YEAST DERIVATIVES
Livestock

Executive Summary

Mannan Oligosaccharide was petitioned for use as a questionable synthetic substance allowed for use in organic livestock production. Mannan Oligosaccharide is a yeast derived natural sugar complex. It is used as an alternative livestock medication for the treatment of toxemia. Mannan Oligosaccharides are used to control pathogenic scours of all kinds in livestock caused by salmonella, and E. coli etc. "Enzymes, yeast culture, and microbial cell wall extract containing β1,3-β1,6 D-glucan and Mannan-oligosaccharide are three important natural growth promoters for modern livestock and poultry production. The advantages of these three promoters over the traditional antibiotic growth promoters are 1) no withdrawal time, 2) no residual effect, and 3) no causes of microbial mutation." [1]

Mannan Oligosaccharide is not officially listed anywhere in the NOP final rule. As in section 205.600 of the NOP final rule, "any synthetic substance used as a processing aid or adjuvant will be evaluated against the following criteria: (2) the substance's manufacture, used and disposal do not have adverse effects on the environment and are done in a manner compatible with organic handling." Mannan Oligosaccharide is not explicitly listed in section 205.603 as a synthetic substance, allowed for use in organic livestock production nor is it listed in section 205.604 as a prohibited substance.

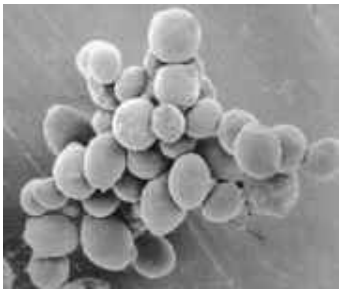
Summary of TAP Reviewer's Analyses[2]

Synthetic/ Nonsynthetic	***Allow without restrictions?***	***Allow only with restrictions? (See Reviewers' comments for restrictions)***
Synthetic (?) Nonsynthetic (?)	Yes No (2)?	Yes (1) No (2)?

Identification
Chemical names: Mannan Oligosaccharide
Other Names: MOS; Bio-Mos

[1] Directly referenced from http://www.cenzone-europe-turkey.com/htm/en/e_yeasture.htm
[2] *This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed by experts on the TAP. The substance is evaluated against the criteria found in section 2119(M) of the OFPA [7 USC 6517(m)]. The information and advice presented to the NOSB is based on the technical evaluation against that criteria, and does not incorporate commercial availability, socio-economic impact, or other factors that the NOSB and the USDA may want to consider in making decisions.*

Characterization



Properties:

"Yeasts are microscopic fungi -- single-cell organisms of the plant kingdom which are generally about 5-10 microns in size." [3]

Natural dry powder

Concentrated MOS Yeast Extract

Ultra Mannan Oligosaccharide: a naturally derived extract from the cell wall of Saccharomyces cerevisiae, is an animal feed ingredient and fermentation additive, with a mannose content of approximately 20% wt/wt basis.

Product Typical Specifications:

Physical form and color: Non-Hydroscopic.....Light brown powder
Particle size (through a 20 mesh screen).....100.0%
Protein..... 30.0%
Ash.....8.0% max.
Moisture.....5.0% max.
Lipid.....5.0% max.
Total plate count.....5000/g max.
Yeast and molds.....100/g max.
Coliforms.....Negative
Salmonella.....Negative(25g)

Typical usage:

Typical usage levels range from 300 to 500 grams/ton/feed.

Benefits and Advantages: Blocking of colonization pathogens [4]

How Made:

[3] Directly referenced from http://www.diamondv.com/articles/booklet/booklet.html
[4] Directly referenced from http://www.ublcorp.com/petfood.html

"M.O.S.500: a naturally derived extract from the cell wall of Saccharomyces cerevisiae, is a food grade ingredient and fermentation additive. The mannan oligosaccharide content is approximately 50% of the carbohydrate fraction." "MOS is a Mannanoligosaccharides derived from the cell wall of the yeast Saccharomyces cerevisiae. Mannan is a sugar recognized by certain bacteria, including many strains of E. coli and salmonella. In the oligosaccharide form however, the mannan is not available for the pathogen to grow. When MOS is added to calf diets, lectins of these pathogens are tricked into attaching to the mannan sugar instead of the carbohydrates attached to the intestinal villi. These lectins are then flushed out without being able to metabolize the sugar, (see diagram) resulting in a "cleansing" effect of the intestinal wall and preventing permanent damage to the villi (finger-like protrusions on the intestinal wall containing sights for nutrient absorption). This allows improved animal performance."[5]

Specific Uses:

"Yeasts (of Saccharomyces cerevisiae) are widely used in Beer and Wine Brewing, Baking of foods such as bread and cookies and in Feeding of humans and animals. It is very important to emphasize that yeast are able to naturally metabolize inorganic minerals into organic forms, similar to what plants do. Plants do the conversion for us taking the minerals from the soil. Mineral enriched yeast do this by taking the minerals from enriched molasses providing one of the best natural food forms of minerals human can consume. Furthermore, yeast has an excellent storage mechanism for B-vitamins, as do other organisms, for factors needed for growth and life. Yeast is a naturally rich source of proteins, minerals and B-complex vitamins. Not only does mineral enriched yeast offer a natural form of mineral, it also provides other nutrients when consumed."[6]

"Besides its excellent nutritional value, yeast or yeast cell walls can also be used as adsorbents for mycotoxins (Gru¨nkemeier, 1990; Bauer, 1994). The in vitro adsorption of ochratoxin by yeast (consisting of 40% sterilized yeast and 60% fermentation residua of yeasts used for beer production)is dependent on the pH being at maximum in acidic solutions (at pH 3: 8.6 mg/g, at pH 8: 1.2 mg/g). However, in trials with pigs employing feed supplement of 5% of yeast, only a slight reduction of the ochratoxin A concentration blood plasma, bile, and tissues was achieved. By the use only of yeast cell walls instead of whole cells, the adsorption of mycotoxins can be enhanced. The cell walls harboring polysaccharides (glucan, mannan), proteins, and lipids exhibit numerous different and easy accessible adsorption centers including different adsorption mechanisms, e.g. hydrogen bonding, ionic, or hydrophobic interaction. Therefore, it was possible to bind2.7 mg zearalenone per gram of cell walls. The binding was rapid and reached equilibrium after only 10 min, which is superior to commercial available clay-based toxin binders (Vo¨ lkl and Karlovsky, 1998, 1999). In another context, it was shown that yeast killer toxins were adsorbed by the polysaccharides and not by the proteins or fatty acids of yeast cell walls (Radler and Schmitt, 1987) and that this adsorption was not unspecific because cellulose and glycogen were not able to bind killer toxins."[7]

"The benefits of MOS are based on specific properties which include modification of intestinal flora, reduction in turnover rate of intestinal mucosa, stimulation of the immune system and selective binding and inactivation of aflatoxin in the intestinal lumen. These properties have the potential to enhance growth rate, feed conversion efficiency and livability in commercial broilers and turkeys and to increase egg production in breeders and table egg flocks." [8]

Action:

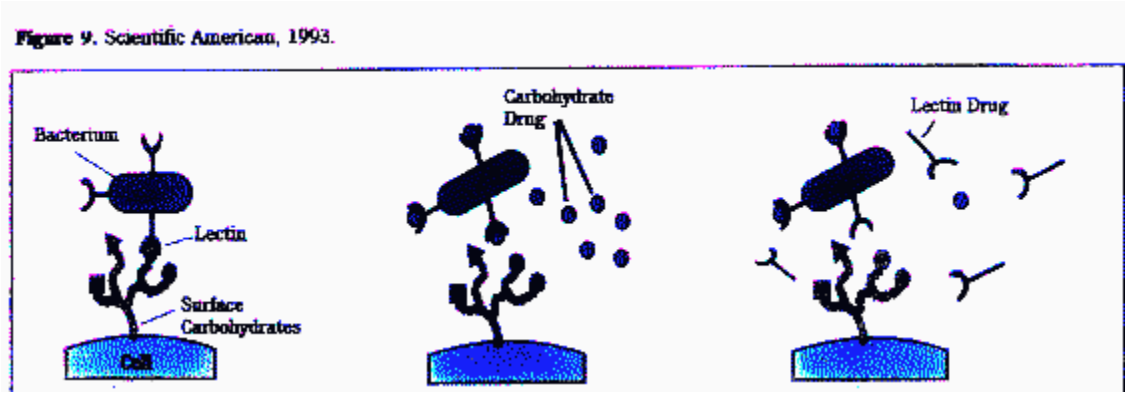
"One mode of action for mannan-based oligosaccharides involves interference with colonization of intestinal pathogens. Cell surface carbohydrates are primarily responsible for cell recognition. At the simplest level is the role of carbohydrates in blood types which are differentiated by cell coat sugars. Bacteria have lectins (proteins or glycoproteins) on the cell surface that recognize specific sugars and allow the cell to attach to that sugar. These sugars can be found on the epithelial cell surface. Binding of Salmonella, Escherichia coli and Vibrio cholera has been shown to be mediated by a mannose-specific

[5] Directly referenced from http://savacaf.com/library/t00144.html
[6] Directly referenced from http://www.nutriteck.com/bulk/mosyeast.html
[7] Directly referenced from http://www.tech.chem.ethz.ch/rysgroup/freimundpdf/toxlet.pdf
[8] Directly referenced from http://www.zootecnica.it/nutrition.html

lectin-like substance on the bacterial cell surface."[9] "Mannan-oligosaccharides are thought to block the attachment of pathogenic bacteria to the animal's intestine and colonization that may result in disease, while acting as a nutrient to other beneficial bacteria. It is also thought to stimulate the animal's immune system, thereby further reducing the risk of disease." [10]

There is an illustration of how MOS works: [11]

Using just 2 grams per feeding in the milk replacer or 2-4 pounds per ton in the calf starter, cost is only $0.01 per feeding or about $0.50 per bag of milk replacer. MOS is an excellent and inexpensive way to naturally improve your calf program.



