This Committee is being asked whether the increased incidence of mastitis and the potential concomitant increase in antibiotic use in cows treated with Monsanto’s rbGH presents a risk to human health. In my presentation, I would like to examine several key issues that must be addressed in order to answer this question. I will try to show how the Committee’s only possible responsible answer to this question must be that it does pose a risk, and that this risk justifies a decision not to approve Monsanto’s rbGH product, Sometribove.

The first important question is how large is the increase in mastitis that occurs as a result of rbGH use? This morning, the FDA (or CVM) has said that the increase in mastitis rates is 16 cases per hundred cows for (primiparous cows from 21 cases to 37 cases, for control and rbGH-treated cows, respectively), and an increase of 18 cases per hundred cows for multiparous cows (from 36 cases to 54 cases, for control and rbGH-treated cows, respectively). This is, in fact, a very substantial increase. Looked at in another way, the data show a 76% increase in mastitis rates for primiparous cows and a 50% increase for multiparous cows. These data represent significant increases in the mastitis rate from a farmer’s perspective. Yet, the FDA would consider this drug “safe” for cows, because the increase in disease rate is smaller than the seasonal variation.

1Consumers Union is a nonprofit membership organization chartered in 1936 under the laws of the State of New York to provide consumers with information, education and counsel about goods, services, health, and personal finances; and to initiate and cooperate with individual and group efforts to maintain and enhance the quality of life for consumers. Consumers Union’s income is derived solely from the sale of Consumer Reports, its other publications and from noncommercial contributions, grants and fees. In addition to reports on Consumers Union’s own product testing, Consumer Reports, with approximately 5 million paid circulation, regularly carries articles on health, product safety, marketplace economics and legislative, judicial and regulatory actions which affect consumer welfare. Consumers Union’s publications carry no advertising and receive no commercial support.
We think this is a very peculiar interpretation of "safe." Consider the following analogy. Children get ear infections. The rate goes up in winter. A drug comes along that, as a side effect, increases the rate of ear infections in children, but no more than the onset of winter does. Would FDA call it safe? We hardly think so. Would FDA approve it? Possibly, if it had some very significant benefit, like curing leukemia, a cancer, or AIDS, but surely not for, say, easing dandruff.

Let's return to cows. This drug admittedly increases disease rates. So what are its benefits? Is it a cure for cow AIDS (BIV)? No. Is it a cure for any known cow disease? No. What is its benefit? It increases output of an agricultural product that is already in surplus and has been for at least a decade. We see absolutely no justification for tolerating an increase in disease rates for a drug that increases milk production, and that the FDA cannot possibly determine to be safe. We draw the Committee's attention to the regulations spelled out in 21 CFR 514.1 which clearly state that a drug must be safe and effective for its labeled use.

**FDA Understates Mastitis Rates**

We are also seriously concerned that the disease rates FDA views as tolerable are, from evidence we have seen, seriously understated. The real incidence of mastitis in rbGH-treated cows in the trials FDA discusses may be significantly higher than that indicated by FDA this morning. First, the FDA has defined a case of mastitis in such a way that it probably understates the real number of cases. In order to use the poisson regression technique to analyze the data, FDA defined mastitis as the presence or absence of mastitis in an individual cow. In the scientific literature, cases of mastitis usually refer to infected quarters (the cow has 4 separate teats which are not directly connected). Thus, in FDA's analysis, a cow with 4 infected quarters is counted as a single case of mastitis as is a cow with only 1 infected quarter. Given that in a Vermont trial four times as many rbGH-treated cows were treated for mastitis compared to control cows, yet there were over seven times as many cases of mastitis from rbGH-treated cows compared to controls (Pell et al., 1992), we would expect that using infected quarters as a measure of mastitis would reveal an even greater increase than what the FDA data showed.

