

William von Meyer, Ph.D.
President

Ms. Jane Alexander
1419 W. Greenleaf
Chicago, IL. 60626

3585
Nov. 24, 99

Dear Ms. Alexander:

Thank you for speaking with me following the recent F.D.A. Hearing in Chicago.

As concerns rBGH derived milk, Our laboratory, through the office of the former Congressman Scot Klug, conducted an investigation of the health data. We learned on July 2nd, 1998, that not a single health study was done wherein test animals were fed rBGH milk. With this information in hand, the concerns over rBGH milk began to increase for the reasons explained below.

In 1965, Sonnenberg (J. Metabolism 1198) published an effect of digested fragments from bovine growth hormone injected into human. They observed a significant effect on diabetes in diabetic patients. (see appended document 1) This means that there are chemical and biological effects of bovine growth hormone which have not been reviewed since this document has not been discussed in any federal hearing or state hearing until Nov. 18th, 1999.

In regard to diabetes risk, we subsequently found that in trials of rBGH by American Cyanamid, the blood serum of treated cows began to leak into the milk soon after injection. These data are shown in Graph I (attached).

It has been shown in Europe and by researchers in Canada that children with diabetes (type I) have a higher antibody level in their blood to cow serum protein than non-diabetic children. This anti-body is derived from contact with milk. Graph I clearly shows the increase of cow serum level with time in the milk. For children prone to form antibodies to cow serum in milk, this could mean an increased risk or intensity of diabetes reaction to rBGH milk vs. normal milk. Graph 2 shows the level of immunoglobulin G-anti bovine serum albumin in diabetic vs normal children. The children with diabetes had much higher titers than normal children.

The Monsanto milk data do not breakout serum vs. other types of protein in milk. However, appendix C shows that rBGH increases protein by about 3% and that this increase was statistically significant vs. untreated controls. Part of this increase may be serum proteins.

The investigation by Rep. Klug, showed clearly that no health data were collected on rBGH milk as whole milk fed to any animal or human. Thus, diabetogenic risk would have been missed entirely. Further,

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the incubation period of diabetes in human children could be a problem. It can be as long as 8 years. For these reasons, the complete omission of chronic health testing of the rBGH milk has become an urgent and very serious matter.

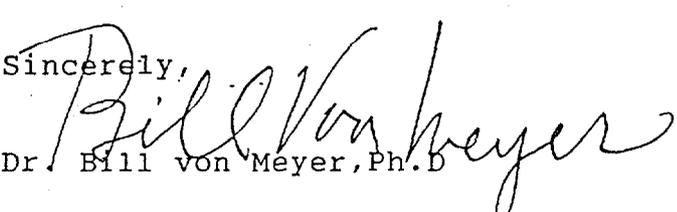
The data presented on antibodies in children have been collected in "human"....not animals. These kinds of data take priority over all animal data as regards their importance. Certain animals, such as BBdp rat, are prone to diabetes and have been used to test different foods for their ability to induce diabetes. A table has been attached to show the effect of skim milk powder and soybean meal in this rat. One can see quite different results. The entire article was attached to my presentation to the FDA.

The Congressional Inquiry into these matters showed that FDA lacked any detailed knowledge of the antigens formed in rBGH milk with time. Because of the frustration of our former Congressman as well as my laboratory by Officials at FDA (in one case putting him off for months in replying to his letters and then having no detail what-so-ever), we have started to speak with the public and at hearings about this matter.

In my experience with testing many toxic materials over the past 30 years, I have concluded that it would be best if rBGH milk were not consumed at all, particularly by children.

The review process for rBGH milk omitted very critical experimental data including diabetes testing. We have contacted the Dept. of Justice about the review process. However, any action by them we believe would be slow. It is my view that we must somehow act with our health officials in towns and schools to make certain no such milk reaches the young people. Here in Wisconsin 40% of the large dairies are employing the hormone, this is of great concern as most of our milk is exported to other areas.

Sincerely,


Dr. Bill von Meyer, Ph.D

cc. Ms. Janet Reno
Attorney General
U.S. Dept. of Justice
Washington, D.C.

Document 1.

