Calcium Borogluconate
Livestock

Identification

Chemical Name:
D-gluconic acid cyclic 4,5 ester with boric acid calcium salt

CAS Number:
5743-34-0

Other Names:
Cal Aqua, Cal-Nate 1069, Cal-MPK, Cal-MP 1700, Calciphos, calcium gluconate, and others

Other Codes: none found

Summary Recommendation

Synthetic / Non-Synthetic:	Allowed or Prohibited:	Suggested Annotation:
Synthetic (consensus)	*Allowed (consensus)*	*Preventive measures and use of non-synthetic alternatives must be documented in the Farm Plan. (consensus)*

Characterization

Composition: $C_{12}H_{2}0B_{2}CaO_{16}$

Properties:
Crystals, freely soluble in water. Solubility in water of 1:1 at 15°C., 2.8:1 at 100°C. Acidic: a 20% aqueous solution has a pH of 3.5 (Budavari, 1996).

How Made:
Calcium borogluconate is prepared by the reaction of five parts calcium gluconate to one part boric acid in an aqueous solution (MacPherson and Stewart, 1938). In Orlando in 1995, the NOSB considered boric acid in a separate TAP review for crop use and voted it to be synthetic and allowed. Annotation is "May be used for structural pest contol. No direct contact with food or crops being certified."

Calcium gluconate is prepared by a number of methods, including the reaction of gluconic acid with calcium hydroxide. Calcium hydroxide was also reviewed by the NOSB for processing at the Orlando meeting and was voted synthetic and allowed. Gluconic acid may be synthesized (Budavari, 1996). However, it is most commonly produced in the U.S. by fermentation (Sergha, 1994). The organism responsible for fermentation is Aspergillus niger. Genetic engineering to improve production of gluconic acid has been the subject of research, but it is not clear if gluconic acid is now produced by GMOs (Nagarajan, 1994).

Specific Uses:
Calcium borogluconate is for treatment of hypocalcemia (also called parturient paresis and commonly called milk fever) in cattle, sheep, and goats, and administered at 1 ml/kg (intravenous, intramuscular, or subcutaneous). No withdrawal time is required (Allen, et al, 1993).

Milk fever is the result of metabolic stress occurring only at or near parturition (giving birth). The mother mobilizes large amounts of calcium to produce milk to feed newborn, and blood calcium levels can drop below the point necessary for impulse transmission along the nerve tracts (Herren & Donahue, 1991). The disease may occur in cows of any age but is most common in high-producing dairy cows more than five years old (Aiello, 1998).

There are three discernable stages of milk fever for cows: in stage one, cows are able to stand but show signs of hypersensitivity and excitability. In stage two, cows are unable to stand. In stage three, cows lose consciousness progressively to the point of coma. Cows in stage three may survive only a few hours (Aiello, 1998).

Formulations may be labeled "calcium gluconate" but the active ingredient, in many cases, is listed as calcium borogluconate.

Action:
Calcium borogluconate raises the calcium level in the blood. No natural calcium sources to do this were suggested in the literature reviewed. Feeding natural calcium sources in stages two and three may not be possible due to the severe illness milk fever causes (Hoard's Dairyman, 1993).

Combinations:
Calcium borogluconate can be combined with phosphorus, potassium, and magnesium and is sometimes administered with an analgesic or local anesthetic. It can also be mixed with calcium oxide, formaldehyde, or dextrose. It usually comes in a 23% solution, equivalent to 19.78 mg/ml calcium (Allen, 1993).

Status

OFPA
Falls under "livestock medicines" in 7 USC 6517(c)(1)(B)(i).

Regulatory
Listed as an animal drug under 21 CFR sections 150.141, 150.161, and 184.199 (calcium gluconate).

Status among U.S. Certifiers
Generally allowed to treat ill animals.