Furthermore, some scientists believe that milk of an infected cow should be cultured to identify which bacteria are causing the problems and that each bacterial species present represents a separate case of mastitis. Given these problems, we believe that use of the poisson regression technique is not appropriate and that the data should be reanalyzed, treating the number of infected quarters, and the number of different bacterial species (if these data are available), as different cases of mastitis. Until these data (or the data on all the animals) are made public, and the statistical questions answered, we should

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2Furthermore, if the data are taken as number of cases there are statistical questions that need to be asked. Are the data normally distributed? If not, the appropriate data transformation must be applied. Are the data homogeneous, i.e. is there a significant treatment/site interaction? If the answer is no, the data cannot be validly lumped together as FDA has done.
reserve judgement. This Committee should tell FDA that they will not make a decision until the data are reanalyzed in this way.

**European and Vermont Studies Show High Mastitis Rates**

Second, the Committee is not being allowed to review all available data on incidence of mastitis, something we think seriously undermines any conclusions it may reach. At the December, 1990 National Institutes of Health Technical Assessment Meeting on rbST we voiced our concern on the issue of the rbGH-mastitis-antibiotic connection (Hansen, 1990). We also made public copies of a letter sent by the FDA to Monsanto which, in part, outlined serious health impacts for rbGH-treated cows (Lehmann, 1988). With respect to mastitis, the letter stated: "[d]ata presented indicate that there is an increase in mastitis at the levels at which you wish to market bovine somatotropin" (Lehmann, 1988: pg. 6). Further, "[y]ou have not established a margin of safety, nor have you established a no effect level for some of the parameters in your submission. Based on available data, this is particularly true of major clinical entities such as mastitis and reproduction" (Lehmann, 1988: pg. 7). Since this letter sharply contrasted with the then published studies on animal health (such as the OTA report) which claimed little or no adverse health effects, we called on the companies to release all their animal health data for independent scientists to review.

In fact, Monsanto did release some data for independent review. Monsanto conducted a large-scale multi-center trial, involving 8 separate experiments in 4 U.S. states and 4 European countries and some 620 cows. (It is possible that 2 (or 3) of these studies are among the 8 (or 7) discussed by FDA today; however, the other six are from different locations.) The experiments all shared a common randomized controlled design so that the animal health data could potentially be pooled (or lumped together) for a more powerful statistical test. In addition to data on the incidence of mastitis, data on somatic cell counts (SCC)—which are indicative of subclinical cases of mastitis and are basically a measure of dispersed pus cells—were also gathered. Monsanto contractees published their analysis of the data, including SCC data, in 1990 (Peel et al., 1990).

In late 1989 Monsanto sent all the raw SCC data to independent researchers in England who had written a previous paper on the subject for England’s Veterinary Products Committee (Millstone et al., 1989). This represented a truly independent look at all the SCC data from the large multi-center trial. Their reanalysis (Brunner et al., 1997) showed that the SCC data were worse than what the previously published data revealed (Peel et al., 1989). Although the paper was accepted on scientific grounds for publication in a British journal, Monsanto has refused to allow it to be published, claiming that it is confidential information and that it would impair the ability of Monsanto scientists to publish data on these trials (see series of letters). The authors have given me permission to release their study and the letters to this Committee.

The data from these trials raises disturbing implications. First, Millstone and Brunner found that Monsanto consultants had not published all the relevant data. The experiment began 7 weeks after calves were born. The Monsanto-
sanctioned article (Peel et al., 1989) had used the last 2 weeks before the experiment began as their baseline for SCC, and had included data from 28 weeks of treatment with rbGH. However, the raw data sent to Dr. Millstone consisted of data for all 7 weeks before the experiment began and for 43 weeks of treatment with rbGH. Dr. Millstone and Brunner used all the data in their analysis. Since Millstone et al. found that the data were highly positively skewed, they did a log-transformation which greatly reduced the skewness. Using all the data and log-transforming it allowed for greater statistical power in their analysis.