1195

SONENBERG ET AL

Table 5.—Source, Degree of Proteolysis, and Biological Activity of Growth Hormone Preparations

| Growth Hormone Preparation | Lot No. | Min. of Digest. | Moles KOH/Mole Protein† | Growth Hormone Potency USP Units/mg. |
|----------------------------|--------------------|-----------------|-------------------------|--------------------------------------|
| BGH A* and D | Average of 19 lots | 0 | | 2.03 |
| BGH-digest D | F-1-260 | 5 | 2.7 | 1.32 ± 0.65 |
| BGH-digest D | F-1-245-1 | 10 | 5.3 | 1.39 ± 0.37 |
| BGH-digest D | F-1-262 | 10 | 6.3 | 0.58 ± 0.21 |
| BGH-digest A | F-11-157 | 18 | 6.9 | 0.72 ± 0.24 |
| BGH-digest A | F-11-105 | 30 | 9.1 | 0.37 ± 0.10 |
| BGH-digest D | F-1-245-11 | 30 | 9.8 | 0.38 ± 0.11 |
| BGH-digest A | F-11-80 | 60 | 13.8 | 0.08 ± 0.03 |
| BGH-digest‡ | F-1-200-1 | 60 | | 0.23 ± 0.05 |
| BGH-digest‡ | F-1-181-1 | 120 | | 0.25 ± 0.05 |
| BGH-digest‡‡ | JD-160 | 60 | | 0.62 ± 0.15 |

*A or D, respectively, indicate BGH prepared from Antuitrin C or by method of Del-lacha and Sonenberg.⁵

†Digestion performed in borate buffer.

‡Prepared from partially purified growth hormone.

§Assumed molecular weight of 45,700.

of proteolysis indicated by base uptake, the electrophoretic patterns, and decreases in biological activity in rats appeared consistent.

Effects in Diabetic Patients. There was significant aggravation of diabetes associated with the administration of 3 tryptic digests of BGH, i.e., 10 min. (study 2), 60 min. (study 11) and 60 min. (study 13).

In study 2 (figs. 2 and 3) there was an average increase of 107 mg./100 ml. in the FBS, 31.8 Gm./24 hr. in the urinary glucose and 7 mg./100 ml. in the BUN associated with the administration of the 10 min. tryptic digest of BGH. These changes occurred within 2 days of the administration of the BGH preparation whereas, the increase in serum alkaline phosphatase of approximately 0.3 Bodansky units (B.U.)/100 ml. did not become apparent until the fifth day of injections. During the treatment period the patient went into negative nitrogen balance with an increase of 3.7 Gm./24 hr. in total urinary nitrogen and, subsequently, 178 mg./24 hr. in urinary creatine (table 3A). Urinary phosphorus, sodium and potassium were increased. The small increase in urinary calcium became evident on the fifth day of treatment and persisted during the post-treatment control period.

In study 11 (figs. 4 and 5) there was an average increase of 29 mg./100 ml. in the FBS and 2 mg./100 ml. in BUN, which occurred within 2 to 3 days of the administration of a 60 min. tryptic digest of BGH. There was no increase in urinary glucose, serum alkaline phosphatase or serum inorganic phosphorus (fig. 4). The total urinary nitrogen increased 1.2 Gm./24 hr. (fig. 5) with an associated increase in urinary creatine of 47 mg./24 hr. (table 3A) which returned to the pretreatment levels when treatment was discontinued. The urinary excretion of calcium, sodium and potassium were also increased (fig. 5).

In study 13 (figs. 6-9) there was little consistent change in the FBS or urinary glucose during the administration of a 60 min. tryptic digest of BGH

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Graph I.

