information are necessary to assess unintended effects because no individual test can detect all possible unintended effects or identify, with certainty, those relevant to human health.*" italics added (paras 17 and 18, CAG/GL 68-2008). Furthermore, this section recognizes that the unintended effects could also be caused by changes in genes are expressed at the molecular level and how the gene products are processed: "Molecular biological and biochemical techniques (that) can also be used to analyse potential changes at the level of gene transcription and message translation that could lead to unintended effects" (para 16, CAG/GL 45-2003).

4. Components and Composition (21 CFR 514.1(b)(4))

FDA believes that the data submitted under this section "should encompass the molecular characterization of the article. It should enable us to determine whether the article contains any potentially mobilizeable DNA sequences, and whether sequences are present that encode pathogens, toxicants, allergens, or substances likely to dysregulate the growth control of cells, tissues, or organs, except by explicit design."

We concur with FDA that molecular characterization data must be submitted, but we believe that a complete molecular characterization should be required, as recommended by the Codex Alimentarius *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals*. Thus, for each separate transformation event, we believe FDA should require the following data: total number of inserts of transgenic DNA; location of each insert (organelle [chloroplast, mitochondria, etc.] or chromosomal; exact chromosomal position of each insert; structure of each insert (whether duplicated, deleted, rearranged, etc.); complete genetic map of each insert including all elements (coding region, non coding regions, marker gene(s), promoter(s), enhancer(s), origins of replication, introns, leader sequences, terminators, T-DNA borders, plasmid sequences, linkers, etc. including any truncated, incomplete sequences; complete (nucleotide) base sequence of each insert; nucleotide base sequence of at least 10kbp of flanking host genome DNA on either side of the insert, including changes in methylation patterns.

For a complete molecular characterization and for detecting unexpected effects, it is crucial that FDA require sequencing of the flanking regions of an insert. Not just the flanking borders of each of the inserts, but at least 10 kilobases of flanking host genome DNA up-stream and down-stream from the insertion site. The study on the Aqua Bounty salmon that found inserts upstream and downstream from the insertion site show that this is an issue for GE animals as well.[10]

New data confirm unintended and unexpected effect from genetic engineering, although the data are more clear-cut for GE plants than GE animals, in part because so few studies have been done on GE animals, as compared to plants. Studies in the last five years have found all sorts of unexpected changes at the molecular level in GE crops. A detailed molecular characterization of various GE crops[11] (three different Bt maizes, an herbicide-tolerant maize, RoundUp Ready soybean, and a male-sterile canola) currently on the market, done in Belgium, has shown that of the transgenic lines looked at, all but one were found to have differences in the molecular characterization in products on the market compared to the original structure reported by the company. Except for the canola, all these reports found that the structure (e.g. molecular characterization) of transgenic inserts as reported by the companies in their initial submission were different than the structure found in subsequent studies. The differences in structure involved rearranged inserts, partial copies of genes inserted, multiple copies of transgenes inserted, scrambling of DNA near the border of the transgenic inserts, etc., suggesting that the transgenic lines are unstable and/or more likely to result in unintended effects. In fact, in virtually all the cases, the SBB/IPH recommends that further analysis "should be done to determine the presence of chimeric open reading frames in the border integration sequences", e.g. an analysis should be done to see if there are any unexpected proteins being produced.

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[10] Mitchell, UH, Khattra, J and RH Devlin. 2006. Transgene constructs in coho salmon (*Oncorhynchus kisutch*) are repeated in a head-to-tail fashion and can be integrated adjacent to horizontally-transmitted parasite DNA. *Transgenic Research* 15(6): 711-727.

[11] Dr. Moens, with the Service of Biosafety and Biotechnology (SBB) of the Scientific Institute of Public Health (IPH), a government agency reported on the molecular characterization of the genetic map for six transgenic crops: 3 different Bt maizes—Bt 176, Syngenta (www.biosafety.be/TP/MGC_reports/Report_Bt176.pdf); MON 810, Monsanto (www.biosafety.be/TP/MGC_reports/Report_MON810.pdf); Bt11, NorthrupKing (www.biosafety.be/TP/MGC_reports/Report_Bt11.pdf)—a herbicide tolerant maize (LibertyLink maize, Bayer)(www.biosafety.be/TP/MGC_reports/Report_T25.pdf) , glyphosate tolerant soybeans (RoundUp Ready soybeans, Monsanto) (www.biosafety.be/TP/MGC_reports/Report_MON810.pdf) , and a canola engineered for male sterility (Ms8 x Rf3, Bayer Cropscience).

