

Hydroxyquinoline sulfate

Livestock

Identification

Chemical Name(s):

8- Hydroxyquinoline Sulfate

CAS Number:

134-31-6

Other Names:

Hydroxyquinoline sulfate; Quinolinol sulfate; Oxyquinoline Sulfate
8-Quinolinol, Sulfate (2:1) (Salt)
Oxine Sulfate
8-Hydroxyquinoline Sulfuric Acid Salt; 8-HQ
HQS

Other Codes:

NIOSH VC8260000
EPA PC 59804, PAI 51

Trade names:

Beltanol L, Chinosol, Cryptonol, Happy, Octofen,
Sunoxol, Superol, Quinosol

Summary of Advised Recommendation*

Synthetic / Non-Synthetic:	Allowed or Prohibited:	Suggested Annotation:
<i>Synthetic (4)</i>	<i>Prohibited (3)</i> <i>Allowed (1)</i>	<i>For use in a topical salve for dairy cattle in concentrations no higher than 0.3%. (1)</i>

Characterization

Composition:

$C_{18}H_{14}N_2O_2 \cdot H_2O_4S$

Manufacturer (Napp, Inc.) lists composition as:

theoretical 8-hydroxy-quinoline content:	71.42%
Sulfuric acid:	24.15%
Water:	4.43%

Properties:

The molecular weight is 406.05. It is a yellow microcrystalline powder with a faint smell of saffron, burning taste, slightly hygroscopic. It is highly soluble in water, even cold. Slightly soluble in ethanol and glycerol, insoluble in ether. The 2% aqueous solution has a pH of 3.2.

How Made:

The compounds known as quinolines and isoquinolines have been the subject of extensive investigation since their extraction from coal tar in the nineteenth century. They are considered a heterocyclic aromatic compound, with a double ring structure similar to a benzene ring; derived from naphthalene with a trivalent nitrogen atom substituted for a carbon atom on one of the rings. Substitution of a hydroxyl group on position 8 of the aromatic nucleus of quinoline converts it to oxyquinoline (also called 8-quinolinol) and confers phenolic properties (Lipnicki, 2001b). Quinoline can be extracted from coal tar distilled by caustic extraction and then by distillation of the oil to produce a methylnaphthalene fraction. This is then washed with dilute sulfuric acid to produce sulfate salts. The mixture of compounds attained can then be further separated using forms of chromatography.

* 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 edited for any identifying comments, redundant statements, and typographical errors. Text removed is identified by ellipses [. . .] Statements expressed by reviewers are their own, and do not reflect the opinions of any other individual or organizations.

A large number of alkaloids and medicinal compounds contain quinoline rings, and this also led to the development of numerous synthetic pathways to produce these compounds. A general method is called Skraup synthesis, and involved heating a primary aniline with glycerol, concentrated sulfuric acid, and an oxidizing agent. This can be a violently exothermic process (Kirk-Othmer, 1996b).

Specific Uses:

Hydroxyquinoline sulfate is used as a topical antiseptic, disinfectant, antiperspirant, deodorant, and fungicide (NTP). It was petitioned for use as antiseptic ingredient in topical salves for livestock (e.g., as an ingredient in bag balm). Although mainly used for dairy cows to soothe chapped teats, the label for a product formula also includes directions for healing scratches and skin irritations for horses and domestic pets.

Human Medicine: The manufacturer claims: it is externally used as a powerful non-toxic, non-caustic antiseptic and for use in treatment of gynecological infections (meritritis, vaginitis) as it restores the vaginal acid balance; treatment of infections in the urinary tract; treatment of diarrhea and colitis without harming the intestinal flora; and a disinfectant use in oto-rhino-laryngology (Napp, 1999). These claims are not currently supported by FDA classification. The only currently listed open uses in the Over the Counter (OTC) Active Ingredient Status Report of Sept. 01, 1994 are for oxyquinoline used for diaper rash and oral health care. (Lipnicki, 2001a) Both of these uses are considered open only at a proposed rule making stage, and are classified as Category III: "available data are insufficient to classify as safe and effective, and further testing is required." There are no currently approved OTC uses for oxyquinoline sulfate, all formerly listed uses skin protectant or antifungal are classed as category II "not generally recognized as safe and effective or misbranded." (21 CFR 310.545). There is one prescription drug listing for human use (FDA, 1998: Indium 111, Injectable). The Merck Index lists therapeutic uses as topical antiseptic and disinfectant. (Windholz, 1983). One review (Gosselin, 1984) states that "at one time used in clinical medicine as a topical antiseptic."