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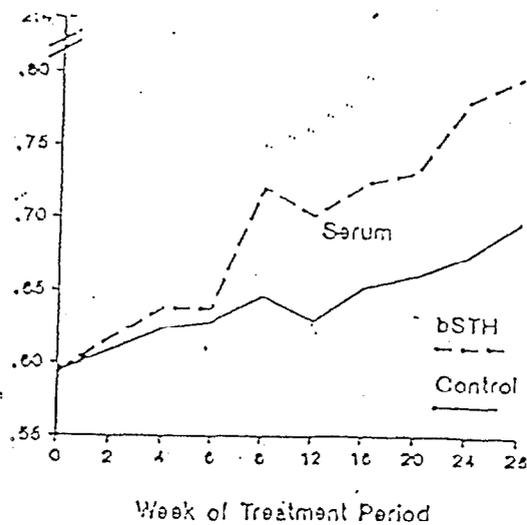


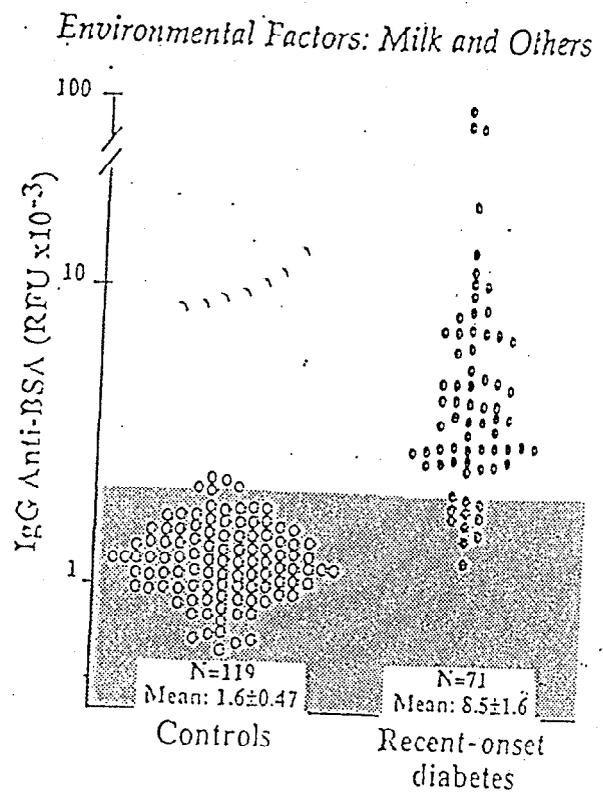
Figure 1. Milk protein content from control and cows injected with recombinant bovine somatotropin (bSTH) during treatment period.

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Note: the increased bovine serum content of the rbGH milk begins at the outset of injection of rbGH. This material is likely to contain more diabetogenic substance than normal milk.

Human Data Showing Diabetes Response.

Graph 2.



← increase of anti-body to bovine serum protein assoc. with diabetes in children

Figure 11.2. Anti-BSA antibody levels in a new series of Finnish children with recent-onset IDDM. Controls were age, sex and region matched. The shaded area includes 95% of all controls (mean ± 2SD), $p < 0.0001$

Immunoglobulin antibovine serum antibody in children with diabetes. (from an article by Dosch et al: Diabetes: Prevention and Genetic Counseling in IDDM. Palmer editor.

The serum could also contain something else which was a cause of diabetes or enhanced diabetes in susceptible humans. We know of several candidate proteins which could be adverse. Some of them we have discussed herein.

Table 24. The effect of sometribove administered intramuscularly (IM) or subcutaneously (SC) to cows on salable 3.5% fat-corrected milk (SSFCM) and 3.5% fat-corrected (SFCM) standardized to 252 days of treatment and on milk composition.¹

| Lactation Group/ Variable | Sometribove Dosage | | |
|------------------------------|--------------------|--------------------|----------------------------|
| | Control | IM (500 mg) | SC (500 mg) |
| Primiparous Cows | | | |
| (N) | 6 | 7 | 7 |
| SSFCM, kg/day | 24.2 ^a | 30.8 ^b | 28.6 ^b |
| SFCM, kg/day | 25.1 ^a | 32.2 ^b | 29.4 ^b |
| Fat, % | 3.17 | 3.29 | 3.34 |
| Protein, % | 3.13 ^a | 3.22 ^b | 3.22 ^b ← serum? |
| Lactose, % | 5.08 | 5.12 | 5.11 |
| Multiparous Cows | | | |
| (N) | 13 | 14 | 14 |
| SSFCM, kg/day | 25.1 ^a | 31.1 ^b | 31.2 ^b |
| SFCM, kg/day | 27.2 ^a | 33.8 ^b | 34.4 ^b |
| Fat, % | 3.45 | 3.39 | 3.41 |
| Protein, % | 3.18 ^a | 3.29 ^b | 3.27 ^b ← |
| Lactose, % | 4.88 ^a | 4.96 ^{ab} | 5.02 ^b |

^{a,b}Means within a row with different superscripts are significantly different (P<0.05).