Historic Use
The first use to treat hypocalcemia in cattle was reported in 1934 (Hayden) and confirmed in 1935 (Dryerre and Grieg; both reported in MacPherson and Stewart, 1938). It is commonly the preferred treatment for milk fever by dairy farmers since then, although Hoard's Dairyman lists calcium gluconate as the method of choice. In a 1990 survey, more than 82% of Hoard's Dairyman readers reported milk fever in their herds, with over eight percent of the cows affected (1993).

International
Codex Alimentarius allows chemical allopathic veterinary drugs or antibiotics to be used "under the responsibility of a veterinarian" if the use of alternative methods are "unlikely to be effective in combating illness or injury." Withholding periods are required to be double of those required by law with a minimum of 48 hours (Codex, 2000). The European Union has a similar standard (EC 1999). IFOAM allows conventional medicines "when no other justifiable alternative is available" (IFOAM, 2000).

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

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

Calcium interacts with phosphorous and vitamin D in the diets of dairy cattle (NRC, 1989) and other mammals. The interaction may be detrimental pre-parturition, but animals are treated at parturition (Aiello, 1998). Other cations, especially magnesium, may be antagonistic (Allen et al., 1993). It is also incompatible with sodium bicarbonate (Allen et al., 1993). Injections of calcium borogluconate and lidocaine have been linked to false positives of antibiotics in slaughter animals (Nouws, 1975).

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

Calcium infusion is associated with lowering blood pH, respiratory acidosis, and heart attacks (Allen, 1993; Farningham, 1985; and Fenwick, 1994). To avoid heart attack or arrhythmias, intravenous injection of calcium borogluconate should be given slowly. For effectiveness, the injection should be heated to blood temperature and administered as soon as the hypocalcemia is detected (Fenwich, 1994).

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

The fermentation step in the process may involve a genetically engineered strain of A. niger, but otherwise has the same environmental impacts of fermentation processes in general. The boric acid and calcium hydroxide steps in the process were considered in previous TAP reviews.

4. *The effects of the substance on human health.*

The substance is used to treat humans for hypocalcemia as well; calcium chloride is the treatment of choice in humans (White et al., 1976). Dairy animals may be treated without any withdrawal period (product label). There is no listing on the National Toxicology Program Database or the Food Animal Residue Avoidance Database as of October 5, 2000.

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.*
Calcium borogluconate is preferred to calcium gluconate because it is more soluble (Budavari, 1996). Rapid administration and high concentrations may cause heart blockage (Allen et al., 1993). The material is metabolized by the animal, with the calcium entering the blood stream and some being expressed as milk. The animal's urine and feces may contain higher levels of boron as a result, but none of the literature reviewed partitioned the fate. Some claim that introduction of boron and sugar is either unnecessary or causes complications, but these are not specified (Carnes et al., 1980).

6. *The alternatives to using the substance in terms of practices or other available materials.*
Proper nutrition is the most effective alternative. Although high calcium in dry cows accentuates milk fever, high calcium intake at calving can reduce its incidence. Maintaining calcium, phosphorous, and Vitamin D levels in their proper ranges for dry cows and at calving can prevent milk fever (NRC, 1989). Cations other than calcium may play an important role in prevention. Data from 75 published trials suggested that the correlation between milk fever and the anion-cation balance (ACB or DCAB) was stronger than that for calcium levels (Oetzl, 1991). This has been further tested in experiments using potassium and sodium without calcium supplementation (Goff and Horst, 1997).

Other prevention strategies are breeding for less milk production, access to pasture, reducing stress prior to parturition, and feeding strategies. Culling milk fever-susceptible cows may be a desirable strategy because milk fever is correlated positively with other disorders, such as dystocia (difficult birth), retained placenta, and metritis (uterine infection) (Erb et al., 1985). Preventative rations may have slightly lower calcium levels and higher phosphorus levels just before parturition and then increased calcium levels after parturition; such rations may result in dangerous depletion of skeletal mineral reserves if continued for long periods in heavy-milking cows (Aiello, 1998). Also, feeding Vitamin D_3 helps stimulate the body to absorb calcium (NRC, 1989). Feeding synthetic bovine parathyroid hormone (PTH) is also a preventative measure. Increasing the amount of acidogenic minerals relative to alkalogenic minerals can also reduce milk fever (Block, 1984 quoted in NRC, 1989).