There has also been evidence from GE animals of unexpected effects, including DNA scrambling near the insertion site and insertions of genetic material upstream and downstream of the insertion site. The GE animal that is closest to commercialization is Aqua Bounty's hybrid GE salmon that have been engineered with a salmon growth hormone gene. Molecular characterization of the GE salmon found that four copies of the growth hormone gene (all in direct-tandem [e.g. head-to-tail] repeat fashion) and two partial copies of the gene were inserted at a single site. In addition, the act of insertion lead to a deletion of 587 base pairs of host DNA at the insertion site, along with insertion of 19 base pairs of unknown DNA upstream of the insertion site and a 14 base pair direct-tandem repeat downstream of the insertion site.[12] Molecular characterization of the sites upstream and downstream found that the downstream insertion is right next to pseudogene from a membrane protein of a parasite that infects salmon. Thus, the GE salmon have the construct inserted near a site that has been modified due to horizontal gene transfer from a salmonid parasite, which could mean that this area of the salmon genome might be unstable mobile insert capable of yet another horizontal transfer to wild salmon stocks. This paper clearly shows the importance of doing a full molecular characterization.

5. Manufacturing Methods, Facilities, and Controls (21 CFR 514.1(b)(5))

FDA states that a "full characterization of the article and insertion site(s) once stabilized genomically" should be submitted and that this "should include information demonstrating the durability of the genotype and phenotype—that is, whether the article is stably inherited, and the phenotype is consistent and predictable. This should include a sampling plan." We commend FDA for requiring both full characterization and stability data, but feel that they should be more specific about the kind of data that are needed. In terms of the molecular characterization, we believe that FDA should require the data as laid out in the Section of the Codex Alimentarius *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals* entitled "Characterization of the Genetic Modification(s) in the Recombinant-DNA Animal Ultimately Used as Food or for Food Production," e.g. paras 37-39 in CAC/GL 68-2008.[13] In the genotypic area, FDA simply require data to show the construct is "stably inherited" although they do not define exactly what they

[12] Mitchell, UH, Khattra, J and RH Devlin. 2006. Transgene constructs in coho salmon (*Oncorhynchus kisutch*) are repeated in a head-to-tail fashion and can be integrated adjacent to horizontally-transmitted parasite DNA. *Transgenic Research* 15(6): 711-727.
[13] Available at: http://www.codexalimentarius.net/web/standard_list.do?lang=en

mean. We feel FDA should require data on both functional stability and structural stability. For functional stability, we mean that the level of expression of the transgene construct remains constant over time and over a number of generations. For structural stability, we mean data on the physical location of the insert in the genome as well as the structure (e.g. molecular characterization) of the insert—throughout the lifetime of the animal as well as over a number of generations. We agree with FDA that the stability data should be from at least two generations, preferably more, and that two of the sampling points should be from non-contiguous generations (e.g. F_2 and F_4). Also, genotypic stability should mean that the construct does not move around in the genome, not simply that the trait is "stably inherited." Consequently, FDA must require that the flanking region and border sites of the insert be sequenced as well. If the border site sequences change over time and/or over generations, it means that the genetic material has been moving internally in the genome. The construct itself should also be sequenced in these different generations to see if it changes over time—as was found for the genetically engineered plants (see footnote 9).

7. Analytical Methods for Residues (21 CFR 514.1(b)(7))

In addition, FDA should, prior to field-testing, require methods by which the GE food could be detected. This would include a method for detecting the inserted DNA sequence as well as a method for detecting the introduced substance. Such a requirement would be very useful in traceability of the food, as well as serving to tell when there is unexpected gene flow. We are disturbed to hear that FDA will require such information, "except when data or other adequate information establish that it is not reasonable to expect the new animal drug to become a component of food at concentrations considered unsafe." CU believes that there should be no exceptions and that a detection method should *always* be required. Since there is a market for non-transgenic or non-engineered food, and since organic foods cannot contain any genetically engineered ingredients, a test would be needed to determine when the foods destined for GE-free markets have been contaminated. In addition, many countries have not approved genetically engineered foods and have laws that state that unless such foods are explicitly approved, it is illegal for them to be on the market. Since the US has approved more engineered varieties than any other country, some of it may be illegal to ship to other countries. For example, not all the varieties of engineered corn approved in the U.S. have been approved in the European Union (EU). The result is that the US has lost a $300 million corn export market to the EU. Shipments of food have already been rejected at foreign ports due to contamination with unapproved varieties, eg., the StarLink fiasco. So detection

methods should absolutely be required. Furthermore, the detection methods should be available for the raw agricultural commodity as well as the representative finished product. We feel that the detection methods should include one for testing the presence of the inserted DNA as well as one for the expressed product. For the former, we suggest the use of a PCR (polymerase chain reaction) test as this is the most sensitive test to date. To facilitate such testing, the agency should require that the complete identity of the primer sequences be made available so that technically-proficient non-governmental laboratories can use them. The agency should require that the detection methods are adequate for detecting the presence of the inserted DNA and its expression products at the level at which it will appear in the food and that the test is of a reasonable cost. This requirement could be done along the lines of the detection method that is required when a new drug or pesticide is put on the market.