Briefly, Brunner et al. found: i) at 7 of the 8 sites, use of rbGH increased SCC; the effect was statistically significant at 3 sites; ii) the pooled analysis showed that SCC counts were, on average, 19% higher in rbGH-treated cows compared to controls, a highly statistically significant effect (95% confidence interval [C.I.]: 5.8 - 33.9, p = .004); iii) when you control for the covariates (baseline SCC, lactational age and trial site), you get the more accurate estimate for the effect of rbGH of 22.3% (95% C.I.: 12.6 - 32.9, p < .001) over the whole lactation; iv) if we just include the data during the later part of the lactation that were not included in the Monsanto-sponsored publication, i.e. weeks 28-43, the increase in SCCs due to rbGH use is 44.6% (95% CI: 27.1 - 64.5, p < .001).

The Brunner et al. paper clearly demonstrates that previous analyses of SCC data from the multi-center trial had been presented in a way that downplayed the supposed effect of rbGH on somatic cell counts.

Data from a controversial Monsanto-sponsored study done in Vermont, published in December, 1992 (Pell et al., 1992), are also disturbing. This study attracted much attention in Vermont because in October, 1991 the University, under orders from Monsanto, refused to release the animal health data to Vermont's Senate and House Committees on Agriculture. In a December, 1991 letter from the FDA to a Congressional committee, FDA revealed that over 40% of the rbGH-treated cows had to be treated for mastitis, compared to less than 10% of the control cows (9 of 21 rbGH-treated cows vs. 2 of 21 control cows [Holcombe, 1991]. In 1992, Monsanto refused to release the data to the General Accounting Office (GAO).

The results, published in December, 1992, show that during the experiment: i) four times as many rbGH-treated cows (8 vs 2) had to be treated with antibiotics for mastitis compared to untreated cows, ii) more than seven times as many cases of mastitis occurred in rbGH-treated cows compared to untreated cows (29 vs. 4), iii) the average length of treatment for a case of mastitis was almost six times longer in the rbGH-treated cows compared to untreated cows (8.9 days vs. 1.5 days), and iv) more than seven times as much milk, on average, had to be discarded due to mastitis in rbGH-treated cows compared to untreated cows (73 kg vs. 10 kg).

Although the Vermont trial only included 46 cows, the facts that the experiment was completed in 1988, yet not published for four years; that Monsanto refused to give the data to both the Vermont legislature and the GAO, the official watchdog agency for the Congress; that the mastitis related results were quite
disturbing when finally revealed; and that this study was not made available to the Committee; lends credence to the view that the company and the agency are publicly trying to downplay the size and significance of the mastitis problem.

The behavior of Monsanto, vis-a-vis the Vermont study as well as the UK reanalysis of their SCC data, is quite troubling. Clearly, this issue will not be fully resolved until all the mastitis data, both clinical and subclinical, are made publicly available for independent scientific analysis. This committee should demand to see all the mastitis data that FDA has before it renders an opinion on a question as important as that FDA has put before it today.

Illegal Antibiotic Use is Widespread

The next critical issue, beyond the mastitis rate in rbGH-treated cows, is whether the increased disease rates will lead to increased antibiotic residues, and whether these residues will exceed legal limits.

This is not an easy question to answer. FDA has implied that its drug withdrawal times and its testing programs will protect the public from illegal residues. We do not think they do. Let us review the realities of drug use on dairy farms.

According to GAO (GAO, 1992a), up to 82 drugs are known or suspected of being used that may leave residues in milk. Of these, only 30 are actually approved by the FDA for some use on dairy cows. The remainder are used illegally. Some of these are used under the Extra-Label Use Policy. Under this Policy, FDA has said it will not take any enforcement action if a drug is approved for some animal use and it is used under the supervision of a veterinarian. FDA intended that extra-label uses would be rare. But, when GAO talked to several vets who treat dairy cows, the vets said that 40 to 85% of the prescriptions they write are for extra-label use. The GAO further found that the FDA lacks scientific data on the need for extra-label uses, on whether veterinarians have sufficient information to use them properly, and on whether, or to what degree, vets are adhering to the policy (GAO, 1992a).