Active principles (each kg contains)
Yeast cell(Saccharomyces Cerevisiae)
1.5 x 1011 CFU up

INDICATIONS

Dairy Cattle
-More milk production -Longer productive
-Better fiber digestion -Improved feed efficiency
-Higer milk fat -Improved breeding

Beef Cattle
-Improved weight -On-feed faster
-Increased weight -Better breeding
-Better feed efficiency -Improved feed intake

Swine
-Bigger & healthier litters -Improved weaning weight
-Increased No. of a litter -Better feed efficiency
-Increased palatability & feed intake -More pigs weaned
-Increased weight gaining -Better sow milk

Poultry
-Greater egg production -Improved hatchability
-Higher fertility -Improved weight gain
-Better feed efficiency -Fewer checks & cracks

[9] Directly referenced from http://www.nutriteck.com/bulk/mosyeast.html
[10] Directly referenced from http://www.biomatrixinternational.com/prodsheet/ProdSheet%20MOS%20104.pdf
[11] Directly referenced from http://savacaf.com/library/t00144.html

DOSAGE

Dairy Cattle
-Calf:1.5~2.0Kg/Ton of feed
-Lactating cow:1.0~2.5Kg/Ton of feed
-Drying cow:1.0~1.5Kg/Ton of feed

Beef Cattle
-Calf:2.0!2.5Kg/Ton of feed
-Grower:1.5~2.0Kg/Ton of feed
-Finisher:1.0~1.5Kg/Ton of feed

Swine
-Piglet:2.0~2.5Kg/Ton of feed
-Grower, Finisher:1.0~1.5Kg/Ton of feed
-Breeder:2.0~2.5Kg/Ton of feed
-Lactating sow:1.0~1.5/Ton of feed

Poultry
-Layer, Breeder:1.5~2.5Kg/Ton of feed
-Broiler starter:2.0~2.5Kg/Ton of feed
-Grower, Finisher:1.0~1.5Kg/Ton of feed [12]

"Although mannan oligosaccharides (MOS) are not living organisms, they are included in this article because 1) they are derived from yeast cells and 2) they act to reduce pathogenic bacteria in the digestive tract. Mannan oligosaccharides are unique carbohydrates extracted from the outer wall of yeast cells. Pathogenic bacteria, such as E. coli and Salmonella, are attracted to MOS and readily bind with the carbohydrate rather than attaching themselves to the intestinal wall lining. When pathogenic bacteria bind to MOS, they cannot colonize the intestinal tract and instead are excreted with the feces.

In addition to binding pathogens, Bio-Mos trials with calves have shown a statistically significant reduction in respiratory problems. This is appears to be because Bio-Mos modulates the immune system to increase macrophage and immunoglobin activity." [13]

Combinations:

"Comparative feeding and group metabolic trials were conducted on sexed cockerels of ROSS hybrid to study the effect of biologicals containing mannan- oligosaccharides (b_1) and *Enterococcus faecium* M-74 (b_2) and their combinations (b_3) in starters BR1 (a single level of proteins) and in feed mixtures BR2 for broiler production with two levels of proteins (a_0 - 20.85%, a_1 - 18.22%), as exerted on growth, feed consumption and basic nutrient digestibility. The live weight of chickens receiving feed mixtures BR2 with lower protein level (a_1) was lower by 1.28% on day 35, and by 2.53% on day 42, than in group (a_0) with higher protein level. The differences were statistically insignificant. The average live weight of chickens at 21 days of age was higher by 2.3% - 2.2% in experimental groups b_1, b_2, b_3 in comparison with control (b_0). This difference was also statistically insignificant. The group of chickens receiving the combination of mannan-oligosaccharides and *Enterococcus faecium* M-74 showed the live weight higher by 4.44% at the age of 42 days than control (b_0) at ($P < 0.1$). The live weight of chickens was significantly ($P < 0.1$) higher when the bacteria *Enterococcus faecium* M-74 were used in diets BR2. This positive effect of biologicals on chicken weight was determined in diets BR2 with higher and lower protein levels. The statistically significantly ($P < 0.1$) lowest feed consumption per 1 kg of weight gain (expressed in kg) was recorded in the group of chickens (b_3) that received feeds with the combination of mannan-oligosaccharides + *Enterococcus faecium* M-74. The difference against control (b_0) was (- 4.87%) at 35 days of age and (- 4.34%) at 42 days of age. A significant difference ($P < 0.1$) was also calculated for total feed consumption per 1 kg of weight gain for feeding periods 1st to 35th day and 1st to 42 day of chicken age. Biologicals

[12] Directly referenced from http://www.choongangbio.com/eng/probiotics-1.html
[13] Directly referenced from http://www.vigortone.com/probiotics.htm

based on mannan-oligosaccharides and *Enterococcus faecium* M-74 had positive effects on the consumption of BR2 feeds at higher and lower protein levels. The effect of protein levels in BR2 diets on N retention and fiber digestibility coefficient was statistically significant. N retention was higher by 5.61% in groups of chickens receiving BR2 diets with lower protein level (a_1) at ($P < 0.05$). Fiber digestibility of this group was higher by 19.14% at ($P < 0.1$). Statistically significantly higher ($P < 0.05$) N retention (by 5.93%) was determined in the group of chickens receiving feeds with combinations of biologicals containing mannan-oligosaccharides + *Enterococcus faecium* M-74 (b_3) in comparison with control (b_0). Groups (b_2) and (b_3) had statistically significantly higher ($P < 0.1$) coefficients of fiber digestibility against control (b_0): by 13.14% and 14%, respectively. The lower percentage content of proteins in BR2 diets was reflected in lower N output in droppings. N output in groups of chickens receiving feeds with lower protein level (a_1) was lower by 10.03% (in g) against control (a_0). Lower average values of N output in droppings (in g) per 1 kg of weight gain were determined in groups of chickens receiving BR2 diets with the combination of biologicals based on mannan-oligosaccharides + *Enterococcus faecium* M-74 (b_3)."[14]

"Over 30 trials have looked at the ability of MOS to stimulate faster growth rates in calves and have shown positive results varying from 5 to 35% better growth rates. Many of these trials have been carried out on university farms where the challenge is obviously lower and responses are typically lower. However, as the summary of 14 trials with 900 calves below shows, MOS has proven effective even in these cases." [15]

	No. Calves	Days	Control	MOS	Improvement
University of Tenn	48	28	25.24	25.63	10.3%
Institute Animal Nutrition, Poland	24	30 d	32.67	44.24	35.4%
North American Biosciences C.	29	35 d	27.95	37.27	33.3%
North American Biosciences C.	28	35 d	26.06	30.82	18.3%
R&L Veal, Ohio	67	42 d	57.32	64.92	13.2%
Nippei, Japan	17	42 d	59.52	76.94	29.3%
Milk Specialties	240	56 d	47.70	50.70	6.7%
North American Biosciences C.	36	56 d	74.07	78.70	6.3%
Federal University R.G.S.	24	56 d	45.67	53.08	16.2%
California State, Fresno	162	60 d	44.71	56.59	26.6%
University of Sao Paulo	36	60 d	41.03	50.22	22.4%
Continental Grain	96	60	58.33	62.96	7.9%
Colorado State University	53	63 d	63.38	66.53	5.0%
Measurement was based on Total Weight Gain (lbs) Mean Average Improvement					17.1%

Status

Historic Use by Organic Farmers:

"Yeast inclusion has been incorporated in the diet of dairy cattle for more than a half century and the application of it has been dramatically increasing in the past few years. Yeasts used for this purpose are

[14] Directly referenced from http://www.vuvz.cz/old/English/Knihy/oligosachar.htm
[15] Directly referenced from http://savacaf.com/library/t00144.html

either by-products of ethanol fermentation, brewer industry, or the product of aerobic cultivation. Since yeast cells contain a variety of amino acids which occupy more than 40% of the total dry weight, its nutritional value is high. However, since the small quantity of high strength living yeast cells can increase the performance of dairy cattle, yeast should also be considered as a bioregulator.