8. Evidence to Establish Safety and Effectiveness (21 CFR 514.1(b)(8))

FDA has stated that the information needed to establish safety of food from GE animals is consistent with that provided in the Codex Alimentarius *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals* (CAC/GL 68-2008). An important component of such a safety assessment is to look for of unexpected effects, which may occur due to the failure to control where the genetic material is inserted. Indeed, a section of the Codex *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals* (CAC/GL 68-2008) is devoted to "Unintended Effects" (paragraphs 15-18). Unintended effects may occur if a promoter used in GE, due to the random nature of insertion, ends up near a gene for toxin production, for example, turning that gene on or silencing another gene that may be involved in limiting levels of a toxin. In the area of human gene therapy, there have been several cases of leukemia in children who were receiving genes to overcome their lack of an immune system (these children had severe combined immune deficiency); research showed this resulted when the inserted genetic cassette inserted itself close to an oncogene which was then turned on[14]. In addition, the Royal Society of Canada pointed out that "examples are accumulating of transgene instability and unexpected patterns of gene expression in transgenic animals. In many cases, the insertional mutation is recessive and is not

[14] Sadelain, M. 2004. Insertional oncogenesis in gene therapy: how much of a risk? *Gene Therapy*, 11: 569-573.

expressed until successive generations."[15] The first pigs genetically engineered with human growth hormone, developed at USDA's Beltsville lab, suffered from many unexpected defects, including gastric ulcers, liver and kidney damage, degenerative joint disease, lameness, lethargy, diabetic condition, loss of libido, lack of coordination, etc.[16]

The issue of unexpected effects became such an important issue that four paragraphs in the Codex Guideline are devoted to it. The Guideline recognizes that such unintended effects can have adverse impacts on human health, states that they should be investigated as part of a proper safety assessment and even recommends methods to investigate such effects: "Safety assessment should include data and information to reduce the possibility that a food derived from a recombinant-DNA animal would have an unexpected, adverse effect on human health. Unintended effects can result from the random insertion of DNA sequences into the animal genome which may cause disruption or silencing of existing genes, activation of silent genes, or modifications in the expression of existing genes. Unintended effects may also result in the formation of new or changed patterns of metabolites. . . . *The safety assessment of foods derived from recombinant-DNA animals involves methods to identify and detect such unintended effects and procedures to evaluate their biological relevance and potential impact on food safety*" (CAG/GL 68-2008: paras 15, 16, 18) italics added. Furthermore, this section recognizes that the unintended effects could also be caused by changes in how genes are expressed at the molecular level and how the gene products are processed: "Molecular biological and biochemical techniques (that) can also be used to analyse potential changes at the level of gene transcription and message translation that could lead to unintended effects" (para 17, CAG/GL 68-2008).

We agree that unintended effects are very important and must be part of any food safety assessment. A paper by respected Dutch scientists reviewing the food safety issues associated with genetically engineered crops listed a range of documented unintended effects and concluded that "The development and validation of new profiling methods such as DNA microarray technology, proteomics, and metabolomics for the identification and characterization of unintended effects, which may occur as a result of the genetic modification, is

[15] Royal Society of Canada. 2001. Chp. 5 Considerations in the use of biotechnology in animal production systems, in *Elements of Precaution: Recommendations for the Regulation of Food Biotechnology in Canada*. The Royal Society of Canada. Ottawa, Canada.
[16] Pursel, VG et al. 1989. Genetic engineering of livestock. *Science* 244: 1288-1289.

recommended."[17] These new profiling methods could just as easily be used with GE animals as with GE plants and we urge FDA to require these methods to detect unexpected effects.

There is recent evidence that shows that animal feeding studies are essential to detect unexpected effects. A comprehensive feeding study commissioned by the Austrian government involving GE corn (NK603 X MON810) demonstrated that the GE corn, when fed to mice, significantly reduced fertility (lower number of offspring and lower weights) in the third and fourth litters born to these mice.[18] In the course of three generations fed on the GE corn, there were significant changes in gene expression with DNA microarray analysis between the GE corn and the isogenic non-GE corn, with more than 400 genes being significantly up- or down-regulated. This meticulous study clearly demonstrated that the GE corn diet had an adverse effect on fertility, clearly an unexpected effect. Thus, we think that FDA should require animal feeding studies as part of the safety assessment of food products derived from GE animals.

[17] Kuiper, HA, Kleter, GA, Notebom, HPJM and EJ Kok. 2001. Assessment of food safety issues related to genetically modified foods. *The Plant Journal*, 27(6): 503-528.
[18] Velimirov, A, Binter, C and J Zentek. 2008. Biological effects of transgenic maize NK603xMON810 fed in long term reproduction studies in mice. Available at: http://bmgfj.cms.apa.at/cms/site/attachments/3/2/9/CH0810/CMS1226492832306/forschungsbericht_3-2008.pdf