¹Results reported as least squares means from covariate analysis from each group.

IM administration of sometribove produced larger increases than SC administration in average and peak circulating somatotropin concentrations and area-under-the-curve estimates (Table 25).

Table 25. The effect of sometribove administered intramuscularly (IM) or subcutaneously (SC) to cows on circulating somatotropin concentrations.¹

| Variable/ Lactation Group | Sometribove Dosage | | |
|--|--------------------|-------------------|-------------------|
| | Control | IM (500 mg) | SC (500 mg) |
| Average Circulating Concentration, ng/ml | | | |
| Primiparous Cows | 0.6 ^a | 5.3 ^b | 3.7 ^c |
| Multiparous Cows | 0.2 ^a | 6.1 ^b | 3.2 ^c |
| Peak Circulating Concentration, ng/ml | | | |
| Primiparous Cows | 2.6 ^a | 12.9 ^b | 7.9 ^c |
| Multiparous Cows | 1.5 ^a | 11.9 ^b | 7.8 ^c |
| Area-Under-the-Curve Estimates, ng·day/ml | | | |
| Primiparous Cows | 9.0 ^a | 78.5 ^b | 56.3 ^c |
| Multiparous Cows | 2.8 ^a | 90.0 ^b | 48.1 ^c |

^{a,b,c}Means within a row with unlike superscripts are significantly different (P<0.05).

¹Results reported as least-squares means of repeated measures analysis of variance.

Data on nutritional variables are summarized in Section 6.h. Reproduction data are discussed in Section 6.i, mastitis data are reviewed in Section 6.j, and cow health data are discussed in Section 6.k. Circulating anti-somatotropin binding data are reviewed in

INFORMATION Document,
SHOWING INCREASED PROTEIN
IN RBGH MILK

but no dietary data.

Table from Scott paper
Submitted to FDA

Table III. Effect of the food diabetogens in NIH on insulinitis and diabetes in BBdp rats*

| Diet | Diabetes frequency | | | | Insulinitis frequency | | | |
|------------------|--------------------|-----------|------|-----------|-----------------------|-----------|------|---------|
| | Diabetes % | No. expts | Rats | p v. HC | Insulinitis % | No. expts | Rats | p v. HC |
| HC | 12 ± 5 | 8 | 172 | - | 34 ± 17 | 6 | 137 | - |
| Casein | 13 ± 6 | 8 | 231 | 0.99 | 42 ± 20 | 7 | 190 | 0.98 |
| Wheat gluten | 47 ± 15 | 12 | 181 | 0.000006 | 71 ± 13 | 7 | 107 | 0.01 |
| Soybean meal | 44 ± 10 | 8 | 134 | 0.0002 | 72 ± 11 | 5 | 83 | 0.02 |
| Skim milk powder | 34 ± 17 | 3 | 99 | 0.19 | 59 ± 21 | 3 | 99 | 0.45 |
| NIH | 63 ± 13 | 8 | 145 | <0.000001 | 91 ± 14 | 5 | 104 | 0.0003 |

*Values are mean ± SD; one-way ANOVA with Scheffé test to determine significance of difference between means. All diets except NIH were modifications of the AIN-76A semi-purified diet for rats and mice^{41,42} as described previously;^{3,43,45} the NIH diet is a mainly (82.5%) plant-based diet.^{41,42} We use the hydrolysed casein (HC) and casein diets as negative control (protective) diets and the NIH diet as the positive control (diabetogenic) diet.

and skim milk powder. Fish meal is not diabetogenic,⁴⁵ while skim milk powder and several other milk products show highly variable, and in general mild diabetogenicity,^{4,8,50} with the mean diabetes incidence and insulinitis frequency not reaching statistical significance (Table III). These findings in the BBdp rat are similar to the overall results of analyses of the cow milk/breast-feeding case-control studies, which also showed a mild effect that was seen in less than half the currently reported studies.^{3,4}