The benefits of yeast supplements in dairy rations have been:

1) increased milk production,
2) increased milk protein or fat content,
3) improved dry matter intake,
4) increased live weight gain in young calves. Feeding yeast has now become a trend in most dairy farms of western countries.

According to the report of Association of American Feed Control Officials (AAFCO), there are 10 different types of yeast products currently listed as ingredients for animal feeding. The most significant yeast products are living dried yeast, torula dried yeast, brewers dried yeast and yeast culture." [16]

"Oligosaccharides. Fructooligosaccharides (**FOS**) and mannanoligosaccharides (**MOS**) have been the most widely studied oligosaccharides as alternatives to antimicrobials in swine diets. There are relatively few reports detailing the influence of FOS on swine growth performance and gastrointestinal health, and most are reported in preliminary form (20, 40,53, 58, 76). Therefore, this section will focus on the literature concerning the impact of dietary MOS on growth performance and immune function of swine. The most common commercial source of MOS is yeast because MOS comprise approximately 45% of the cell wall of *S.cerevisiae* (88). Thus, many of the inconsistencies in the responses of pigs fed yeast are also prevalent in studies in which pigs were fed MOS. ***Growth performance.*** Dvorak and Jacques (20) reported that weanling pigs fed MOS had greater feed intakes than did pigs fed FOS; however, pigs fed a conventional antimicrobial had greater daily BW gains and feed intakes than pigs fed FOS or MOS. Still, the highest gains were reported for pigs fed MOS in conjunction with the antimicrobial. This suggests that the inclusion of MOS and an antimicrobial in the diet might have additive or synergistic effects on growth performance in weanling pigs. In addition, the combination of *S. faecium* and MOS improved weight gain and fiber digestibility of pigs more than those pigs fed *S. faecium* alone, MOS alone, or the basal diet (20). Similarly, Kim et al. (49) found that BW gain, feed intake, and DM digestibility were greater for weanling pigs fed MOS than for control pigs. Although others have reported improved BW gain and feed efficiency in weanling pigs fed MOS (16, 17, 75), these results are not consistently observed (51, 94). A multi-site study involving three different nurseries found that the improvement in growth performance differed among nurseries (75). This suggests, as is the case with dietary antimicrobials, that other environmental factors (sanitation, disease history, health status of the pigs, etc.) may play a role in the observed improvements, or lack thereof, in growth rate and feed efficiency when weanling pigs are fed MOS. Pettigrew (70) reviewed 17 studies in which weanling pigs were fed MOS and reported that 14 of the studies showed numerical, although small, advantages in growth, feed intake, and feed efficiency. However, the overall response of improved growth rate was 4.4% (70), which is smaller than the 16% average increase in growth when antibiotics are fed (66). Pettigrew (70) concluded that there was not enough evidence to suggest a beneficial effect on growth performance of finishing pigs fed MOS. ***Effects on gut health and immune function.*** Some of the early studies that showed a beneficial effect of MOS on gut health and immune function were conducted in poultry. Oyofo et al. (68) observed that the adherence of *Salmonella typhimurium*to enterocytes of the small intestine of chicks, in vitro, was inhibited in the presence of mannose. Later, they found that inclusion of mannose in the drinking water of chicks reduced *S. typhimurium* colonization of the cecum (67). Plasma levels of IgG and concentrations of IgA in bile were elevated in turkeys fed MOS (78). Furthermore, feeding MOS to chickens improved the morphology of the small intestine, as evidenced by increased Goblet cell numbers, reduced crypt depth, and greater villus width (77). The influence of dietary MOS on gut health and immune function in swine is not as well defined. Trials conducted in Europe indicated that dietary inclusion of MOS enhanced

[16] Directly referenced from http://www.cenzone-europe-turkey.com/htm/en/e_yeasture.htm

immunoglobulin levels in both germfree and conventionally reared (CR) pigs. Furthermore, there was a significant increase in the number of Blymphocytes present in the small intestine of CR pigs fed MOS. In vitro, the proliferation of intestinal lymphocytes and phagocytosis of *Staphylococcus aureus* by macrophages were enhanced in germ-free and CR pigs fed MOS. This result might have been caused by increased levels of the cytokines IL-2 and IFN_ observed in MOS-supplemented pigs (83). Davis et al. (16) reported that inclusion of antimicrobial levels of copper or MOS in the diet had no impact on weanling pig immuno competence as determined by an in vitro lymphocyte proliferation assay. However, a similar study (17) observed an interactive effect between dietary zinc and MOS, where in vitro lymphocyte proliferation was decreased in pigs fed zinc without MOS, but lymphocyte proliferation was increased when pigs were fed diets containing zinc and MOS. Kim et al. (49) observed that pigs fed diets containing MOS had lower CD4+ (helper) T-cell and higher CD8+ (killer) T-cell counts than pigs not fed MOS. As a whole, these studies in poultry and swine suggest that dietary MOS is capable of inhibiting colonization of the gut by certain pathogens; however, the mechanism by which dietary MOS influences the immune system of pigs is not well defined." [17]

"In the early 1990s, a team of Alltech scientists and other researchers discovered that a complex carbohydratephosphorylated mannan oligosaccharide protein (Bio-Mos) isolated from the cell wall of yeast bound certain pathogenic bacteria, such as E. coli and salmonella. Further studies revealed that this yeast-derived oligosaccharide enhanced immunity and improved intestine tissue structure in supplemented animals. The discovery of Bio-Mos was very timely. Growing consumer concern about the development of antibiotic-resistant pathogenic bacteria has caused a ban on the use of feed-grade antibiotics as growth promotors. As a result, poultry producers are searching for alternatives to antibiotics. According to a number of university and field studies, Bio-Mos increases body weight gain and improves feed efficiency of various classes of livestock and poultry." [18]

OFPA, USDA Final Rule:

Mannan Oligosaccharide is not officially listed anywhere in the NOP final rule. As in section 205.600 of the NOP final rule, "any synthetic substance used as a processing aid or adjuvant will be evaluated against the following criteria: (2) the substance's manufacture, used and disposal do not have adverse effects on the environment and are done in a manner compatible with organic handling." Mannan Oligosaccharide is not explicitly listed in section 205.603 as a synthetic substance, allowed for use in organic livestock production nor is it listed in section 205.604 as a prohibited substance.

Regulatory: EPA/NIEHS/Other Sources

FDA:

[Code of Federal Regulations]
[Title 21, Volume **3**]
[Revised as of April 1, 2001]
From the U.S. Government Printing Office via GPO Access
[**CITE**: **21CFR170.3**]

[Page 5-9]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 170--FOOD ADDITIVES--Table of Contents

Subpart A--General Provisions

[17] Directly refereneced from http://www.ansc.purdue.edu/courses/ansc443/PDF/antibioticsub.pdf
[18] Directly refereneced from http://www.alltech-bio.com/alltech%5CAlltech2.nsf/pages/News_The_list_of_positive_results_gets_longer

Sec. 170.**3** Definitions.

For the purposes of this subchapter, the following definitions apply:

(a) Secretary means the Secretary of Health and Human Services.

(b) Department means the Department of Health and Human Services.

(c) Commissioner means the Commissioner of Food and Drugs.

(d) As used in this part, the term act means the Federal Food, Drug, and Cosmetic Act approved June 25, 1936, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392).

(e)(1) Food additives includes all substances not exempted by section 201(s) of the act, the intended use of which results or may reasonably be expected to result, directly or indirectly, either in their becoming a component of food or otherwise affecting the characteristics of food. A material used in the production of containers and packages is subject to the definition if it may reasonably be expected to become a component, or to affect the characteristics, directly or indirectly, of food packed in the container. ``Affecting the characteristics of food'' does not include such physical effects, as protecting contents of packages, preserving shape, and preventing moisture loss. If there is no migration of a packaging component from the package to the food, it does not become a component of the food and thus is not a food additive. A substance that does not become a component of food, but that is used, for example, in preparing an ingredient of the food to give a different flavor, texture, or other characteristic in the food, may be a food additive.

(2) Uses of food additives not requiring a listing regulation. Substances used in food-contact articles (e.g., food-packaging and food-processing equipment) that migrate, or may be expected to migrate, into food at such negligible levels that they have been exempted from regulation as food additives under Sec. 170.39.

(f) Common use in food means a substantial history of consumption of a substance for food use by a significant number of consumers.

(g) The word substance in the definition of the term ``food additive'' includes a food or food component consisting of one or more ingredients.

(h) Scientific procedures include those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance.

(i) Safe or safety means that there is a reasonable certainty in the minds of

[[Page 6]]

competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

(1) The probable consumption of the substance and of any substance formed in or on food because of its use.

(2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.