Veterinary Medicine: The manufacturer claims a wide range of uses, including "in the composition of many products for the treatment of poultry diseases; as a fungicide which is harmless to intestinal flora; as an antiseptic widely used in artificial insemination techniques; and as a disinfectant of stables contaminated with brucellosis" (Napp). It is not listed in FDA's database as a New Animal Drug or as an Approved New Animal Drug (FDA 2001). The Merck Veterinary Manual lists the hydroxyquinolines as a group of synthetic compounds with antibacterial, antifungal and antiprotozoal activity. They are not absorbed from the GI tract and are thus used for intestinal infections caused by bacteria or protozoa (such as *Girardia*). They are also mentioned for topical use for bacterial and fungal skin infections (Aiello, 1998).

FDA's Center for Veterinary Medicine considers the product 'Bag Balm' to be an "unapproved new animal drug. Based on CVM's current resources and priorities, Bag Balm most likely does not have a high priority for regulatory action at this time" (Bataller, 2001). FDA exercises regulatory discretion and does not object to some non-approved products or non-regulated drugs when they feel the safety problems do not warrant the effort needed to remove a product from the marketplace. In these cases, FDA will send a letter to the sponsor of the product stating that they do not object to its sales, and if more information challenging the product becomes available they will notify the manufacturer. Manufacturers of non-approved drugs are required register with FDA to identify the products and site of production, but this is not considered approval, and FDA does not have adequate safety or efficacy data to consider them approved. (Keller, 2001)

Cosmetic: Used as an antiseptic in ointments and creams used for skin treatment and in certain hair lotions; as an antiperspirant (deodorant) (Napp, 1999), as a fungicide and stabilizer in hair and skin preparations at concentrations of 1.0% or less (Anon. 1992). These appear to be over-the-counter uses not specifically prohibited by FDA regulation.

Food Processing: Hydroxyquinoline sulfate was recently banned as a coagulant in food products; it was previously used as a component of cottage cheese (FDA 2000). Federal registration of a related compound, 8-hydroxyquinoline benzoate, was withdrawn for food use in 1969 because repeated doses caused cancer in lab animals (Gosselin, 1984).

Crop Protection: Hydroxyquinoline sulfate is used as a bactericide and systemic fungicide. 8-Hydroxyquinoline is considered a strong chelating agent that precipitates heavy metals. Formulations are used to control certain vascular wilts and bacterial diseases of crop plants (citus, fruit trees, vegetables, vines). It is also used for fungus control of cut flowers (Meister, 2000).

Action:

The synthetic is claimed to have antiseptic use. In Bag Balm, it is primarily designed to treat cows' udders that have been cut, scraped, chapped, or sunburned. It is used for cows' udders that have become caked or congested due to calving or bruising, and is put on teats to prevent freezing. Oxyquinoline sulfate is considered to be primarily bacteriostatic (suppresses bacteria) since it is only weakly bactericidal. The believed mode of action is by chelating various metals required by microorganisms for metabolism. Other drugs have a similar mode of action, including salicylates, thiourea, tetracyclines,

cortisone and penicillin. It is thought to form a chelate of copper derived from the host tissues which easily passes into the cell of an invading pathogen, and is then released to kill the pathogen (Lipnicki 2001c).

Combinations:

In the Bag Balm product, 8-Hydroxyquinoline is mixed with sulfuric acid and water. This is then added to a base of petroleum and lanolin, making up 0.3% of the final product. Compounds related to hydroxyquinoline sulfate include iodochlorohydroxyquin (clioquinol), diiodohydroxyquin (iodoquinol), and broxyquinoline (Aiello, 98).

Status

Historic Use

The formulation sold as Bag Balm has been marketed for over 100 years and is widely used in the US and Canada.

OFPA, USDA Final Rule

OFPA 6509(d) requires that producers not use any subtherapeutic doses of antibiotics, use synthetic internal parasiticides on a routine basis, or administer medication, other than vaccinations, in the absence of illness. OFPA 6509(c)(3) requires that producers shall not use growth promoters and hormones, including antibiotics and synthetic trace elements used to stimulate growth or production. OFPA 6517 (c)(1)(B)(I) provides that a synthetic substance can be added to the National List in the categories that include livestock parasiticides and medicines.

