Chlorhexidine

Livestock

Identification

Chemical Names: 1, 6-di-(4-chlorophenyldiguanido) hexane; N,N1-Bis(4-chlorophenyl)-3,12-diimino-2,4, 11,13,tetraazatetradecanediimidamide

CAS Numbers: 55-56-1

Other Codes: none

Other Names: Chlorhexidine Diacetate, Chlorhexidine gluconate, Chlorhexidine Hydrochloride

Characterization

Composition:

$C_{22}H_{30}Cl_2N_{10}$

Properties:

White to pale yellow, odorless powder. Is only slightly soluble in water and most organic solvents. Several acids (chlorhexidine diacetate, chlorhexididne digluconate, and chlorhexidine dihydrochloride) form stable salts. In aqueous solutions, chlorhexidine salts display a maximum of biological activity and chemical stability within a pH range of 5-8. Melts at 130-148° F.

How Made:

Manufactured by a two step process. Starting from sodium dicyanamide, hexamethylene-biscyanoguanidine (HMBCG) is synthesized by reaction with hexamethylene diamine. Subsequently, HMBCG is reacted with p-chloroaniline to yield chlorhexidine base.

Specific Uses:

Chlorhexidine is used as a germicidal compound in teat dips. Also used as navel treatment, udder and eye wash, surgical scrub and sterilization material.

Action:

Chlorhexidine precipitates bacterial cell contents and, in low concentrations (0.01%), rapid and irreversible loss of cytoplasmic contents occurs.

Combinations:

Chlorhexidine teat dips usually will include 0.5-2% chlorhexidine, 50% glycerin (as an emollient), alcohol, and a dye.

Status

OFPA

Chlorhexidine falls under section 6517(1)(B)(i) of the OFPA code that describes livestock medicines.

Regulatory

FDA regulated as a surgical scrub, not as a veterinary medicine. FSIA (USDA meat inspectors) have a United States regulation requiring a 3 day withdrawal of treatment before slaughter to help ensure no residue requirements in edible animal tissues (Rossoff, 1974).

Status among Certifiers

No record of it being regulated by organic certifiers.

Historic Use

It has been used as a “cold” sterilization preparation for surgical use.

International
IFOAM standards indicate the withdrawl period for all livestock medications should be at least twice as long as the current legal period.

OFPA 2119(m) Criteria

(1) The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems.

One reference to chlorhexidine milk contamination on FDA website; however, no original reference given. Chlorhexidine can be rendered inactive with soap, urine, and physiological sodium chloride.

(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.

Chlorhexidine remains active 5-6 hours longer than any other teat dip preparation. It also is an effective antibacterial substance in the presence of blood and other organic materials.

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

No information was found on the environmental impacts of the manufacture of chlorhexidine.

(4) The effect of the substance on human health.

Oral toxicity is low. In laboratory tests and in human clinical use, chlorhexidine was relatively non-toxic to unbroken skin and mucous membranes. However, skin irritation resulted from use of chlorhexidine teat dips. Emollients are incorporated in commercial products to minimize irritation. It has a LD50 orally in mice as a diacetate at 2gm/kg. In digluconate form the LD-50 is 1800 gm/kg (Merk Vet. Manual, 1998).

P-chloroaniline was selected by the National Cancer Institute for bioassay because of the high incidence of bladder cancer observed among those who worked with it. Studies strongly suggest carcinogenicity in rats and mice (NTIS website). There are established recommended minimum allowances by the EU's Pharmacopoe 2.90. Some manufacturers follow these standards, others do not.

(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.

Chlorhexidine is a broad spectrum antimicrobial, effective against both Gram-positive and, to a slighter lesser degree, Gram-negative bacterium. Effective against *E. coli , S. Aureus, Bacillus subtilis, Psuedomonas aerugenosa,* and *C. Albicans* (Allen, 1994). Also effective against ringworm. Its efficiency is not dependable in myobacteria, fungi, and viruses. Bacteria spores are resistant.

An outbreak of *Serratia marcescens* occurred in a university tertiary-care hospital when an alcohol-free chlorhexidine solution was contaminated. It was recommended that chlorhexidine without alcohol should not be used as an antiseptic (Vigeant et al., 1998).

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

Mostly synthetic dips such as iodophors, quaternary ammonium, sodium hypochlorite, dodecyl benzene sulfonic acid. Also there are synthetic physical barriers such as latex and acrylic latex-based products. Also ozone treated water, chlorine (sodium hypochlorite).

Other milking management techniques to control mastitis that are considered alternatives to chlorhexidine are the following:

1) Monitoring for mastitis.
2) Wiping or cleaning debris from teats.
3) Massaging each teat to loosen debris and stimulate milk letdown.
4) Wiping off the teat dip using individual cloths or paper towels.
5) Applying the milking unit without air admission and, at the end of milking, shutting off the vacuum, and removing the milking unit.
6) Isolate infected cows and cull cows that have repeat attacks.
7) Examine and test all herd additions and treat clinical infections as they occur.

(7) Its compatibility with a system of sustainable agriculture.

See conclusion under discussion, below.

Discussion

Condensed Reviewer Comments

None of the reviewers have a direct, comercial or financial interest in chlorhexidine. One reviewer uses it frequently as a topical antiseptic during surgery and “cold” sterilization of his instruments.

Reviewer 1
This is a synthetic compound. It is generally thought of as a topical disinfectant (i.e., teat dips) or used for surgical purposes (“cold” sterilization and surgical scrub).