Soybeans. The finding that soy is diabetogenic is supported by several studies using BBdp rats (Figure 1).^{41,49,58} Studies in NOD mice also show that a soymeal diet produced 45% diabetes incidence,⁶⁹ and in one unpublished study, by age 30 weeks 35% of NOD mice fed a soy protein isolate (SPI)-based diet developed diabetes, compared with 50% incidence in animals fed a cereal-based diet.⁴³ There is one other contrasting report that an SPI-based infant formula completely protects low-incidence NOD mice from developing diabetes.⁵⁹

Soybeans are processed extensively to extract soybean oil and protein for food or feeds.⁶¹ The beans are cleaned and heated at 55°C to help remove undesirable "beany" flavours and later heated to 85°C to inactivate enzymes and destroy heat-sensitive soybean trypsin inhibitors; the oil is then extracted using hexane. The resulting defatted soy flakes or soy flour are used to make the high-protein (90%) SPI that is the protein source in soy-based

infant formulas. Therefore, even the relatively crude, soybean meal or soy flake preparations have undergone extensive heating and processing.

The classic Osborne fractionation of (wheat) proteins published in 1907⁶² is based on relative solubilities as follows: albumins are soluble in water; globulins are soluble in salt solutions such as 10% NaCl but insoluble in water; prolamins are soluble in 70-80% alcohol; and glutelins (insoluble in the aforementioned neutral, aqueous conditions but soluble in dilute acids and alkali) and scleroproteins are insoluble in aqueous solvents.⁶²⁻⁶⁵

Soybean proteins consist of two major fractions: the globulin fraction (containing the 15S, 11S, 7S and 2S proteins) which makes up 85% of total protein, and the whey fraction.^{63,67} Much of the albumin fraction is lost in the preparation of soy protein isolates, depending on the method used.⁶³ The 2S globulin protein fraction has been described as the most allergenic of the soy proteins, but these proteins are generally absent from the SPI used in commercial infant formulas.⁶⁷ These processing differences can therefore provide much useful information to help identify and characterize which soy proteins are diabetogenic. The fact that the allergenic 2S protein fraction is missing or reduced in the SPI in infant formulas suggests that (1) soy diabetogens may not be the same as soy allergens, and (2) because SPI- and soy-based infant formulas can retain 50% or more of the diabetogenic activity associated with the crude soybean meal preparation

This rat may have unique immune response. It should not be equated to human in all aspects but shows a test method.

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Please check the question from the October 25, 1999, Federal Register that you want to comment on. You may comment on as many questions as you wish.

Scientific/Safety Issues

- 1. Has FDA's consultation process achieved its intended purpose? Based on experience to date, should this regulatory approach "sunset," continue in its current state, be made mandatory, or otherwise be revised?
- 2. What newly emerging scientific information related to the safety of foods derived from bioengineered plants is there, if any? Are there specific tests which, if conducted on such foods, would provide increased assurance of safety for man or animals consuming these foods?
- 3. What types of food products derived from bioengineered plants are planned for the future? Will these foods raise food safety issues that would require different approaches to safety testing and agency oversight? If so, what are those approaches?

Public Information Issues

- 4. Should FDA's policy requiring labeling for significant changes, including changes in nutrients or the introduction of allergens, be maintained or modified? Should FDA maintain or revise its policy that the name of the new food be changed when the common or usual name for the traditional counterpart no longer applies? Have these policies regarding the labeling of these foods served the public?
- 5. Should additional information be made available to the public about foods derived from bioengineered plants? If so, what information? Who should be responsible for communicating such information?
- 6. How should additional information be made available to the public: e.g., on the Internet, through food information phone lines, on food labels, or by other means?

Please use back of page for additional comments

William von Meyer, Ph.D.
President

Further comment:

The panel meeting I just attended in Chicago was a 3 or 4 day meeting crammed into one afternoon.

Speakers were given 2 minutes who had extensive data while professional panelists had essentially no data and were given several hours.

William von Meyer, Ph.D.
President

1. The FDA consultation process has resulted in the allowance of materials into the food supply which have no chronic health data on the food or the pure material prior to its introduction into the food. Such diseases as diabetes (tests on) via food contact have been omitted completely.