Hydroxyquinoline sulfate is listed by the US Pharmacopeia as a “pharmaceutic aid (complexing agent)” rather than as an anti-microbial agent (USP 2000). The term antibiotic is generally considered to include a wide number of diverse classes of chemical structures, and can be described as “chemical substances produced by microorganisms and other living systems that are capable in low concentrations of inhibiting the growth of bacteria or other microorganism” (Kirk-Othmer, 96a). Quinolines do not fall into the generally described classes of antibiotics. However, another medical text defines antibiotics as “any of a variety of natural or synthetic substances that inhibit growth of or destroy microorganisms,” and further defines a bacteriostatic as an “antibiotic that inhibits growth of microorganisms” (Taber, 1981). Quinolines are precursors to quinolones, which are produced from quinoline by heating with potassium hydroxide under anhydrous conditions (Budavari 1996).

The NOP final rules at 7 CFR 205.238(b) allows the use of synthetic medication in the case of illness, provided the medication is listed in 205.603.

Regulatory

As noted under Uses, hydroxyquinoline sulfate is considered an over-the-counter human medication by FDA and has cosmetic applications. A product containing hydroxyquinoline sulfate is considered non-approved by the FDA-CVM, but is permitted by discretion for livestock use.

EPA/NIEHS/Other Appropriate Sources

EPA – considered a List 3 inert ingredient in pesticide formulations. Reported in the TSCA (Toxic Substances Control Act) Inventory, 1983. Regulated under the Clean Water Act 304B as a pesticide pollutant that must be pretreated and not discharged into public waste water systems (40 CFR 455.67).

NIEHS – toxicity information listed below under Question 2.

Other regulations – NIOSH – none. ACGIH – none. NFPA hazard rating – none.

Status Among U.S. Certifiers

Topical salves containing petrolatum and lanolin have been generally allowed by certification agencies, though hydroxyquinoline sulfate has not been specifically listed.

International

CODEX – Livestock standards at Step 8 (final adoption scheduled for July 2001) allows chemical allopathic veterinary drugs or antibiotics, when acceptable alternative preventive methods do not exist, provided that they are used under a veterinarian’s care with a minimum withholding of 48 hours or double the withdrawal time.

EU 2092/91 – Similar to CODEX, with an additional proviso that animals treated more than 2 times or a maximum of 3 times per year with chemical veterinary drugs can no longer be marketed as organic (Annex I, Section B 4).

IFOAM – Similar to CODEX and EU. Natural products and preventive methods preferred, but use of veterinary medicines is permitted under control of certification agency.

Canada – Similar to CODEX with the withdrawal period “at least double the permitted federal withdrawal period allowed for veterinary drugs” (CGSB, 1999).

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.*

When used as topical salve, it is unlikely to interact with other materials.

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.*

8-Hydroxyquinoline sulfate is reported as a poison by ingestion, with mutation data reported (Sax, 1992). Moderately toxic in rats orally, and distinctly toxic when injected (Gosselin 1984).

Quinoline is a poison, when ingested orally or through subcutaneous injection. Contact with the skin produces a moderate toxic reaction and can result in severe irritation (Kirk-Othmer 1996b, BIBRA 1990). Quinoline derivatives can also be dangerous, and 8-quinolinol is considered especially toxic intraperitoneally, with an LD 50 (mouse) of 48 mg/kg. It is reported to cause neoplasia of various parts of the body when ingested, implanted or administered intravenously (Kirk-Othmer, 96b).

It is reportedly potentially neurotoxic when used topically for prolonged periods (Aiello, 1998). Its use in cosmetics was reviewed comprehensively by the Cosmetic Ingredient Review Expert Panel in 1992. It was found to be a mild skin irritant in rabbits and mutagenic in mouse and salmonella assays. No evidence of carcinogenicity was found in feeding studies. Lack of dermal carcinogenesis and skin sensitization data led the CIR panel to conclude that it could not determine if hydroxyquinoline sulfate or oxyquinoline could be safely used in cosmetics (Anon. 1992).

Its persistence and breakdown in the environment is not indicated in the literature, however, FDA has no established tolerance levels for residues listed under 21CFR556. As mentioned, FDA does not consider that it has adequate data on this material to classify it as safe or effective.

