Position Paper: Bovine Spongiform Encephalopathy (BSE)

Bovine Spongiform Encephalopathy (BSE) and New Variant Cruetzfeldt-Jakob Disease (nvCJD) — March 1, 2004

Executive Summary

Metagenics has been aware of the BSE problem since 1992 and has introduced strict quality control and quality assurance procedures to reduce the risk of exposure. Metagenics has evaluated all of its bovine-derived materials and its quality control procedures for these materials meet or exceed the regulations established by the FDA and USDA to protect the United States population from BSE.

Bovine Glandular Ingredients

All bovine glandular ingredients used in Metagenics products are required to be certified from a BSE-free country with an accompanying Certificate of Analysis. This Certificate of Analysis is inspected for each batch of ingredient.

Metagenics has obtained its bovine glandular tissues exclusively from New Zealand since 2000. There has never been a case of BSE in New Zealand. Metagenics believes that New Zealand has one of the best BSE prevention programs in the world and the most reliable evidence of herd purity. The rigorous BSE control standards maintained in New Zealand include:

- Strict import controls that have banned cattle from England since 1987 and only allow a few head of carefully selected, closely monitored breeding stock to be imported each year.
- A requirement that only allows feeding of New Zealand cattle by natural grassland grazing or hay and silage (fermented hay). This assures no slaughterhouse animal by-products (SHAB) are present in the cattle feed, which is the source of BSE contamination.

Because bovine neural and optic tissues are the primary sources of BSE contamination, Metagenics discontinued the sale of all neural tissue (e.g., pituitary, hypothalamus, pineal gland) in 2000.

Non-glandular Bovine Ingredients

Although these ingredients are not considered at risk to BSE contamination, as an extra precaution, in 2000 Metagenics instituted a specific BSE prevention quality assurance program for all of its non-glandular bovine ingredients.

Metagenics' microcrystalline hydroxyapatite concentrate (MCHC) from bovine bone has been obtained exclusively from New Zealand cattle since its introduction in 1985. New Zealand is a BSE-free country and Metagenics believes that MCHC from New Zealand is safe for use in food and dietary supplements.

Extensive animal research as well as human data indicates that milk and dairy products do not pose a risk of BSE contamination. Scientific data show that milk and milk products (e.g., whey) are safe regardless of whether the country producing them has had cases of BSE, and that milk does not transmit BSE.

Bovine-derived Gelatin Capsules

Although certain highly processed ingredients such as gelatin are considered not to pose risk of BSE, Metagenics requires that all gelatin capsules used in its products are certified as having met the standards of the (1) 2001 Japanese Ministry of Health Policy for drugs from bovine materials, (2) FDA policy on use of gelatin in FDA-regulated products for human use, and (3) European Parliament 2001 and 2002 regulations for eradication of transmissible spongiform encephalopathies.

The concern of BSE to humans is related to contacting the new variant Creutzfeldt-Jakob (nvCJD) disease by consumption of BSE-contaminated products. Bioassays have shown that in contaminated beef, BSE is present primarily in the brain, spinal cord, retina, and dorsal root ganglia, with possible contamination in distal ileum and bone marrow. Muscle from infected animals is considered an unlikely source of BSE, and BSE has not been identified in dairy products. The overall risk of nvCJD from BSE appears to be quite low; for example, in the UK (the source of the majority of cases today); it is estimated to be at 1 case per 10 billion servings of beef.[1]

The primary countries of concern are certain European countries, in particular the UK, Belgium, France, Germany, Spain and Switzerland. Between 1995 and 2003, a total of 153 cases of nvCJD have been reported in the world. Of these, 143 are from the UK and 8 from other European countries. One case of nvCJD was identified in Canada and 1 in the U.S.; both of these occurred in people who had resided in the UK during the height of the BSE exposures, between 1980 and 1996. For example, the case in the U.S. occurred in a young adult who had grown-up in the UK and moved to the U.S. as a teenager. There have been no cases in New Zealand or in Canadian or U.S. residents without an extensive history of residence in the UK.[2, 3]