Drugs are also used in a way that FDA regards as completely illegal. Farmers have easy access to many drugs. FDA inspections during 1990 and 1991 revealed that 62 drugs not approved for use in dairy cows were found on farms. Of these, 42 drugs were not approved for use on any food-producing animal. Farmers’ use of such illegal drugs is extensive according to an FDA official (GAO, 1992a).

Some of these drugs are used illegally to treat mastitis. Most ominously for the deliberations of this Committee, Monsanto even used a number of drugs illegally in their trials. A letter from FDA to Monsanto stated that “[y]ou [Monsanto] should address the use of gentamicin and tetracycline which are not approved for the treatment of mastitis in dairy cattle” (Lehmann, 1988: 5)
Residue Testing is Very Limited

A critical question, therefore, given the widespread use of unapproved drugs in dairy cows, is whether FDA effectively enforces its safety standards for drug residues in milk. Even FDA admits that its policing program is totally inadequate. Of the 82 potential drugs in use, FDA has established tolerances or “safe” levels for 35; for the remainder, the allowable level is therefore legally zero. Yet state agencies routinely test for only 4 of these drugs, all in the penicillin family (i.e. beta-lactams). FDA has recently expanded its own monitoring program. Yet it tests for only 12 drugs, notifies the dairies in advance of the sampling, and analyzes only 500 or so samples per year. On average, that is less than one sample per state per month. Indeed, reliable tests do not exist for more than a dozen drugs.

It is certainly good news that these programs have not detected serious drug residue problems in milk. But what of the 60 to 70 drugs for which no one is doing any testing? Can we assume farmers are always using them in a way that guarantees public safety? If mastitis rates increase by 50%, as FDA suggests, or increase sevenfold, as the Vermont study suggests, will farmers then use drugs in a way that leaves no residues? FDA has not even established withdrawal times for the bulk of the antibiotic and other drugs in use on farms. How can farmers even be expected to know what safe use is, much less to follow such protocols, particularly when there are no penalties for failing to do so?

Consumers Union finds FDA’s lack of control over this situation extremely alarming.

At the very least, this Committee should be looking at quantitative data on the amount of antibiotics used, and the concentrations of these antibiotics in the milk, from control and rbGH-treated cows. In a letter to Health and Human Services Secretary Donna Shalala following up on the GAO 1992 report Recombinant Bovine Growth Hormone: FDA Approval Should be Withheld Until the Mastitis Issue Is Resolved, GAO stated, “[i]f rbGH use does result in increased antibiotic milk concentrations, current withdrawal and withholding requirements may well be inadequate to deal with such considerations. Consequently, without having answered the empirical question of what antibiotic concentrations would occur, the assumption that withdrawal and withholding requirements eliminate the antibiotic food safety concern cannot be made. Simply put, your response did not address our concern: does rbGH use result in higher concentrations of antibiotics in milk or not, and if so, is the higher level acceptable from a food safety standpoint?” (Chelimisky, 1992: 2). The letter concluded “that the increase in mastitis levels reported in the rbGH pivotal studies suggests that the potential for an increase in milk antibiotic levels is very real. The approval of rbGH products should not be forthcoming until the antibiotic risk is validly assessed. The Department’s response suggests that our recommendations have not been seriously addressed” (Chelimisky, 1992: 4).
Given the data before the Committee now, I cannot see how the Committee could possibly conclude that antibiotic residues are certain to stay within legal limits if mastitis rates increase.

**Expertise Needed on Human Health**

The final question the Committee has been asked to consider is whether antibiotic residues that may occur in milk as a result of rbGH use pose a hazard to human health. With all due respect to the Committee, we are concerned about whether its voting members have the expertise to answer this question. We note that there are no medical doctors, especially those specializing in human allergic reactions to antibiotics, on this Committee. I would think the Committee would also need expertise on the problem of the spread of antibiotic resistance associated with increased use of antibiotics, and on antibiotic resistant food-borne infections, in order to responsibly address FDA’s question.