Calcium chloride is more effective than calcium borogluconate at quickly raising ionized plasma calcium in sheep (Farningham, 1985). (Calcium chloride was voted on by the NOSB at the Orlando meeting as natural and allowed for processing; at Indianapolis it was voted on for crops use as natural and not part of the National List scope.) Calcium chloride may result in metabolic acidosis (Aiello, 1998). Oral administration of calcium propionate in a propylene glycol gel is also effective. A combination of IV and oral treatment has been shown to reduce the re-treatment rate over administering IV calcium alone (Oetzel et al., 1997, quoted in Fitzpatrick, 1998). Calcium borogluconate remains the most widely mentioned material, in the literature, used for hypocalcemia.

7. *Its compatibility with a system of sustainable agriculture.*
To the extent that calcium borogluconate provides relief of unnecessary animal suffering, treatment is compatible. However, breeding and measures to provide a better anion-cation balance in the diet may be a more sustainable approach to managing milk fever in dairy herds in the long run.

TAP Reviewer Discussion

TAP Reviewer Comments

OMRI's information is enclosed in square brackets in italics. Where a reviewer corrected a technical point (e.g., the word should be "intravenous" rather than "subcutaneous"), these corrections were made in this document and are not listed here in the Reviewer Comments. The rest of the TAP Reviewer's comments are listed here minus any identifying comments and with corrections of typos.

Reviewer #1
[Veterinarian with substantial ovine (sheep) experience and no direct interest in the product]
Calcium borogluconate, while a synthetic product, is used for the specific purpose of treating parturient paresis, a condition that is life-threatening.

I have several comments about the OFPA criteria. There is a chance that a genetically engineered strain of A. niger may be used, but since this is a fermentation process, the strain of the yeast should not be an issue. On top of that, we are talking about a medicine that will probably be used only once in an animal's life, if that much. The need to have the use of this medicine in an organic livestock operation is too crucial to let the source of the cells ever be a determining factor.

I could find no reference to the boron portion of this product. The calcium portion is excreted in the milk in a proportion directly related to the total amount of milk produced. When injected intravenously, a considerable part of the calcium is excreted in the urine within 24 hours, but the majority is still excreted in the feces. The fecal content of calcium excreted is directly proportional to body weight, and is little influenced by short-term dietary changes (Jones, 1965).

Given that this is all I can find on the metabolism or the excretion of calcium borogluconate, I would say that there is just no danger to the environment. We know that both boron and calcium are essential soil nutrients.

I feel it is essential to change any management practices to reduce the incidence of milk fever. However, no matter how good of a job a farmer does, some animals are going to get sick in spite of their good work.

I could not find an LD50. I wouldn't think there would be one. If a bolus of the drug was given IV, then the animal would be dead very quickly. So the lethal dose depends more on the administration of the drug instead of the danger of the individual portions.

I strongly agree with the summary recommendation on page 1. This was a good summary of the product with excellent references detailing the use of calcium borogluconate as well as preventive measures for hypocalcemic conditions.

Reviewer #2
[Veterinarian with substantial bovine experience who does not have an interest in the sale or marketing of the product, but administers it as part of normal practice.]

I agree with the summary recommendation on page one. I think the review materials are well organized and I can add only clinical judgements as a dairy vet.

[Regarding the OFPA criteria]

(1) I do not see that there are any potential detrimental chemical interactions with other materials used in organic farming systems. Bottles are sealed new until usage and administered I.V. to correct a pathophysiologic metabolic disturbance usually one time, maybe twice, to an animal just at calving.