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

Extraction from coal tar or synthesis from petrochemicals is likely to have environmental impact, though this use as an antiseptic is undoubtedly a minor use for this material.

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

See toxicity information under number 1. Although it is not generally reported as a carcinogen or teratogen, a test of the food additive formerly used as cheese preservative (8-hydroxyquinoline) found tumors in the bladder, brain, and uteri of rats and mice when administered intravaginally (NTP, Peterson, 1978). FDA's antimicrobial review panel found in 1990 that although benzoquinone, oxyquinoline, and oxyquinoline sulfate had previously been permitted alone or in combination for the treatment of athlete's foot, jock itch, and ringworm, that there was not sufficient data to consider the material safe or effective for this use or as diaper rash. The antifungal uses were withdrawn completely by 1994 (Lipnicki, 2001b).

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.*

Topical ointments used as health care substances are unlikely to have chemical interactions with the agroecosystem.

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

Chapping of the teat in dairy cows may be caused by wind, cold, wetness, sunburn, chemical irritation from teat dips or sanitizers, or from contaminated bedding. Several types of dermatitis can also form lesions. Veterinary texts recommend a “vigorous treatment with suitable antiseptic cream” after each milking (Radostitis, et. al 1994). The preferred antiseptics mentioned are chlorhexidine and iodophors (a combination of iodine and phosphorous). Soluble lanolin and glycerin are used as emollients. An iodophor teat dip used post-milking containing 15% glycerin is an effective emollient, and usually cures sore and chapped teats (Radostitis, 1994). Iodine can contaminate milk, and

investigation has determined that the minimum effective concentration appears to be 0.1% (3.5 ppm of free iodine) rather than 1.0% which is usually recommended. Other dairy texts mention the use of an emollient combined with a teat disinfectant post-milking, but no mention is made of hydroxyquinoline sulfate (Webster, 1993; Holmes, 1987). The National List at 7 CFR 205.603 currently includes glycerin, iodine, hydrogen peroxide, and chlorhexidine. Lanolin was voted on in D.C. 1999 as natural and not within the scope of the National List. It is possible that good sanitation practices before and after milking, combined with lanolin or other approved emollient creams that did not contain this antiseptic, may also be effective.

7. *Its compatibility with a system of sustainable agriculture.*

This product appears to have a long history of accepted use in conventional agriculture, but literature about toxicity and safety is not reassuring. Its derivation from coal tar, the incomplete studies on dermal and skin sensitivity, and lack of information on this older product render it questionable. Alternatives may be sufficient so that this material is not needed for the welfare of animals in the organic system.

TAP Reviewer Comments*

Additional questions asked of Reviewers:

- 1) Do you know of more alternatives?
- 2) Can you provide any more information on the mode of action of HQS as an antiseptic?
- 3) Is this product widely used in your experience?

Reviewer 1

[a veterinarian who works with a substantial number of organic dairies]

Alternatives:

There are a myriad of udder ointments sold commercially. Bag Balm probably has been used the longest in the dairy industry. Med-Aide (which has other ingredients, possibly questionable) also is popular as is Udder Mint (a peppermint type ointment) and also Calendula-Echinacea ointment (in a lanolin-petrolatum base), among others.

More information of mode of action of HQS?

I think the information supplied covers most aspects of its use in the human and animal realm.

Is this product widely used in your experience?

Yes, without a doubt.

How does it fare under OFPA criteria? List objections or reservations under each heading.

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

I don't think an ointment that is put on a small percentage of teats at any one milking will create any detrimental chemical interactions within the farm system, especially since it is wiped off during preparation of the udder before the next milking.

- (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.*

I think the Review sheet points out some potential problems with HQS, but only when it is administered differently than the intended occasional use as a topical ointment.

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

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Since this is a coal tar derivative, I imagine there could be environmental impacts during its manufacture. But once on the farm, the occasional use of a minute amount of the material shouldn't give any cause for concern

- (4) *The effects of the substance on human health.*

Since it is not being used orally in cottage cheese manufacture anymore, I don't think a minor usage of HQS applied topically to teats occasionally would make for any potential of harm to humans.

- (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.*

The insignificant amount of HQS makes this a moot point. To put it in perspective, I have seen small (4oz?) containers of Bag Balm in farm medicine cabinets for years before being used up.