On December 23, 2004, the USDA reported a case of BSE in an animal located in the state of Washington.[4] The USDA moved quickly to identify the origination of this animal, locate the 80 original herd members of this animal in the U.S. and Canada, and to recall any bovine products that may have been produced from this animal. As of February 9, 2004, 2000 tons of bovine products have been destroyed, 75000 animals had been inspected, and over 700 have been depopulated from herds in Washington, Oregon, and Idaho. Of these, 255 animals were selected for examination for BSE. All of these animals tested negative for BSE.[5] The USDA has said:

"We feel confident that the remaining animals represent little risk. Even in countries like the UK where the prevalence of BSE has been very high, it is very uncommon to find more than one or maybe two positive animals within a herd."[5]

Furthermore, the USDA and FDA note that this animal was born in Canada on April 9, 1997, and the U.S. FDA's ruminant feed ban, which banned the use of ruminant tissue which is considered the source of BSE infections, from ruminant feed was fully instituted in October 1997. It is considered probable that this animal contacted BSE from feed obtained before the feed ban was in place. Therefore, on January 26, 2004, the FDA has implemented more stringent rules to assure the safety of human food, dietary supplements, and cosmetics. 6 This includes a ban on the use of any tonsils or portions of the small intestine from any bovine animals; banning the use of brain, skull, eyes, and spinal cord from bovine over 30 months; and not allowing the use of any "downer" or "dead" cattle. In addition, mechanically separated beef are

no longer allowed. The FDA is also planning to institute further measures for protection in the next several months.

Metagenics supports the strong steps taken by the FDA and the USDA and will continue their high-level of scrutiny in the use of bovine materials to assure its products are safe for all its customers.

Updated February 2004

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4. FDA Statement: Statement of Probable Case of BSE in Washington State. http://www.,fda.gov/bbs/topics/NEWS/2003/NEW00999.html Accessed Feb. 19, 2004.
5. USDA Statement: Final BSE Update – Monday, February 9, 2004. Release No. 0074.04.
6. U.S. Department of Health and Human Services: News Release: Expanded "Mad Cow" Safeguards Announced to Strengthen Existing Firewalls Against BSE Transmission. http://www.hhs.gov/news/press/2004pres/20040126.html Accessed Feb. 19, 2004

FAQ: Bovine Spongiform Encephalopathy (BSE) and New Variant Cruetzfeldt-Jakob Disease (nvCJD)

What are BSE and TSE?

First diagnosed in 1986 in Great Britain, bovine spongiform encephalopathy (BSE), widely known as "mad cow disease," is a chronic, degenerative disorder affecting the central nervous system of cattle. BSE is part of a class of conditions called transmissible spongiform encephalopathies (TSE), which include scrapie and a chronic wasting disease found in deer and elk. Though about 95 percent of all BSE cases have occurred in the United Kingdom (UK), the disease also has been confirmed in native-born cattle in other European countries such as Belgium, France, Germany, Spain, and Switzerland.

There are six TSE diseases that affect people, all of which are rare and affect fewer than about one case per one million people. The six TSE diseases are: kuru, classical Creutzfeldt-Jakob disease (CJD), new variant Creutzfeldt-Jakob disease (nvCJD), Gerstmann-Staussler-Scheinker syndrome, fatal familial insomnia, and sporadic fatal insomnia.

Why is BSE of concern to humans?

Since its identification, evidence has been accumulating to suggest a causal relationship between BSE and a variant of classical Creutzfeldt-Jakob disease (CJD) called new variant CJD (nvCJD). Both BSE and nvCJD are invariably fatal brain diseases with unusually long incubation periods measured in years. NvCJD appears to differ from classical CJD, which is not related to BSE, by its predominance in younger persons (median age at death around 27 years). NvCJD presents with prominent psychiatric or sensory symptoms with delayed onset of neurologic abnormalities including ataxia within weeks or months, dementia and myoclonus late in the illness and for the duration of illness of at least 6 months, and a diffusely abnormal non-diagnostic electroencephalogram.

How common is new variant Creutzfeldt-Jakob (nvCJD) disease and how many people have been affected by BSE?