(2) Since calcium borogluconate is used in animals with irregularly low levels of calcium (hypocalcemia), I do not think its use would cause toxicity in an animal needing it. If given too rapidly, however, its mode of action certainly can cause heart block. As far as breakdown products (any contaminants are a non-issue since the product is sterile), the only possible issue that someone could mention is what happens to the boron. Although I am not familiar with the fate of boron in any animal, I would suspect it is either excreted by the kidneys as urine or is metabolized and complexed by the liver via various biochemical transformations. In either case, the amount of boron that may leave the cow would be a drop in the ocean compared to all the pathogens that are routinely excreted in manure and urine into the environment. And remember, it's a one or two time treatment in an individual cow.

(3) The probability of environmental contamination during its manufacture may be of question since genetic engineering of *A. niger* exists. But, if the fermentation product (gluconic acid) of a genetically modified organism has none of the organism in it, isn't this allowed for Livestock Health products if no other commercially available preparation exists? I see no problems with environmental contamination during use, misuse, or disposal of calcium borogluconate (see #2 above).

(4) I do not see any negative effects of the substance on human health.

(5) The boron aspect of calcium borogluconate allows for greater solubility and availability of calcium to the cow. The fate of boron into the agroecosystem is insignificant, in my opinion, from an individual cow in a herd needing treatment (see #2 above).

(6) As far as other available materials, there are none for I.V. administration. I checked my supply of various over-the-counter and vet prescription calcium products for I.V. use and all are calcium borogluconate (even the products labeled "23% calcium gluconate"). I do have one product that I use in an I.V. fashion but it is manufactured to be given orally. That product uses calcium hypophosphite as its calcium source.

I fully agree that dry cow nutrition is critical in preventing milk fever. But in one of the studies supplied for this review, even with anionic salts provided, milk fever occurred (but much less than with cationic salts). I work with

30+ certified organic dairy farmers (out of 90 total clients) and not one that I know of uses anionic salts. The reasons ranging from non-palatability, to having to segregate "close-up" dry cows, and many other reasons. Thus, I believe that I.V. and/or calcium supplementation will always be necessary. As far as breeding for less milk production, this is antithetical to dairy farming in general. Culling milk fever-susceptible animals may be a solution, but only if they show other problems as well. In my clinical experience, milk fever pre-partum is rare and so hypocalcemia inducing dystocia is minor. The vast majority of milk fevers have passed their placenta. Problems with retained placenta and metritis, in my clinical experience, would have a stronger association with assisted calvings (large calf, mal-positioned, uterine torsion, etc.). I would be quicker to mention culling cows with chronic high somatic cell counts and clinical mastitis than I would for milk fever.

I would mention that one possible preventative (as an acidogenic substance) would be to give dry cows vinegar for a few weeks before freshening. This seems more palatable and appears to be more acceptable to the thinking of organic dairy farmers.

Mention of calcium gels is made as an adjunct to I.V. treatment. Although I agree fully with their use, do not mention them if they are not allowed. That's not fair.

(7) I do not see a problem in compatibility with calcium borogluconate in sustainable agriculture. I agree that preventative (nutritional) measures need to be emphasized as part of the management of dry cows in organic dairy herds. If this substance were to be prohibited, I will guarantee angry responses from dairy farmers and veterinarians as well as humane groups that are closely watching developments of approved and prohibited substances for organic livestock health issues.

[There was nothing on this material in FARAD and NIEHS/NTP.] If FARAD has nothing on this material, I would agree that it is considered very safe so as to be of no concern.

[LD50 test? There isn't one on the MSDS.] I believe that is probably species specific and depends on *rate* of administration. I do not like the LD50 test as it purposely induces pain, suffering, and death on animals that usually have no benefit from the substance being tested. It is an archaic test, in my opinion, and could be replaced by mathematical modeling of known physiologic processes.