A consultation process should have as its first step meetings with the public and scientists therein to determine what the public's concerns are before the review with a petitioner to sell a product.

Somewhere in the process there has to be a screening out by asking the simple question "do we need this product" and how many people will the untested residues contact for how long etc.

2. Newly emerging information on biotechnology is so large that very frequent public reviews are required where scientists may present data. The peer system represented by such magazines as Science magazine has been corrupted by special interests. The management is close to Monsanto but not the general public concern about eating untested foods. An example of an untested food is rBGH milk where an inquiry by the former Representative Scott Klug showed the milk was not health tested in any animal at all...except tests underway on human in the marketing sector.

New tests which should be carefully implemented on new peptides in foods, particularly enzymes with partial amino acid sequences in common with human enzymes and cell surface proteins, should be on diabetes induction and the result of circulating anti-bodies in the test animals over time. Where do the anti-bodies go (kidney deposition, liver, pancreas etc.) This will decide over time whether or not the material effects diabetes.

3. We have mentioned above that chronic toxicology is being omitted based on the untested hypothesis that because a new plant is derived from wheat (+X protein) that the product is safe. This is wrong, the hypothesis should be "That the new plant is not safe!!!" and then the material is tested to show that it is safe. These tests can not omit diabetes because plant protein has been widely implicated in many animal tests.

We have a glut of corn, wheat, beans and meat in the USA. These circumstances do not demand that we make a bio-engineered plant which is largely untested and then distribute it widely.

resistance to disease
All the ~~pests~~ and yield necessary is already in corn. If we did nothing for 5 years we would not lose a cent in corn.

Fairview Industries, Inc., 2836 Jefferson Dr., Blue Mounds, WI. 53517

We have in Wisconsin alone tens of thousands of set aside acreage if we need more corn or beans etc.

What could be worked on to advantage would be the production of improved industrial and drug crops. These would not require the long food test regimens and thus would give a quicker payback.

4. Concerning labelling, all recombinant foods should be labelled. Anything with a new peptide spot showing up in a 2-D gel electrophoretic pattern, if untested chronically, is a potential health problem. The drug approval scheme requires that contaminant material be defined, the same goes for a plant.

The policy which is unwritten so far is the most troubling. It has been to "avoid all chronic health testing," and in most cases the conductance of 2-D gel electrophoresis on the protein milieu of the products and plants has been avoided and not published.

We are uncertain of all the written policies because we do not have time to study the details of your work. All we see are the occasional review which on materials like rBGH shows large gaps in the data and understanding of the material.

5. Information on the label of all bio-engineered products should list as follows:

max. months tested in one species _____

number of tests on diabetes and cancer _____

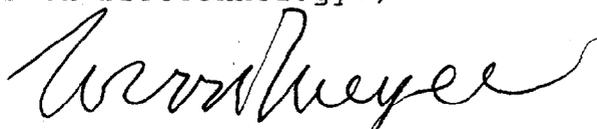
FDA office in the
The state in which the food is made should be responsible for food label enforcement. We can keep an eye on them better here. Also all tests done on a product should be tabulated in a file accessible to the public by test name. Acute/ chronic/ eye damage/ reproduction etc.

6. The phone deal at FDA is lousy. You call there and are given a huge run around. The listing of data should be on the internet and by mail order. The state library should also have a copy of the lists of tests done on each registered food.

Food and water quality are the most important matters which we must maintain at a high level. Accessable data are needed for researchers and doctors, for citizens and the general public.

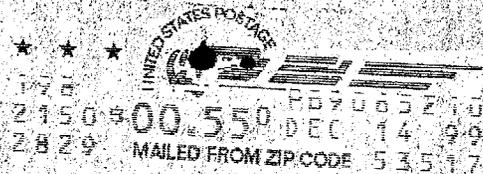
It might interest you to know that while IGF-I reportedly was increased in rBGH milk and being considered of little concern such that rBGH was approved. It was termed myotropin in your drug section and cancelled for reasons of injury to humans (see Barron's magazine articles on biotechnology.)

11-19-99



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