As mentioned above, there are many forms of transmissible spongiform encephalopathies (TSE), including all types of CJD, which is the most common form in humans. The Centers for Disease Control and Prevention (CDC) has monitored the trends and incidence of CJD for over the past 20 years by analyzing death certificate information. Only new variant Creutzfeldt-Jakob (nvCJD) has been associated with BSE, and as of February 2004, only one case of nvCJD has been identified in the U.S. This case occurred in a person who had grown up in the UK and moved to the U.S. as a teenager, and it was concluded his BSE contact occurred when he resided in the UK.

Rare cases of non-BSE CJD are noted, which occurs for unknown reasons but may be related to genetic predisposition to the disease. The CDC has documented annual death rates from CJD between 1987 through 1998 as relatively constant at about one case per one million persons, and primarily in people well over the age of 30 years. Cases of CJD in individuals under 30 years of age are extremely rare, and are documented as less than five per one billion people per year. The CDC has published a recent summary of these data.

As of February 5, 2004, a total of 153 definite or probable cases of nvCJD have been reported. This total includes all cases since the first report of nvCJD, which occurred in 1995. The vast majority of these cases are from the UK, with eight cases in other European countries, and only two outside of Europe. Both of the non-European cases have been in individuals who had lived extensively in the UK during the time of the BSE outbreak and it has been concluded these individuals contacted BSE while living in the UK.

How is BSE transmitted?

Transmission of BSE is attributed to infectious agents called prions. Once transmitted, prions affect the brain and spinal cord of cattle, resulting in the development of lesions characterized by sponge-like changes visible with an ordinary microscope. Prions are believed to be proteins that produce damage by inducing an autocatalytic misfolding of specific normal cellular proteins. The result of this misfolding is a change in the protein structure, and the protein is then not able to carry out its function appropriately.

Transmission of BSE to humans is believed to have occurred through the food supply, in which beef products contaminated with BSE from brain tissue were ingested. The specific foods that may have been associated with this transmission of BSE to humans are unknown; however the highest infectivity of BSE is known to be from brain and spinal cord tissue of animals in the final clinical stages of BSE, a time in which the animals are showing signs of BSE.

BSE has not been found in skeletal muscle and it is presumed that any BSE present in animal muscle products (like steak) occurs from contamination with spinal cord tissue.

It has been shown that BSE is not transmitted through milk, even in animals that are positive for BSE and showing clinical signs of BSE. According to the Center for Disease Control and Prevention (CDC), milk and milk products are not believed to pose any risk for transmitting the BSE agent. Milk and milk products are considered

safe and do not present a risk to BSE.

BSE transmission is not known to occur from other animals, such as porcine.

BSE-contaminated food has not been found in the U.S.

The UK Department of Health and other agencies have identified risk factors or characteristics associated with most of the people who have acquired nvCJD that include: residence in the UK; a particular genetic susceptibility; and age of less that 30 years. Studies also show that the infectivity of BSE depends on other factors, such as the nature of the material used, how much is used, and the route of administration. The CDC suggest that travelers to high-risk countries, such as Great Britain, should avoid beef products altogether or select beef products that should have less chance of contamination with BSE, such as solid pieces of muscle meat, to reduce the risk of ingesting BSE-contaminated food.

Can BSE be treated or removed from infected materials?
Prions are highly stable, resisting freezing, drying and heating at normal cooking temperatures, such as those used for pasteurization and sterilization. Since they are not microorganisms, treatments such as antibiotics, which are effective against bacterium, are not effective against prions; but they can be destroyed by stringent sterilization procedures such as strong base solutions and high temperatures. The World Health Organization (WHO) has investigated sterilization procedures for BSE and recommends 1 N sodium hydroxide and autoclaving at 134?C for sterilization, which has been shown effective against BSE. More moderate sterilization procedures such as washing repeatedly with proteinase and detergent solutions, and exposing washed equipment to less harsh chemicals such as 6 M urea or 4 M guanidinium thiocyanate may provide some protection from BSE contamination as well.

Where did BSE come from?
Epidemiological studies conducted in the UK suggest that the source of BSE is cattle feed prepared from carcasses of ruminants infected with BSE. The emergence of BSE corresponds to a change in the rendering process used to produce meat and bone meal feed in the UK, and it is thought that BSE may have been removed or destroyed during processing procedures prior to that time. There is strong evidence and general agreement that the outbreak was amplified by feeding meat and bone meal prepared from cattle to young calves.