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

I must say that I looked up various skin conditions and teat conditions in, "Diseases of Dairy Cattle" by William C. Rebhun (Williams & Watkins, 1995) and not once did I find mention of any HQS emollients under treatment sections. I did see aloe and lanolin based medications mentioned frequently. I consider this text the leading text in conventional dairy medicine and surgery. In my clinical practice I tend to promote calendula-echinacea ointment for teat scrapes, bruises and scabs as a good promoter of healing. Chlorhexidine ointments are also available and chlorhexidine is approved as a veterinary treatment. So, yes, there are alternatives.

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

If we begin to question this product's derivation from coal tar (which is a valid question), then we may need to also question the use of diesel fuel for farm tractors – its procurement, refining, toxicity and pollution. I don't think this product, which is used occasionally to help the cows' teats feel better if chapped, etc. will negatively impact sustainable agriculture, especially if compared to diesel fuel usage when cultivating row crops.

Advised Recommendation:

I agree with the summary recommendation on page one that hydroxyquinoline sulfate (HQS) is a synthetic. I feel the amount used is negligible in the face of everything else that is used in dairy farming, but that the derivation from coal tar and some potential toxicity if not used as intended as a topical salve for sore cow teats could be a problem. Since there are alternatives that are available, I do not find this material necessary and recommend it be prohibited.

Reviewer 2

[a dairy consultant and inspector for organic certifiers]

1. Alternatives:

From Juliet de Bairacli Levy's book *The Complete Herbal Handbook For Farm and Stable*, I found a recommendation to use warm almond oil as a salve alternated with brewing of elder blossom or leaves and marsh-mallow leaves. Another recommendation was to use raw cucumber juice.

Another book titled *The Green Pharmacy*, by Dr. James Duke recommended Aloe vera, Calendula officinalis, Camomile (*Matricaria recutita*), Cucumber (*Couches sativa*), Gotu Kola (*Centella asiatica*), and Witch Hazel (*Hamamelis virginiana*) to name a few.

Descriptions of the different herbs listed, as found in 'The Green Pharmacy':

Aloe vera: The gel inside aloe's leathery leaves was shown to speed the healing of radiation burns, many studies have shown this herb to be effective in treating a variety of skin problems

Calendula officinalis: Research has shown that this herb is antibacterial, antifungal, anti-inflammatory and antiviral. Calendula also stimulates white blood cells to gobble up harmful microbes and helps speed wound healing.

Chamomile (Matricaria recutita): The tasty herb is approved in Europe for treatment of inflammatory skin conditions, notably yeast infections. Compounds in chamomile (bisabolol, chamazulene and cyclic ethers) are anti-inflammatory, bactericidal and fungicidal.

Cucumber (Cucumis sativa): cucumber has a long folk history of use for soothing dermatitis and burns and for treating wrinkles.

Gotu kola (Centella asiatica): This herb stimulates the regeneration of skin cells and underlying connective tissue. In clinical trials, gotu kola has proven useful in treating eczema, wounds and other skin conditions.

Witch hazel (Hamamelis virginiana): Witch hazel contains generous amounts of tannins, potent astringents that are useful in treating skin problems. According to studies with laboratory animals, witch hazel also increases the tone of the blood vessels in the skin, which enhances blood supply to the damaged areas.

A lot of these herbs are readily available as salves or ointments, oils and aqueous solutions. After talking to a few dairy farmers, the consensus is, that there are a lot of other options of acceptable products and if they were not allowed to use *Bag Balm* (for example), they wouldn't complain.

2. Any more information on the mode of action of HQS as an antiseptic?

No.

3. Is this product widely used in your experience?

Yes, I would have to say that in almost every barn that I visit, I will find a container of Bag Balm. It has been around for so long with good results. There are plenty of alternatives made from accepted ingredients, that I feel like the farmers can be informed of other options and where to find them.

Concerns about the use of Hydroxyquinoline:

- The fact that Quinoline is a poison, when ingested orally makes me a little wary since livestock are apt to lick a wound and would more than likely ingest some if this if it were topically applied. If this were applied to a teat that was not properly cleaned at milking, then trace amounts could get into the milk. This is a risk for animal and human consumption.
- If Hydroxyquinoline Sulfate were permitted as a regulated or allowed topical synthetic, I would hope that there would be some limit to the amount of Hydroxyquinoline allowed within a product. 0.3% seems so small (i.e. Bag Balm), I would not like to see the use of this get taken advantage of.
- Actual mode of action of this material was not evident from the literature, and its persistence and breakdown in the environment was not indicated.