Chlorhexidine can have a residual effect with up to 26% active ingredient remaining on the skin after 29 hours (Allen, Handbook of Veterinary Drugs, J.B. Lippencott, 1993, p.370). But I am not sure if this is in the liquid or ointment form. And there is mention of its use as an eye lotion containing 1 part in 1000- and also as a powder for eye infections (ibid.). Iodine would seem to be a suitable "allowed" alternative (although I don't know the details of its manufacture). However, the efficacy of iodine is reduced due to its relatively easy inactivation in the presence of organic debris, whereas chlorhexidine retains its effectiveness in the same situation. Build-up of iodine residues in milk may be problematic and has set-off alarm bells in anti-dairy circles as to possible interaction with the thyroid.

I do not believe chlorhexidine, as a teat dip, is compatible with the criteria of compatibility with sustainable agriculture as set forth on 2119(m)(7) due to its original source, manufacture and persistence. Therefore, I do not think it should be added to the List as an allowed teat dip.

There is no proposed annotation in the Status section. I would suggest the use of chlorhexidine to be used as teat dip under the heading "regulated" and only to be used during those times where an iodine teat dip has lost effectiveness in controlling infectious or environmental types of mastitis. I would definitely allow chlorhexidine for veterinary surgical procedures or for veterinary prescription on a herd by herd basis (as a teat dip used in a rotation with others).

Reviewer 2
Statements seem vague as to the safety to human health and environment to be added to the list.
Since the compound used to make chlorhexidine, p-chloroaniline is a known carcinogen and some manufacturers follow the standards of minimum allowances set by EU's Pharmacopoe 2.90 and others don't it would be impossible to recommend it on the list at this time.

Reviewer 3
Chlorhexidine is considered a germicide for teat dips and it is used as an antibacterial agent in humans to control gingivitis and over all plaque control in preventative dentistry. It has a LD-50 orally in mice as a diacetate at 2 gm./kg. In digluconate form the LD-50 is 1800 gm./kg. (Merk Index, 11th edition)

According to OFPA [6502 (21)] Chlorhexidine is clearly a synthetic compound as I have found no evidence of it occurring in nature. Its synthesis is clearly a multi-step chemical reaction that involves a final purification step in order to enhance its overall germicidal functionality.

Overall the content of the NOSB database appears to be accurate in technical detail. My concern is that since there are a number of possible alternatives such as chlorine (i.e. sodium hypochlorite) and possible ozonated (O_3) water that would appear to be very effective. From the OFPA, the major advantage of chlorhexidine lies in the fact that it remains active 5-6 hours longer than comparable teat dip preparations and its effectiveness in the presence of blood and other discharges. In my opinion, for animals with severe teat/udder infections, it may be the most effective germicidal agent. As a potential alternative, ozonated water may prove to be effective but there must be suitable scientific studies showing its efficacy and effectiveness in the presence of blood and discharges.

After much thought, the production, manufacture, disposal and agro ecosystem biology of chlorhexidine is not compatible with organic agriculture, I would at this time recommend that chlorhexidine be added to the National List of Allowed Synthetics. I also would recommend that chlorhexidine be further reviewed as other germicidal agents with more compatibility to organic agriculture be developed or found.

I tend to agree with the overall status section of the database. I am especially in agreement with IFOAM's position that "the withholding period shall at least double the legal period".

Additionally, I would like to propose an annotation that clearly states: "Chlorhexidine may only be used in cases as determined by veterinary science where due to presence of blood and discharge its use can be justified and recommended and where use of alternative germicidal agents and/or physical barriers would not be an effective treatment."

My goal here is to limit its use as an allowed synthetic for such cases where its major germicidal advantage (i.e., effectiveness in presence of blood and discharge) can be determined on a case by case basis and by a DVM. I would not recommend that chlorhexidine be used at the onset of symptoms where other alternatives may be effective.

I recommend that chlorhexidine be added to the National List of Allowed Synthetics with the language of IFOAM and my proposed restriction/annotation. I have no commercial or financial interest in this compound.

Conclusion

While it would be reasonable to consider chlorhexidine incompatible with organic standards, there may be well-defined situations where treatment should not result in the loss of organic certification status for an animal. The use of chlorhexidine as a teat dip in rotation with other teat dips may serve as a sanitation practice that can reduce the chance of mastitis. If chlorhexidine is added to the National List, dairy producers should consider it the teat dip of last resort before treating an animal and / or removing her from the organic string. Even though it appears to have no withdrawal time for dairy animals, the NOSB may want to impose a withdrawal time before a cow can be milked into the organic pool. Also, use in surgical procedures as an antiseptic may be preferable to other alternatives.

References

1) Allen, 1993. Handbook of Veterinary Drugs. J.B. Lippencott Publisher. Philadelphia.

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3) Food and Drug Administration. Green Book. Rockville, MD: US Department of Health and Human Services.

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5) Merk Veterinary Manual. 1998. 8th ed. pp. 1013-1015. National Publishing, Inc., Philadelphia, PA

6) National Technical Information Service website.
http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr189.html

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9) Rossoff. 1974. Handbook of Veterinary Drugs. Irving S. Springer Publ Co, NY pp. 102.

10) Vigeant, P, VG Loo, Bertrand, Dixon, Hollis, Pfaller, McLean, Briedis, Perl, Robson. 1998. An outbreak of Serratia marcescens infections related to contaminated chlorhexidine. *Infect Control Hosp Epidemiol* 19:791-794.

11) Wheeless Textbook of Orthopoedics website. www.medmedia.com