**rbGH Approval Could Hasten the Spread of BSE**

Finally, a potential adverse animal and human health hazard that has not been yet considered by the FDA concerns the change in diet associated with rbGH use. Cows receiving rbGH require more energy-dense food than control cows. One major source of energy-dense food are the protein and energy supplements that come from rendering animals. (Indeed, as a CVM official states in a 1991 memo: “There is a growing trend in the use of meat and bone meal for calf rations ... Most is used as a protein source for high production dairy cattle and for feed lot cattle” (Osborne, 1991: 4)). Use of rbGH will increase the amount of rendered protein fed to dairy cows. We are concerned that some of the rendered animals may be contaminated with bovine spongiform encephalopathy (BSE) or a BSE-like disease, and that rbGH use will accelerate the spread of this disease.

A group of degenerative diseases affecting the central nervous system—particularly the brain, called transmissible spongiform encephalopathies, occur in both human and animals. These diseases have been shown to be transmissible, in part, by eating the meat of infected animals. The group of diseases gets its technical name from the fact that the brains of infected animals develop holes filled with tangled protein fibrils. These diseases have disturbing attributes: long incubation period, invariably fatal, as yet unknown infective agents that are unusually resistant to most forms of sterilization (formaldehyde, 70% alcohol, heat, etc.), and produce no host immune response. A sheep form of the disease, called scrapie, has been known for hundreds of years. A new form of this disease, known technically as bovine spongiform encephalopathy (BSE) and popularly as “mad cow disease” (because the animals act nervous and aggressive and jump around just before dying), appeared in England in 1985. To date, over 80,000 cows have been diagnosed with the disease in England, with more than 880 new cases a week.

Epidemiological work has shown that the cattle most likely acquired the disease by eating scrapie-infested animal protein feed supplements (primarily meat and bone meal), that the lag time between infection and development of
clinical symptoms is between 2-8 years, and that the original infection in Britain probably happened around 2-8 years before the appearance of the first case. Two of the major risk factors that are thought to have contributed to the emergence of the disease are the use of meat and bone meal for up to 4% of the diet of young dairy cows and a change in the rendering process in the early 1980’s. In the early 1980’s, rendering facilities in Britain moved away from the old system of using solvents (such as carbon tetrachloride, hexane, etc.) to extract fat from animal carcasses, followed by heating the mixture to very high temperatures to remove the solvent, and replaced it with a processing step which involves much lower temperatures and no solvents. It has been postulated that the combination of solvents and the high heat killed the infectious agent prior to the start of the early 1980s.

A blue-ribbon panel chaired by Sir Richard Southwood (a famous zoologist and ecologist) released a report in February 1989 (MAFF, 1989) that tried to allay fears by stating that there was no evidence that BSE could infect people, in large part because cows were deemed to be a "dead end host" for the infection, i.e. they couldn’t transmit it to other organisms.

Data reported after the publication of the Southwood report, however, show that cows are not a dead-end host. Mice (Fraser et al., 1988) and pigs (Dawson et al., 1990) experimentally inoculated with BSE developed a spongiform encephalopathy. In 1990, a number of domestic cats (Wyatt et al., 1990) and zoo animals such as eland (Gibson, 1990), puma and cheetah (Walton, 1992) developed spongiform encephalopathies, thought to be due to contaminated feed. In 1992, it was reported that BSE had been successfully transferred to marmosets, sheep and goats (Walton, 1992).

Scientists and government officials tried to stem public panic by saying that there is no evidence that BSE can affect humans. However, as a precautionary measure, feeding of sheep and cow brains and organs to cows and humans was prohibited in England in July 1988 and other European countries where BSE has been confirmed (France, Switzerland, and Ireland). In England, all cows with the disease must be destroyed by incineration, and milk from infected animals is not permitted to be used for human consumption. (The rendering process does not destroy the infective agent.)