[Any other regulatory limitations or concerns?] Codex-I know of no alternative methods which would likely "be effective in combating illness or injury" due to/ associated with clinical hypocalcemia. I do not believe that a 48-hour withholding period is logical since you are simply supplementing a cow that is severely deficient in available calcium in her bloodstream. Legally, no cow's milk goes into the tank in the first 2-3 days when milk fever hits, since it is colostrum technically. *[There are now colostrum products on the market for human consumption.]*

Reviewer #3
[Analytical chemist with animal production experience.]

I spent some time on the Internet, and the information that I accessed pretty much agreed with yours. I also spoke with a couple of vets, and one cow owner (beef cows with a dairy cow for home use (for 40 years or so). General agreement is that some breeds are more susceptible, even in dairy herds (i.e., the Channel Island breeds), and that the tendency towards milk fever is somewhat heritable.

All sources emphasize management practices that can help diminish the occurrence of milk fever first, including lowering calcium uptake three weeks prior to partuition, and increasing it immediately afterward. Also the monitoring of cation/anion states and correcting with phosphorus and magnesium can be effective. Keeping track of urine pH can help, too.

Several notes were made on dispensing Ca Borogluconate: that it could cause cardiac arrest; that something like 40% of the cows would relapse and require a second dose, as the first was inadequate; that cows that got milk fever could be considered to have 3-5 years of productive life lost; and that cows that got it once were more prone to get it again.

Because of the possibility of complications, there is some feeling in the vet community that treatment should be under the direct supervision of an attending vet. I'm sure that the cow management crowd objects to that (cost, rapidity of treatment, straightforward symptoms).

Agree *[with the summary]* as long as management practices are followed to eliminate the conditions that cause milk fever (including changing feed as necessary and supplementing or restricting minerals as necessary, pasturing dairy herds, use under vet supervision, and culling for elimination of M.F. prone stock).

A good discussion/lecture that covers management practices from Michigan State: URL: zebu.cvm.msu.edu/courses/vm556/milkfev/sld032.htm.

[Regarding the OFPA criteria]

(1) Pretty straightforward chemically, feed through should not be an issue.

(2) Generally not detrimental to animal, if administered properly; therefore should be used under vet supervision. Designed to tide cow over until her calcium chemistry is better; provides available calcium until she rebalances herself; pretty much a chemical reaction. The chemicals appear to be metabolized in a normal way, and excreted with little impact on the environment; changes in urine pH could have a long-term effect, if this was a long-term treatment, but it's not.

(3) Possible product of GMO *A. niger*: none of the fermentation media, or the *A. niger* remains in the product. No protein remains in the product.

(4) Approved for use on humans. No withdrawal period for cows; no detrimental products are available to go through to the milk, or the meat.

(5) Nothing significant.

(6) Calcium chloride, although it has serious problems, according to the literature, it's been the drug of choice since 1935. Primarily prophylactic good nutrition and herd management; management of anion/cation exchange issues by monitoring urine pH was recommended. Although there are some recommendations regarding oral calcium propionate, the general agreement appears to be that once the symptoms have appeared, oral administrations are too slow; that Ca borogluconate is essentially the only method of choice.

(7) Compatible synthetic; saves cows from needless suffering; easy on ecology; no feed through issues; no re-entry period.

I'm not sure that there needs to be much more on fate issues; it seems pretty straightforward. Far more so than, say, antibiotics, or wormers.

[LD-50] No. Not listed in the Merck, or the food additives manual.

[Other regulations] Not that I could find.

Conclusion: Calcium borogluconate is a compatible synthetic with organic animal husbandry operations; needs management and feeding systems in place as first line of defense. Needs to be used under veterinary supervision. Recommendation: allowed (with management and supervision caveats).

Conclusion

The consensus of the TAP reviewers is that without this synthetic drug, animals on organic farms may die slow and avoidable deaths. However, use should be considered a supplement to preventive measures, and not a substitute for them. Repeated use should require justification and measures in the Farm Plan to prevent hypocalcemia.

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