(**3**) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

(j) The term nonperishable processed food means any processed food not subject to rapid decay or deterioration that would render it unfit for consumption. Examples are flour, sugar, cereals, packaged cookies,

and crackers. Not included are hermetically sealed foods or manufactured dairy products and other processed foods requiring refrigeration.

(k) General recognition of safety shall be determined in accordance with Sec. 170.30.

(l) Prior sanction means an explicit approval granted with respect to use of a substance in food prior to September 6, 1958, by the Food and Drug Administration or the United States Department of Agriculture pursuant to the Federal Food, Drug, and Cosmetic Act, the Poultry Products Inspection Act, or the Meat Inspection Act.

(m) Food includes human food, substances migrating to food from food-contact articles, pet food, and animal feed.

(n) The following general food categories are established to group specific related foods together for the purpose of establishing tolerances or limitations for the use of direct human food ingredients. Individual food products will be included within these categories according to the detailed classifications lists contained in Exhibit 33B of the report of the National Academy of Sciences/National Research Council report, ``A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe'' (September 1972), which is incorporated by reference. Copies are available from the National Technical Information Service (NTIS), 5285 Port Royal Rd., Springfield, VA 22161, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408:

(1) Baked goods and baking mixes, including all ready-to-eat and ready-to-bake products, flours, and mixes requiring preparation before serving.

(2) Beverages, alcoholic, including malt beverages, wines, distilled liquors, and cocktail mix.

(**3**) Beverages and beverage bases, nonalcoholic, including only special or spiced teas, soft drinks, coffee substitutes, and fruit and vegetable flavored gelatin drinks.

(4) Breakfast cereals, including ready-to-eat and instant and regular hot cereals.

(5) Cheeses, including curd and whey cheeses, cream, natural, grating, processed, spread, dip, and miscellaneous cheeses.

(6) Chewing gum, including all forms.

(7) Coffee and tea, including regular, decaffeinated, and instant types.

(8) Condiments and relishes, including plain seasoning sauces and spreads, olives, pickles, and relishes, but not spices or herbs.

(9) Confections and frostings, including candy and flavored frostings, marshmallows, baking chocolate, and brown, lump, rock, maple, powdered, and raw sugars.

(10) Dairy product analogs, including nondairy milk, frozen or liquid creamers, coffee whiteners, toppings, and other nondairy products.

(11) Egg products, including liquid, frozen, or dried eggs, and egg dishes made therefrom, i.e., egg roll, egg foo young, egg salad, and frozen multicourse egg meals, but not fresh eggs.

(12) Fats and oils, including margarine, dressings for salads, butter, salad oils, shortenings and cooking oils.

(13) Fish products, including all prepared main dishes, salads, appetizers,

[[Page 7]]

frozen multicourse meals, and spreads containing fish, shellfish, and other aquatic animals, but not fresh fish.

(14) Fresh eggs, including cooked eggs and egg dishes made only from fresh shell eggs.

(15) Fresh fish, including only fresh and frozen fish, shellfish,

and other aquatic animals.

(16) Fresh fruits and fruit juices, including only raw fruits, citrus, melons, and berries, and home-prepared ``ades'' and punches made therefrom.

(17) Fresh meats, including only fresh or home-frozen beef or veal, pork, lamb or mutton and home-prepared fresh meat-containing dishes, salads, appetizers, or sandwich spreads made therefrom.

(18) Fresh poultry, including only fresh or home-frozen poultry and game birds and home-prepared fresh poultry-containing dishes, salads, appetizers, or sandwich spreads made therefrom.

(19) Fresh vegetables, tomatoes, and potatoes, including only fresh and home-prepared vegetables.

(20) Frozen dairy desserts and mixes, including ice cream, ice milks, sherbets, and other frozen dairy desserts and specialties.

(21) Fruit and water ices, including all frozen fruit and water ices.

(22) Gelatins, puddings, and fillings, including flavored gelatin desserts, puddings, custards, parfaits, pie fillings, and gelatin base salads.

(23) Grain products and pastas, including macaroni and noodle products, rice dishes, and frozen multicourse meals, without meat or vegetables.

(24) Gravies and sauces, including all meat sauces and gravies, and tomato, milk, buttery, and specialty sauces.

(25) Hard candy and cough drops, including all hard type candies.

(26) Herbs, seeds, spices, seasonings, blends, extracts, and flavorings, including all natural and artificial spices, blends, and flavors.

(27) Jams and jellies, home-prepared, including only home-prepared jams, jellies, fruit butters, preserves, and sweet spreads.

(28) Jams and jellies, commercial, including only commercially processed jams, jellies, fruit butters, preserves, and sweet spreads.

(29) Meat products, including all meats and meat containing dishes, salads, appetizers, frozen multicourse meat meals, and sandwich ingredients prepared by commercial processing or using commercially processed meats with home preparation.

(30) Milk, whole and skim, including only whole, lowfat, and skim fluid milks.

(31) Milk products, including flavored milks and milk drinks, dry milks, toppings, snack dips, spreads, weight control milk beverages, and other milk origin products.

(32) Nuts and nut products, including whole or shelled tree nuts, peanuts, coconut, and nut and peanut spreads.

(33) Plant protein products, including the National Academy of Sciences/National Research Council ``reconstituted vegetable protein'' category, and meat, poultry, and fish substitutes, analogs, and extender products made from plant proteins.

(34) Poultry products, including all poultry and poultry-containing dishes, salads, appetizers, frozen multicourse poultry meals, and sandwich ingredients prepared by commercial processing or using commercially processed poultry with home preparation.

(35) Processed fruits and fruit juices, including all commercially processed fruits, citrus, berries, and mixtures; salads, juices and juice punches, concentrates, dilutions, ``ades'', and drink substitutes made therefrom.

(36) Processed vegetables and vegetable juices, including all commercially processed vegetables, vegetable dishes, frozen multicourse vegetable meals, and vegetable juices and blends.

(37) Snack foods, including chips, pretzels, and other novelty snacks.

(38) Soft candy, including candy bars, chocolates, fudge, mints, and other chewy or nougat candies.

(39) Soups, home-prepared, including meat, fish, poultry, vegetable, and combination home-prepared soups.

(40) Soups and soup mixes, including commercially prepared meat, fish, poultry, vegetable, and combination soups and soup mixes.

(41) Sugar, white, granulated, including only white granulated sugar.

[[Page 8]]

(42) Sugar substitutes, including granulated, liquid, and tablet sugar substitutes.

(43) Sweet sauces, toppings, and syrups, including chocolate, berry, fruit, corn syrup, and maple sweet sauces and toppings.

(o) The following terms describe the physical or technical functional effects for which direct human food ingredients may be added to foods. They are adopted from the National Academy of Sciences/ National Research Council national survey of food industries, reported to the Food and Drug Administration under the contract title ``A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe'' (September 1972), which is incorporated by reference. Copies are available from the National Technical Information Service (NTIS), 5285 Port Royal Rd., Springfield, VA 22161, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW., suite 700, Washington, DC 20408:

(1) ``Anticaking agents and free-flow agents'': Substances added to finely powdered or crystalline food products to prevent caking, lumping, or agglomeration.

**(2) ``Antimicrobial agents'':** Substances used to preserve food by preventing growth of microorganisms and subsequent spoilage, including fungistats, mold and rope inhibitors, and the effects listed by the National Academy of Sciences/National Research Council under ``preservatives.''

(**3**) ``Antioxidants'': Substances used to preserve food by retarding deterioration, rancidity, or discoloration due to oxidation.

(4) ``Colors and coloring adjuncts'': Substances used to impart, preserve, or enhance the color or shading of a food, including color stabilizers, color fixatives, color-retention agents, etc.

(5) ``Curing and pickling agents'': Substances imparting a unique flavor and/or color to a food, usually producing an increase in shelf life stability.

(6) ``Dough strengtheners'': Substances used to modify starch and gluten, thereby producing a more stable dough, including the applicable effects listed by the National Academy of Sciences/National Research Council under ``dough conditioner.''

(7) ``Drying agents'': Substances with moisture-absorbing ability, used to maintain an environment of low moisture.

(8) ``Emulsifiers and emulsifier salts'': Substances which modify surface tension in the component phase of an emulsion to establish a uniform dispersion or emulsion.

(9) ``Enzymes'': Enzymes used to improve food processing and the quality of the finished food.

(10) ``Firming agents'': Substances added to precipitate residual pectin, thus strengthening the supporting tissue and preventing its collapse during processing.

(11) ``Flavor enhancers'': Substances added to supplement, enhance, or modify the original taste and/or aroma of a food, without imparting a characteristic taste or aroma of its own.

(12) ``Flavoring agents and adjuvants'': Substances added to impart or help impart a taste or aroma in food.

(13) ``Flour treating agents'': Substances added to milled flour, at the mill, to improve its color and/or baking qualities, including bleaching and maturing agents.

(14) ``Formulation aids'': Substances used to promote or produce a desired physical state or texture in food, including carriers, binders, fillers, plasticizers, film-formers, and tableting aids, etc.