Ominously, in a Reuters news report from March 12, 1993, there is a story of an old dairy farmer in England who recently died from Creutzfeldt-Jakob disease (CJD), the human form of spongiform encephalopathy; the farmer had a herd of BSE-infected cattle that had to be destroyed in 1989 and had been drinking milk from the herd for at least seven years. Dr. Fred Shank, Director of FDA’s Center for Food Safety and Applied Nutrition, sent a letter on Nov. 9, 1992 to manufacturers of a dietary supplement asking them to look into their sources of sheep and cow neural and glandular material. FDA had received a complaint from a woman who had come down with CJD, and who had taken a dietary supplement that contained bovine tissue (Food Chemical News, 1992).
Although U.S. officials have said that there are no cases of BSE in this country and that the disease is unlikely to occur here, there are some disturbing developments here. As a national average, 14% of all dead cattle are rendered and end up as protein supplements (Marsh 1992).

In 1985, an outbreak of transmissible encephalopathy (called TME for transmissible mink encephalopathy) was discovered in a mink ranch in Setsonville, Wisconsin (Marsh, 1992). The mink's diet consisted of 95% "downer cow" (cows that die prematurely for unknown reasons) and 5% horse meat. The minks received no sheep meat so scrapie can be ruled out as the infectious agent. It appears that cows were the source of the infectious agent. In an experiment, cows inoculated with TME died of a spongiform encephalopathy (Marsh et al., 1991).

An experiment done in Mission, Texas, found that cattle inoculated with tissue from scrapie-infected sheep also develop a spongiform encephalopathy. However, the symptoms of this spongiform encephalopathy differs slightly from BSE in England. First, rather than exhibiting "mad cow" symptoms, these animal simply keel over and die. This symptomology (apparently healthy looking cows simply dropping dead) is known as "downer cow disease" and is thought due to a number of causes. Second, the brain lesions seen in the Texas experiment are more variable than those seen in England, yet the animals definitely have spongiform encephalopathy. Both the behavioral and morphological traits associated with spongiform encephalopathy in the U.S. would make it much harder to detect. Thus, it appears that a different strain of BSE than the one in England, or a BSE-like disease, could be in some unknown portion of the 100,000 cows that die annually from "downer cow disease" in the United States (Marsh, 1992).

The government has set up a BSE surveillance plan and has looked at some 459 cases of cows that died; none of them were confirmed BSE cases (Walton, 1992). This is not completely reassuring, however, because the surveillance program has a potential flaw: the only two risk categories of cows sampled are rabies-suspect cattle that are rabies negative, and cattle over two years of age that have been given protein supplements for a good part of their diet and have developed signs of neurological disease. Given Marsh's work and the work in Texas, it is possible that the USDA is looking at the wrong population of cows; they need to be sampling "downer cows." Since rendering does not appear to destroy the transmissible agent, and given the fact that authorities are only on the lookout for cows exhibiting "mad cow"-like behavior, the agent causing the spongiform encephalopathy may be spreading through the use of rendered ruminant protein.

In conclusion, at a minimum, we believe the feeding of cows to cows should be discontinued, not expanded. We urge the Committee to recommend that rbGH not be approved on the grounds that it may promote dissemination of BSE, or a BSE-like disease, because cows given rbGH require high-protein feed. We urge Monsanto, on moral grounds, not to sell this product for the same reason. If the moral argument isn't persuasive, perhaps an economic argument would be. Monsanto should consider the possibility that they could be held liable if use of
their product increases the risk of a cow contracting BSE. We note that in England, indemnification costs, paid to the farmers, is running at 1 million pounds a week (Brown, 1993).

Summary

In summary, we believe that the Committee ought to protest the incomplete and inadequate background information FDA has made available to it on mastitis and rbGH. Nevertheless, based on the information at hand, we believe the Committee has no choice but to inform FDA that the drug does present a risk to human health and that there is no reason at all to take that risk.

References


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