The epidemic peaked in January 1993 in the UK, with almost 1,000 new cases in cattle every week, and has been decreasing since the late 1990s. More than 176,000 cases of BSE have been confirmed in the UK overall, but the clear decrease in cases since the late 1990s indicates that the steps taken by the British Government have been effective against the spread of BSE. These steps included a ban on using ruminant protein in feed; removal of high-risk material, such as brain, from animals at the time of slaughter; and a ban on cattle over 30 months of age being used for food. These measures were enacted between 1988 and 1996 and are still in effect today.

What tissues have BSE?
In cattle naturally infected with BSE, high levels of the BSE agent has been found only in the brain tissue, spinal cord, and retina, with lower levels in some portions of

the small intestine and bone marrow.

How is BSE monitored?
Veterinary pathologists confirm BSE by postmortem microscopic examination of brain tissue or by the detection of the infectious prion. BSE is so named because sections of brain tissue from infected cattle display a spongy appearance when examined under a microscope.

What is the risk of getting new variant Creutzfeldt - Jakob disease (nvCJD) from BSE?
The current risk of acquiring nvCJD from eating beef (muscle meat) and beef products produced from cattle in Europe cannot be precisely determined, however in the UK, this current risk appears to be extremely small at about one case per 10 billion servings of beef. In the other countries of Europe, this current risk, if it exists at all, would not be any higher than that in the UK, and in most cases considerably smaller. The U.S. CDC statistics suggest Portugal may harbor a risk similar to the UK, and it is noted as having less experience with implementing the BSE-related public health control measures. In the 12-month period ending June 15, 2000, Portugal had about half the reported incidence of BSE cases per one million adult cattle as that reported in the United Kingdom.

In June 2000, the European Union Commission on Food Safety and Animal Welfare adopted a decision requiring all member states to remove from animal feed and human food chains any materials considered at risk for harboring BSE; such bans had already been instituted in most member states.

Has BSE or new variant Creutzfeldt - Jakob disease (nvCJD) been found in the United States?
The U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) have been active in programs to guard food and drug products in the U.S from BSE contamination. For instance, an active surveillance program for BSE in animals has been in effect since May 1990, and since June 5, 1997, the FDA has prohibited the feeding of bone and meat meal derived from mammals to ruminants. The USDA has examined over 11,700 bovine brain specimens over this time period.

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“We feel confident that the remaining animals represent little risk. Even in countries like the UK where the prevalence of BSE has been very high, it is very uncommon to find more than one or maybe two positive animals within a herd.”10

Furthermore, the USDA and FDA note that this animal was born in Canada on April 9, 1997, and the U.S. FDA’s ruminant feed ban, which banned the use of ruminant tissue which is considered the source of BSE infections, from ruminant feed was fully

instituted in October 1997. It is considered probable that this animal contacted BSE from feed obtained before the feed ban was in place. Therefore, on January 26, 2004, the FDA has implemented more stringent rules to assure the safety of human food, dietary supplements, and cosmetics. This includes a ban on the use of any tonsils or portions of the small intestine from any bovine animals; banning the use of brain, skull, eyes, and spinal cord from bovine over 30 months; and not allowing the use of any “downer” or “dead” cattle. In addition, mechanically separated beef are no longer allowed. The FDA is also planning to institute further measures for protection in the next several months.

As of February 2004, 153 cases of nvCJD have been reported worldwide; of these, all cases were located in Europe with the exception of one case in Canada and one in the U.S. Both the Canada and U.S. cases involved people who had lived in the UK during the height of the BSE exposures, between 1980 and 1996. For example, the case in the U.S. occurred in a young adult who had grown-up in the UK and moved to the U.S. as a teenager. There have been no cases New Zealand or in Canadian or U.S. residents without an extensive history of residence in the UK.

What is Metagenics doing to provide products safe from BSE?

Metagenics maintains the highest quality assurance and quality control standards for its glandular and tissue extract products. Metagenics has implemented quality control procedures to prevent BSE contamination since 1992. This program assured that all our bovine tissue extract ingredients, including glandulars, were purchased only from the countries known to be BSE-free. In 2000, Metagenics further limited its bovine glandular source to exclusively New Zealand cattle, due to New Zealand’s outstanding BSE prevention program and strong evidence of herd purity.