(15) ``Fumigants'': Volatile substances used for controlling insects or pests.

(16) ``Humectants'': Hygroscopic substances incorporated in food to promote retention of moisture, including moisture-retention agents and antidusting agents.

(17) ``Leavening agents'': Substances used to produce or stimulate production of carbon dioxide in baked goods to impart a light texture, including yeast, yeast foods, and calcium salts listed by the National Academy of Sciences/National Research Council under ``dough conditioners.''

(18) ``Lubricants and release agents'': Substances added to food contact surfaces to prevent ingredients and finished products from sticking to them.

[[Page 9]]

(19) ``Non-nutritive sweeteners'': Substances having less than 2 percent of the caloric value of sucrose per equivalent unit of sweetening capacity.

(20) ``Nutrient supplements'': Substances which are necessary for the body's nutritional and metabolic processes.

(21) ``Nutritive sweeteners'': Substances having greater than 2 percent of the caloric value of sucrose per equivalent unit of sweetening capacity.

(22) ``Oxidizing and reducing agents'': Substances which chemically oxidize or reduce another food ingredient, thereby producing a more stable product, including the applicable effect listed by the National Academy of Sciences/National Research Council under ``dough conditioners.''

(23) ``pH control agents'': Substances added to change or maintain active acidity or basicity, including buffers, acids, alkalies, and neutralizing agents.

(24) ``Processing aids'': Substances used as manufacturing aids to enhance the appeal or utility of a food or food component, including clarifying agents, clouding agents, catalysts, flocculents, filter aids, and crystallization inhibitors, etc.

(25) ``Propellants, aerating agents, and gases'': Gases used to supply force to expel a product or used to reduce the amount of oxygen in contact with the food in packaging.

(26) ``Sequestrants'': Substances which combine with polyvalent metal ions to form a soluble metal complex, to improve the quality and stability of products.

(27) ``Solvents and vehicles'': Substances used to extract or dissolve another substance.

(28) ``Stabilizers and thickeners'': Substances used to produce viscous solutions or dispersions, to impart body, improve consistency, or stabilize emulsions, including suspending and bodying agents, setting agents, jellying agents, and bulking agents, etc.

(29) ``Surface-active agents'': Substances used to modify surface properties of liquid food components for a variety of effects, other than emulsifiers, but including solubilizing agents, dispersants, detergents, wetting agents, rehydration enhancers, whipping agents, foaming agents, and defoaming agents, etc.

(30) ``Surface-finishing agents'': Substances used to increase palatability, preserve gloss, and inhibit discoloration of foods, including glazes, polishes, waxes, and protective coatings.

(31) ``Synergists'': Substances used to act or react with another food ingredient to produce a total effect different or greater than the sum of the effects produced by the individual ingredients.

(32) ``Texturizers'': Substances which affect the appearance or feel of the food.

[42 FR 14483, Mar. 15, 1977, as amended at 47 FR 11835, Mar. 19, 1982; 53 FR 16546, May 10, 1988; 54 FR 24896, June 12, 1989; 60 FR 36595, July 17, 1995]

EPA:

"EPA registers and regulates antimicrobial pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). To obtain registration, manufacturers of antimicrobial products must meet the basic standards, the foremost being: 1) that the product will not cause unreasonable adverse effects to human health or the environment, and 2) that product labeling and composition comply with the requirements of FIFRA. Moreover, manufacturers are required to submit to EPA detailed and specific information concerning the chemical composition of their product; effectiveness data to document their claims against specific microorganisms and to support the directions for use provided in labeling; labeling that reflects the required elements for safe and effective use; and toxicology data to document any hazards associated with use of the product.

Recently, increased concern has emerged regarding whether public health products used to kill microorganisms pathogenic to man on inanimate surfaces and objects in hospitals, schools, restaurants, and homes work as claimed on the label. The private and public sector communities, including competitor registrants, have made the Agency aware of sterilizers and hospital disinfectants which may be ineffective. EPA has responded to this situation by developing a comprehensive strategy to improve the regulation of antimicrobial pesticides

Since public health products are crucial for infection control, and because of the increased controversy regarding product effectiveness, the Agency is conducting pre-registration confirmatory and post-registration enforcement testing of certain public health products. More specifically, EPA has entered into an Interagency Agreement with the FDA, and is jointly testing all sterilants except gases (registered and those seeking registration) and registered products which make unsubstantiated claims of controlling the bacterium which causes tuberculosis (including sterilants and hospital disinfectants). These two types of public health products are the most crucial to infection control and their failure could pose grave danger to the public and the medical community.

Furthermore, EPA has greatly improved communications with the public, all levels of government, academia, user communities, industry, health professionals, trade organizations, and independent testing groups. Also, EPA has committed funds to ensure that the tests used to demonstrate the efficacy of antimicrobial products are reliable and reproducible; is in the process of developing a complaint system to handle concerns regarding ineffective products; amplified internal controls to ensure the integrity of data submitted by registrants; and is currently publishing a quarterly newsletter designed to educate the general public about the status and direction of the regulation of antimicrobial products. The Agency is actively working to ensure that all antimicrobial products sold and distributed in the marketplace are effective in protecting public health and the environment from potential health risks." [19]

Status Among U.S. Certifiers

Oregon does not have specific limitations on materials used for crops and livestock. If the materials comply with USDA regulations, they are deemed acceptable for use in the state of Oregon. (Contact- Ron McKay) [20]

[19] Information was referenced from http://www.epa.gov/pesticides/citizens/antimic.htm#regulation

[20] Information was referenced from a phone interview with Ron McKay, State Certifier, June 5, 2002.

Pennsylvania is in accordance with guidelines proposed by OMRI.
(Contact- Martha Melton- state certifier) [21]

Minnesota does not have specific limitations on materials used for crops and livestock. If the materials comply with USDA regulations, they are deemed acceptable for use in the state of Minnesota. (Contact- Mary Hanks- state certifier) [22]

International

IFOAM: not specifically mentioned in approved list [23]
JAPAN: not specifically mentioned in approved list [24]
EUROPEAN UNION: not specifically mentioned in approved list [25]

News

June 1, 2001

Yeast culture receives EU approval

Alltech's **Yea-Sacc^{1026}** is the only yeast culture to gain European Union approval as a performance-enhancing yeast additive for dairy cows, fattening cattle, and calves. The Standing Committee for Animal Nutrition (SCAN) granted the approval.

The approval is in accordance with EU Council Directive 70/524/EEC (Council Regulation No 937/2001 of May 11, 2001). Alltech developed Yea-Sacc^{1026} from a naturally-occurring strain of *Saccharomyces cerevisiae* yeast. In the early 1980s, Alltech researchers observed that this particular strain of yeast had beneficial effects on rumen function and cattle performance. Because yeast has been safely used in human food for many years, its inclusion in animal feed is acceptable to consumers. [26]

Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

1. ***The potential of the substance for detrimental interactions with other materials used in organic farming systems.***

"Saccaromyces cerevisiae is one of the highly resistant bug[s]. **It neither get[s] interfered nor interferes with the activity of antibiotics.** It's a strain of Yeast, which releases the mannaoligosaccarides through its cell wall. MOS having mannan sugar can preferentially bind to bacterial lectins before they get attached to surface carbohydrates of Gut epithelia and literally carry them out of the gut. Hence, pathogens pass through the gut without getting colonized. It is a classic competitive exclusion. Several pathogenic E-coli and Salmonella sp. possess lectins which are specific to mannos and hence gets bound by MOS. Apart from that Yeast provides certain cofactors which are beneficial to birds. In addition, they are also proved to bind Mycotoxins present in feed." [27]

2. ***The toxicity and mode of action of the substance and of its break down products or any contaminants, and their persistence and areas of concentration in the environment.***

"Mannan oligosaccharide (MOS) is derived from the cell wall of *Saccharomyces cerevisiae* and is commercially available as a feed supplement which is included in diets as a GRAS (generally regarded as safe) compound." [28] "The yeast product is similarly called "MOS", the acronym MOS standing for mannanoligosaccharide (an oligosaccharide is a polysaccharide which is only 3-10 sugar molecules long instead of hundreds of molecules, suggesting that it is a short chain mannan). When these short-chained

[21] Information was referenced from a phone interview with Martha Melton, State Certifier, June 5, 2002
[22] Information was referenced from a phone interview with Mary Hanks, State Certifier, June 12, 2002
[23] Directly referenced from http://www.ifoam.org/standard/ibs_final02.html
[24] Directly referenced from http://www.fas.usda.gov/gainfiles/200004/25647377.pdf
[25] Directly referenced from http://www.foodstandards.gov.uk/multimedia/pdfs/elist_numbers.pdf
[26] Directly referenced from http://www.alltech-bio.com/alltech%5CAlltech2.nsf/pages/News_Yeast_culture_receives_EU_approval
[27] Directly referenced from http://www.vetcareindia.com/probiotics_poultry.htm
[28] Directly referenced from http://www.zootecnica.it/nutrition.html

mannans are fed, they are not digested by the animal, but are consumed by select bacteria in the gut which grow rapidly and have a probiotic effect against bad bugs." [29]

3. The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.

The probability of environmental contamination during use, misuse, or disposal of polysaccharides and carbohydrates is unlikely. There are no advisable conditions to avoid and both polysaccharides and carbohydrates decompose into CO and CO2. CO will pose health risks but CO2 will not.

==========

Fire and Explosion Hazard Data

==========

Flash Point Method: CC
Extinguishing Media: USE EXTINGUISHING MEDIA APPROPRIATE FOR SURROUNDING FIRE.
Special Fire Fighting Proc: WEAR PROPER PROTECTIVE EQUIPMENT & SELF CONTAINED BREATHING APPARATUS W/FULL FACEPIECE OPERATED IN POSITIVE PRESSURE MODE.
Unusual Fire And Expl Hazrds: NONE

==========

Reactivity Data

==========

Stability: YES
Cond To Avoid (Stability): AIR, LIGHT
Materials To Avoid: STRONG OXIDIZING AGENTS
Hazardous Decomp Products: CO, CO2
Hazardous Poly Occur: NO
Conditions To Avoid (Poly): NONE

==========

==========

Health Hazard Data

==========

LD50-LC50 Mixture: ORAL LD50(RAT): 518 MG/KG (SEE SUPP)
Route Of Entry - Inhalation: NO
Route Of Entry - Skin: NO
Route Of Entry - Ingestion: NO
Carcinogenicity - NTP: NO
Carcinogenicity - IARC: NO
Carcinogenicity - OSHA: NO
Explanation Carcinogenicity: NONE
Emergency/First Aid Proc: INGESTION: IF CONSCIOUS, IMMEDIATELY GIVE LARGE AMOUNTS OF WATER. INHALATION: REMOVE TO FRESH AIR. SKIN: IMMEDIATELY WASH W/PLENTY OF SOAP & WATER FOR 15 MINS. EYES: IMMEDIATELY FLUSH W/PLENTY OF WATER FOR 15 MINS. OBTAIN MEDICAL ATTENTION IN ALL CASES.

==========

==========

Precautions for Safe Handling and Use

==========

Steps If Matl Released/Spill: WEAR SUITABLE PROTECTIVE CLOTHING. CAREFULLY SWEEP UP & REMOVE.
Waste Disposal Method: DISPOSE OF IN ACCORDANCE W/LOCAL, STATE & FEDERAL REGULATIONS.

[29] Directly referenced from http://www.diamondv.com/articles/booklet/booklet.html

Precautions-Handling/Storing: KEEP CONTAINER TIGHTLY CLOSED. SUITABLE FOR ANY GENERAL CHEMICAL STORAGE AREA. STORE IN LIGHT-RESISTANT CONTAINERS. Other Precautions: WHEN HANDLING LIQUID PRODUCTS, SECONDARY PROTECTIVE CONTAINERS MUST BE USED FOR CARRYING. HANDLING OF MATERIAL SHOULD BE BY A PERSON TRAINED IN/SUPERVISED BY A PERSON TRAINED IN, CHEMICAL HANDLING. AVOID BREATHING DUST & SKIN/EYE CONTACT. [30]

4. The effects of the substance on human health.

"Several species have proven very beneficial to man, while a few imperfect yeasts are known to be pathogenic. But, most yeasts are benign saprophytes and have proven neither useful nor harmful to man or animal. Yeasts are a good source of protein or amino acids. Approximately 40% of the weight of dried yeast consists of protein. The quality of yeast protein is excellent for a vegetable protein and it is about equivalent in quality to soybean protein. Both are rich in lysine, and are excellent supplements to cereals, whose proteins are generally low in lysine. As with other plant proteins, yeast protein is low in the sulfur amino acids, but supplementing dried yeast with 0.5% methionine can raise its protein quality up to that of casein. However, there is a limit to how much yeast can be fed, because about 20% of the crude protein nitrogen in yeast is in the form of nucleic acids. Nucleic acids can cause problems if over fed, because excessive nucleic acid intake results in elevated uric acid levels in the blood. High levels of uric acid tend to crystallize in the joints and in man and this can cause gout and arthritis or even renal stones. " [31]

"Prion is an infectious agent represented by conformationally changed form of a cellular protein. Prions self-propagate, since the prion form of a protein induces conversion of a normal protein into the non-functional prion form. Thus prions are nonMendelian genetic determinants of protein nature. Prion proteins cause some neurodegenerative diseases in vertebrates such as Creutzfeldt-Jakob and GerstmannStreussier-Scheinker diseases in humans and mad cow disease in cattle. Recently two cytoplasmically inherited determinants in Saccharomyces yeast were suggested to be prion-like proteins (Wickner,1994). One of them the [PSI] factor, an omnipotent cytoplasmic nonsense suppressor, is the subject of this proposal. The [PSI] factor has been proposed to be a prion form of Sup35p(eRF3), release factor protein, encoded by the SLTP35 gene. According to this model Sup35p prion-like isoform is only present in [PSI+] strains, where it converts Sup35p into the prion conformation. It is known that the N-terminal domain of Sup35p consisting of 254 amino- acids contains the peptide which is required for [PSI+] maintenance but is not required for release factor function (TerAvanesyan ..., Inge-Vechtomov et. al., 1993- Ter-Avanesyan et. al., 1994). It was shown that overproduction of this domain is sufficient for [PSI+] induction (Derkatch,..., IngeVechtomov, Liebman, in preparation). The finding that the "prion-inducing domain" of SUP35, like that of the other yeast prion Ure2, is in the N-terminus and is distinct from the functional domain of the protein, suggests that such a chimeric organization may be a common feature of prion-like elements. We propose to study the specificity of prionization by 1) making fusions of the eRF3 N-terminal extension with other proteins; 2) investigating the possibility of the Pichia methanolica Sup35p prionization after introduction of P.methanolica SUP35 gene into S.cerevisiae cells; ' 3) identifying other components of yeast genome involved into the genetic control of SUP35 expression and [PSI] factor induction and maintenance. The aim of the work is to elucidate the biological significance of prionization effect that could be a mechanism of regulation of protein activity." [32]

5. The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms(including the salt index and solubility of the soil), crops and livestock.

"There are a number of mechanisms for poultry to exclude pathogenic organisms from their gastrointestinal tract. High acidity, antibodies, digestive enzymes, peristalsis and mucous secretion can breakdown or flush microbes from the system. However, pathogens have developed ways to deal with the latter two mechanisms. Some bacteria have overcome peristalsis and mucous secretion by attaching directly to the

[30] Directly referenced from http://msds.pdc.cornell.edu/msds/siri/msds/h/q319/q266.html
[31] Directly referenced from http://www.diamondv.com/articles/booklet/booklet.html
[32] Directly referenced from http://www.crdf.org/Abstracts/fund/RB1238.html

host's intestinal epithelial cells. Bacteria cells typically have fimbriae, which they use to attach to the host's gut cells giving them resistance from being removed and an opportunity to colonize. Host epithelial cells have "antennae" of oligosaccharides sticking out into the lumen of the gut and bacterial fimbriae are specific for some types of oligosaccharides. Once bacteria are attached, temperature and nutrients within the gut favour their proliferation. Oligosaccharides are a class of carbohydrates, strings or chains of simple sugar compounds 3-6 units long. They are an integral component of cell walls found in many species including birds and often function as receptors or have cell recognition factors. Individual sugars that make up the chains include mannose (mannanoligosaccharide), arabinose, galactose and others. Host epithelial cell membranes are rich in mannanoligosaccharides (MOS) so the question is raised as to whether or not feeding MOS to birds will prevent bacterial colonization of the intestines. Studies suggest that giving MOS via drinking water to birds can reduce *Salmonella enterititidis* colonization, however MOS is not readily digested and microbes can utilize it as well. Studies in turkey production and MOS supplementation show that poults given MOS at 0-4 weeks or 4-8 weeks of age and challenged with pathogens had higher weight gain than their control counterparts in both categories. There was no significant difference in feed conversion between control and MOS feed birds. Similarly, studies in broiler bird performance and MOS show that MOS supplemented birds had higher live weights at 22 days than the control groups. However there was no significant difference between group weights at 49 days. Interestingly, there was no difference in feed conversion between groups at 22 days but there was at 49 days. In conclusion, oligosaccharides show a number of positive effects when fed to poultry and further research on the mechanisms underlying their influence will be beneficial. They may prove to be a useful alternative to antibiotics, particularly when competitive exclusion micro flora is being used on birds." [33]