BSE was caused by “cannibalistic” feed practices. That is, feeding “slaughter-house animal by-products” (SHAB) to ruminants. Ruminants consume grasses and other plants. They do not eat other cattle. Feeding SHAB, disguised as feed, to beef cattle was a form of animal cannibalism. Cannibal practices by humans, specifically eating human brain, have resulted in a disease called Kuru. Kuru in humans is very similar to BSE, and produces a similar premature dementia and death in humans as BSE does in cattle. BSE has only occurred in cattle that have been fed SHAB containing feed.

New Zealand has one of the best BSE prevention programs in the world. New Zealand has been diligent in maintaining the health of their bovine herd for over 75 years. They have had laws preventing the importation of cattle from other England since 1987 to avoid transmission of disease form less healthy herds. They have never imported cattle from other countries with cattle suffering from BSE. New Zealand has wisely fed their cattle through the natural practice of grazing their abundant grassland, supplemented by hay and silage. (Silage is fermented hay.) As a result of their pristine environment, abundant grassland and natural grass feed practices; they have one of the healthiest bovine herds in the world. They also have a rigorous autopsy program to monitor the health of their herds and there has never been a case of BSE in New Zealand. Metagenics believes that glandular ingredients from New Zealand are safe for use in food and dietary supplements.

The raw bone concentrate, microcrystalline hydroxyapatite concentrate (MCHC), has only been obtained from New Zealand cattle since the introduction of the product in

1985. Metagenics originally chose New Zealand bovine bone as the source of its MCHC because of the clean environment and absence of lead air pollution. As a result, Metagenics MCHC has one of the lowest levels of lead found in any calcium supplement. Because of New Zealand's rigorous efforts in keeping their bovine herds healthy, Metagenics believes that MCHC from New Zealand is also considered BSE-free and safe for use in food and dietary supplements.

There has been considerable negative publicity surrounding dietary supplements containing neural tissues including brain and pituitary. Therefore in spite of the purity and safety of New Zealand glandulars, Metagenics elected to discontinue the sale of all glandular neural ingredients including pituitary, hypothalamus, pineal and brain in 2000. This decision was made for PR reasons only as the neural tissue concentrates from New Zealand are considered BSE-free and safe for use as foods or dietary supplements.

Furthermore, Metagenics requires that all bovine tissue extracts, including New Zealand glandulars, be documented with a Certificate of Analysis indicating source, as well as a Product Specification Form or Veterinary Health Certificate certifying the cattle are from countries where no evidence of BSE has been found. In addition, whenever appropriate, Metagenics uses non-bovine ingredients for its tissue extracts such as porcine pancreatic enzyme concentrate and porcine duodenal extracts. There has never been a case of BSE in pigs.

Metagenics uses several other types of animal-derived ingredients in some of its products; however, not all of these present a concern of BSE. For instance, as mentioned previously, the CDC indicates that milk and milk products do not pose a risk for transmitting the BSE agent. In addition, the FDA's position is that animal-derived ingredients that are highly processed, such as gelatin used in capsules, are not a risk due to the extreme alkaline and acidic conditions of processing which destroys the prions that cause BSE. As an additional precaution beyond FDA requirements, Metagenics also verifies that its other processed bovine ingredients that are not considered a risk, such as chondroitan sulfate and whey protein are also accompanied with a Certificate of Analysis indicating these ingredients were obtained from animals in countries that are BSE-free, and are from manufacturers who document compliance with published recommendations by the USDA and FDA for prevention of BSE contamination.

The FFDA has set several guidelines for minimizing risk of BSE contamination. Metagenics meets or exceeds these guidelines. In addition, Metagenics investigates all ingredient manufacturers thoroughly, maintains a close relationship with them and requires notification of any changes in procedures or manufacturing of these ingredients. Once ingredients are delivered to our manufacturing facilities, Metagenics maintains the strict quality control for standard of identity of these materials. Appropriate testing to verify the quality and purity of the material is conducted before the material is released for use in Metagenics' products.

Documentation files for every batch of ingredient are carefully maintained to assure quality and purity.

Metagenics continues to improve and upgrade its quality assurance procedures to maintain the highest standards of quality and safety for its products.

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