6. The alternatives to using the substance in terms of practices or other available materials.

"Formic, sorlic, fumaric, sorbic and lactic acids can help provide a stomach acidity of around 4.9-5.4, which helps the beneficial bacteria found in the pig's [or other animal's] gut[s] (Adding acids to pig feed helps the animals take in more food and grow). "Both organic and inorganic acids have been included in pig diets for several years (Easter, 1988). The addition of acids generally lowers the pH and buffering capacity of the diet, reduces pH within the stomach, increases both gastric proteolysis and nutrient digestibility, promotes beneficial bacteria at the expense of pathogenic organisms and decreases intestinal bacterial growth. As a consequence there is an improvement in gastro-intestinal health, resulting in enhanced growth performance and improved feed efficiency. The growth promoting effects of acids are most prominent in the first few weeks after weaning, when the gastro-intestinal tract of the piglet is not fully developed and is most vulnerable to infection. Several individual acids, or a mix of acids may be used. The role of acids in pig nutrition has recently been reviewed by Roth and Kirchgessner (1998) and Partanen and Mroz (1999). Overall, the application of acids to pig feeds can be a viable alternative to the use of antibiotic growth enhancers and, compared with a negative control, improvements in growth rate as high as 23% have been obtained in some trials (Paulicks *et al*, 1996). There is also a considerable decrease in the frequency of diarrhoea; comparable to that found in piglets fed antibiotic growth enhancers." [34]
Adding enzymes to a pig's diet can help control colitis and diarrhea. Extra enzymes help weaned piglets that cannot produce enough of their own as they adjust to new feed. Studies on the effects of fermented feeds are promising. Fermented feed changes the bacteria colony in the gut. Less E. coli is shed when pigs eat fermented feed."[35] "Herbs have been widely used as alternative therapies in both human and animal medicine. Certain herbs contain a sophisticated composition of organic elements that are known to have specific therapeutic effects. Herbs have been found to enhance anti-microbial activity, have anti-viral and anti-oxidative properties and are said to stimulate the endocrine and immune system. They promote a higher metabolic and immune status within the animal, as well as enhancing welfare. Their inclusion in the diet has also been shown to stimulate
appetite by improving palatability." [36]

7. Its compatibility with a system of sustainable agriculture.

[33] Directly referenced from http://www.poultryindustrycouncil.ca/pathogen.pdf
[34] Directly referenced from http://www.afns.ualberta.ca/bps/bps2000/PDFs/Chap06%20-%20Close.pdf
[35] Directly referenced from http://www.producer.com/articles/20000203/production/20000203prod03a.html
[36] Directly referenced from http://www.afns.ualberta.ca/bps/bps2000/PDFs/Chap06%20-%20Close.pdf

"Two experiments were conducted to study effects of dietary Mannan Oligosaccharide (Bio-Mos) and aflatoxin on bird performance, cholesterol and basic nutrients contents of eggs and meat, and serum chemistry of laying hens and broiler chicks. In experiment 1, twenty-four commercial strain white Leghorn hens were randomly assigned to a 2 x 2 factorial arrangement with two levels of Bio-Mos (0 and 0.1% of the diet; (B_0 and B_1) and two levels of aflatoxin (0 and 3 ppm; A_0 and A_1) in the diet. In experiment 2, twenty-four 1-day old commercial Cornish Rock broiler chicks were randomly assigned to a 2 x 2 factorial arrangement with two levels of Bio-Mos (O and 0.1%; B_0 and B_1) and two levels of aflatoxin (0 and 5 ppm; A_0 and A_1) in the diet. Results showed that the Bio-Mos fed group (A_0B_1) significantly ($P<0.05$) increased the total protein in livers of laying hens compared to aflatoxin fed groups. Dietary 3 ppm aflatoxin (A_1 B_0) caused a significant ($P<0.05$) elevation of hepatic fat in laying hens compared to the control, while dietary Bio-Mos significantly reduced ($P<0.05$) fat in liver. A significant hypocholesterolemic effect in liver and eggs was observed in Bio-Mos fed laying hens. At least 123 mg/100g cholesterol in eggs was reduced by dietary inclusion of Bio-Mos. On the other hand, aflatoxin fed group showed significant increase (97 mg/100g) in egg cholesterol, which may be detrimental for nutritional quality of eggs. In broiler chicks, the dietary aflatoxin depressed body weight gain ($P<0.05$), and elevated ($P<0.05$) relative weights of liver, proventriculus, heart and gizzard. Dietary aflatoxin increased lipid ($P<0.05$) and decreased protein ($P<0.05$) in livers of broilers, while dietary Bio-Mos decreased lipid ($P<0.05$) and increased protein ($P<0.05$) in livers of the birds. Supplementation of dietary Bio-Mos exhibited and apparent nutritional benefaction as well as suppression of aflatoxicosis in performance and nutritional values of tissues in laying hens and broiler chicks." [37] Overall mannan oligosaccharides are helpful not harmful to systems of sustainable agriculture primarily when dealing with livestock.

TAP Reviewers Discussion

Reviewer 1 *[PhD in Food Chemistry. Specialized interest regarding the interface between human health and food processing. Southeast US.]*

Reviewer 1 Comments on Database

There is a lot of information in the petition that is supportive and provides good background information. However, most of the critical and relevant information for NOP or any Federal Regulative branch to make a decision is thin and glossed over.

Reviewer 1 Conclusions

Reviewing the information given in the report provides the following analytical conclusions regarding the substance:

This petition is unduly complicated because there are at least two phenomenon being proposed a) the use of spent (dead) yeast cells composed primarily of mannan carbohydrates (CHO) used to absorb toxic substances for example from endophyte (fungal) infected fescue grasses and b) the growth of an active yeast culture in a mineral supplement as a feed additive. This confusion could be eliminated by separating these two concepts rather than blending them in one petition.

Page 5 speaks to this controversary of dead vs live culture benefits.

Work by Boyles from Ohio State provides some supporting data for petition "a", however it is not at all clear if Boyles' animals were challenged with endophyte fescue, the levels etc, This is the lead scientific basis for supporting the petition and it is weak. Nothing is presented for petition "b" from Boyles' work.

[37] Directly referenced from http://www.umes.edu/ard/SESSION2.html

Dosage from Boyles' data would suggest the "dried yeast culture" fed as part of a mineral supplement at 1.2 oz / day had an effect; while in the petition the presenters request is for 1/8 to ½ oz which may be below any effective limit. Why request an ineffective dosage. It is assumed that the yeast Boyles used was in fact dried to be admixed into a mineral supplement.

The proposal points out, "The need for a bacterial DFM to actually attach and colonize gut surfaces in order to have a beneficial effect is also questionable". This is a similar controversary as to the benefits of human consumption of various bacterial suspensions where the "colonization" is transient at best.

Page 7 further specifies that only a certain sub-species Paecilomyces sp. and Saccharomyces cerevisiae be considered as producing the mannan oligosaccharide.

It is difficult to assess the validity of this statement. The petition gives the background information presented in the introduction to the petition and the likelihood that most yeast will have a significant amount of their cell wall composed of mannan. The proprietary benefit for the petitioner can be readily seen, but this is certainly *not* the main point.

The mechanism of action for M.O.S. 500 is highly speculative. This is similar to work done in humans on dietary fiber and much of the mechanistic work is still in its early stages with more than enough controversy. The petitioner may be able to produce data to show "know how"; but there is very little "know why" information presented. The summary of 30 feeding trials need to be individually and critically examined to clarify if there is a proposed mechanism of action and any potential benefit.

It is unclear if M.O.S. 500 is manufactured according to organic standards or an extract of Brewers/Baker's yeast that would be grown under conditions that may not meet these guidelines given the requirements for yeast to have soluble mineral supplements.

It is not clear from the petition, Pages 13-15, if either USDA or FDA allow yeast or extract as a feed ingredient.

This is a critical point. If the thousands of pounds of spent Brewer's yeasts (mostly non-Organic) that are produced each month are not allowed as feed or food additives, then this petition is highly suspect.

There has been a controversy "brewing" for at least 25 years on the benefits versus the risk of "single cell protein" for human consumption.

It appears that the European Union has given approval on 01 June 01 to a similar yeast product, however this is not indicative that this culture or product will meet this guideline for Organic Food Ingredient or Food Additive because almost all yeasts are grown with the use soluble mineral supplements (non-organic) to get the cell volumes and production of gas required in the use of yeast by the baking industry. Again further clarification on the organic policy is needed.

The last part of the petition has to do with mold inhibitors and control of moisture in feed and feed ingredients without clear linkage to the petition.

In conclusion, without a) extensive revision along the lines proposed in this review, b) re-review by a ruminant nutritionist and physiologist and c) an indication from both FDA and USDA on the possibility of non-Organic yeast and yeast extract for use as a feed additive, this substance *cannot* be recommended for addition to the NOSB list of allowed substances.

Reviewer 1 Recommendations Advised to the NOSB

Whether yeast derivatives used in organic feed is synthetic or not is questionable. Due to the many unanswered questions regarding its overall use and composition, it should not be added to the NOSB list.

Reviewer 2 *[University Professor in Food Science Department. Western United States]*

Reviewer 2 Comments on Database

It is mentioned in a single sentence that MOS acts as a nutrient to other beneficial bacteria. This point needs a detailed discussion. A discussion is also needed on why MOS doesn't act as a nutrient for harmful bacteria. It is also mentioned that MOS adsorbs mycotoxins from animal stomach and stimulates animal's immune system. Two references are listed to support mycotoxin adsorption, but the sources of these studies are missing in the report. Most of the information presented is based upon commercial websites. Reference to scientific studies would have been more appealing.

It is discussed that USDA neither allows nor prohibits the use of MOS in animal feed. Its status with EPA is not discussed clearly. The status with other national and international organizers is presented vaguely. The discussion on its status among FDA is confusing. A lot of material on FDA's regulations is presented without specifically mentioning its relation to MOS. The discussion on the effect of MOS on agroecosystem is based primarily on birds. A more detailed discussion on other components of the agroecosystem is needed.

Additionally, a more balanced discussion on its effects on environment and ecosystem is required. A further study/discussion on its effects on humans and livestock is also necessary.

Reviewer 2 Conclusions

The report discusses that Mannan Oligosaccharide (MOS), a yeast derived from natural sugar complex, is used to control scours caused by microorganisms such as Salmonella and E. coli in livestock stomach. The mode of action involves binding of MOS to lectins at the surface of microorganisms and hindering their attachment to animal stomach. It is mentioned that MOS acts as a nutrient to other beneficial bacteria.

Reviewer 2 Recommendations Advised to the NOSB

Although several benefits of MOS are discussed, this report is not sufficiently comprehensive to either recommend or prohibit its use in animal livestock. Being that MOS is derived from a naturally occurring complex, it can be assumed that it is nonsynthetic.

Reviewer 3*[Organic Certification Program Manager. Eastern United States]*

Reviewer 3 Comments on Database

Much of the information provided was found on a variety of websites promoting the product for sale, were cited in the TAP Report in footnotes, and seemed to be primarily synthesized and generalized university-based research. The information and research results provided were entirely focused on the benefits to livestock and poultry health and productivity. No information was provided as to how Mannan Oligosaccaride is actually manufactured which is essential to determining whether the product is natural or synthetic.

Reviewer 3 Conclusions

Since it is unclear as to whether or not Mannan Oligosaccharide is synthetic, the substance has been analyzed assuming both synthetic *and* nonsynthetic, using the OFPA rulings as guidelines.

Criteria for Evaluating Products as provided for in OFPA of 1990

(c) **Guidelines for Prohibitions or Exemptions**.

(1) **Exemption for Prohibited Substances**. The National List may provide for the use of substances in an organic farming or handling operation that are otherwise prohibited under this chapter only if

(A) the Secretary determines, in consultation with the Secretary of Health and Human Services and the Administrator of the Environmental Protection Agency, that the use of such substances

(i) would not be harmful to human health or the environment;

Nothing in the technical report provided would suggest that Mannan Oligosaccharides would be harmful to the environment.

(ii) is necessary to the production or handling of the agricultural product because of unavailability of wholly natural substitute products; and

Mannon Oligosaccharide does not seem necessary to the production of livestock or poultry. It can be understood that as a product, it is unique in its function and appears to be a viable alternative to the heavy use of antibiotics in animal feed in conventional livestock and poultry. It is moderately to highly beneficial (depending on the animal species) in improving the intestinal health and digestive efficiency of livestock and poultry, and supports and improves their general immune system function which results in improved growth and weight gain in young animals and improved production in dairy cattle and layers.

(iii) is consistent with organic farming and handling;

It is not clear as to whether Mannan oligosaccharide is consistent with the paradigm of organic farming if allowed to be used regularly as an additive or supplement in animal feed. Its intent is more akin to the use of antibiotics in feed in conventional farming. The only alternative to the yeast derivative is providing natural yeast. Providing natural live yeast to the livestock or poultry does not benefit the animals because the mannose sugars in natural yeast are available to intestinal pathogens. The pathogens consume mannose, proliferate in the gut, and can cause illness and decreased immune function and productivity, according to the information provided. Mannan bound as oligosaccharide is not biologically available to pathogens although they are still attracted to it as a potential food source. The pathogens attach to the mannan oligosaccharide rather than the animals intestinal cell wall, and are then naturally expelled with normal intestinal function.

(B) the substance

(i) is used in production and contains an active synthetic ingredient in the following categories: copper and sulfur compounds; toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock paraciticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers;

This product falls into the category of livestock paraciticides and medicines but can also be viewed as a feed additive or supplement.

(ii) is used in production and contains synthetic inert ingredients that are not classified by the Administrator of the Environmental Protection Agency as inerts of toxicological concern; or

Brand names of the product would need to be evaluated for the presence of inerts or preservatives.

(iii) is used in handling and is non-synthetic but is not organically produced; and

Not applicable

(C) the specific exemption is developed using the procedures described in subsection (d) of this section.

Not applicable

(2) **Prohibition on the use of Specific Natural Substances**. The National List may prohibit the use of specific natural substances in an organic farming or handling operation that are otherwise allowed under this chapter only if

(A) the Secretary determines, in consultation with the Secretary of Health and Human Services and the Administrator of the Environmental Protection Agency, that the use of such substances

(i) would be harmful to human health or the environment; and

Nothing in the technical report provided would suggest that Mannan Oligosaccharides would be harmful to the environment.

(ii) is inconsistent with organic farming or handling, and the purposes of this chapter; and

It is not clear as to whether Mannon Oligosaccharide is necessary to the production of livestock or poultry. Whether animals would become ill without the regular use of this product is questionable. It is understood that as a product, it is unique in its function and appears to be a viable alternative to the heavy use of antibiotics in animal feed in conventional livestock and poultry. It is moderately to highly beneficial (depending on the animal species) in improving the intestinal health and digestive efficiency of livestock and poultry, and supports and improves the general immune function which results in improved growth and weight gain in young animals and improved production in dairy cattle and layers.

Whether mannan oligosaccharide is entirely consistent with the paradigm of organic farming if allowed to be used regularly as an additive or supplement in animal feed is questionable. Its intent is more akin to the use of antibiotics in feed in conventional farming. The only alternative to the yeast derivative is providing natural yeast. Providing natural live yeast to the livestock or poultry does not benefit the animals because the mannose sugars in natural yeast are available to intestinal pathogens. The pathogens consume mannose, proliferate in the gut, and according to the information provided can cause illness and decreased immune function and productivity. Mannan bound as oligosaccharide is not biologically available to pathogens although they are still attracted to it as a potential food source. The pathogens attach to the mannan oligosaccharide rather than the animals intestinal cell wall, and are then naturally expelled.

(B) the specific prohibition is developed using the procedures specified in subsection (d) of this section.

Not applicable

Criteria for Evaluating Products as provided for in National Rule

Items currently

(c)As feed supplements

Milk replacers - without antibiotics, as emergency use only, no nonmilk products or products from BST treated animals

Precedence in organic standards would suggest that Mannan Oligosaccharides may have a role as a medicinal feed supplement or additive when there is an identified herd or flock health issue diagnosed that would benefit from Mannan Oligosaccharide as recommended by a veterinarian. The animals would need to be diagnosed with an intestinal pathogen. The research on Mannan Oligosaccharide was not conducted with this approach in mind. The research was focused on either giving the animals the yeast derivative or not, and comparing their growth and productivity after a specified time period.

(d) As feed additives

(1) Trace minerals, used for enrichment or fortification when FDA approved, including:

(i) Copper sulfate

(ii) Magnesium sulfate

(2) Vitamins, used for enrichment or fortification when FDA approved

Precedence in organic standards may also suggest that Mannan Oligosaccharides could be perhaps classified as a feed additive for enrichment or fortification - a classification currently limited to vitamins and minerals which are essential to life. Vitamins can be given in regular doses as insurance to make sure animals get their minimum daily requirement. Minerals are frequently provided as a "free choice" option for animals to seek out when they want it instead of always being present in their feed. The distinction is that Mannan Oligosaccharides are not essential to life.

Reviewer 3 Recommendations Advised to the NOSB

1) Natural or Synthetic - cannot be determined with available information
2) Recommend Approval with restrictions
    a) limited for use only when a vet has diagnosed a problem with intestinal pathogens in a herd or flock,
    b) limited to 30 days or until herd or flock health issue is resolved, and
    c) the organic farm system plan should include a more aggressive plan for preventing problems with intestinal pathogens in the future.

TAP Conclusion

All three reviewers are in agreement that Mannan Oligosaccharide cannot be determined as either a synthetic or a nonsynthetic. Because of this uncertainty, the reviewers seem very tentative about their decision to grant approval or refute addition to the NOSB list of allowed substances. It can be understood that the reviewers are hesitant to grant permission about the substance based on the information provided. Of the three, only one said that the yeast derivatives, specifically referring to Mannan Oligosaccharide should be permitted with restrictions. The other two do not see any harms in the substances, but simultaneously do not see the need for its addition to the list. In general, all three reviewers agreed that more extensive research is needed before a complete decision can be made.