Advised Recommendation:

There are so many topical ointments that do not have synthetic ingredients, I don't think that it is necessary to have Hydroxyquinoline Sulfate listed as an allowed synthetic. I vote that this product is a synthetic and that it should be prohibited.

Reviewer 3

[Doctor of Veterinary Medicine with experience in animal nutrition, holistic animal health and organic agriculture]

1. Alternative

It was stated in the review that, "It is possible that good sanitation practices before and after milking, combined with lanolin or other approved emollient creams that did not contain this antiseptic, may also be effective." I agree with this but I wonder if there are any "approved emollient creams" available to the organic producer at this time. If there are none then I think this product should be approved.

Lanolin is an excellent emollient but has little, if any, antiseptic action. Products such as iodine and chlorhexidine if used alone tend to be drying to the teats and udder and this alone can often cause teat problems. Glycerin is a good emollient that softens the tissue but does not provide a barrier to more contamination.

2. Any more information on the mode of action of HQS as an antiseptic?

I have no information on the mode of action other than that already cited.

3. Is this product widely used in your experience?

As stated above this product has been used for a long time, I doubt you could find many dairy farms where the product was not being used. Over the years I have even used it on myself as a topical ointment with good results.

Given the low usage rate and the fact that the concentration is only 0.3 percent of the final product, it is difficult for me to see any adverse effect on the animal, the ecosystem or the final food product.

Review according to the OFPA Criteria

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

I agree with the following statement from the original TAP Review. "When used as topical salve, it is unlikely to interact with other materials."

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.*

Given the low usage rate as a topical salve and the fact that the concentration is only 0.3 percent of the final product, it is difficult for me to see any adverse effect on the animal, the ecosystem or the final food product.

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

I agree [with the Tap review...] that the impact is minor if it even exists.
I believe the occasional use does not constitute a hazard to the environment. The chances for misuse or contamination by improper disposal are minimal.

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

The product is already being used in many cosmetics, OTC remedies and medications allowed by FDA.
Opportunity for any human contamination resulting from it's use in cattle is minimal at best, in my opinion.

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.*

Given the low usage rate as a topical salve and the fact that the concentration is only 0.3 percent of the final product, it is difficult for me to see any adverse effect on the animal, the ecosystem or the final food product. Original TAP Review indicates that they are not absorbed from the gut and I believe that even if small quantities were licked by the cow it would pose no threat to animal or human health. ("The Merck Veterinary Manual [states...] **They are not absorbed from the GI tract** and are thus used for intestinal infections caused by bacteria or protozoa (such as *Giardia*). [...] (Aiello, 1998)).

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

Of course there are many alternatives to almost anything. However, in my opinion, the mere presence of these relatively obscure (and not always readily available) products should not preclude the use of another product that has been used safely by dairymen for decades. The review of possible herbal alternative treatments was interesting and appropriate for those who have the time, knowledge and the inclination to formulate their own herbal remedies... many dairymen do not.

7. *Its compatibility with a system of sustainable agriculture.*

Given the low usage rate as a topical salve and the fact that the concentration is only 0.3 percent of the final product, it is difficult for me to see any adverse effect on the animal, the ecosystem or the final food product.

From your original TAP Review: "Topical ointments used as health care substances are unlikely to have chemical interactions with the agroecosystem." I agree.

Advised Recommendation:

I consider the material to be synthetic but I vote to allow its use as a topical salve for dairy cattle in concentrations no higher than 0.3%.

Reviewer 4

[Doctor of Veterinary Medicine with a degree in public health, former state health department official, a researcher in pharmaceuticals and biological products, with experience in organic certification]

I don't believe that the use of 8-hydroxyquinoline sulfate is compatible with a system of sustainable agriculture. First, there do seem to be more compatible alternatives (e.g., calendula, aloe vera, lanolin, etc. assuming these products would pass muster under organic materials review). Second, the manufacture of hydroxyquinoline does contribute to contamination of the environment (and unlike diesel fuel for farm tractors, there seems to be suitable, readily available alternatives). Third, and perhaps most importantly, hydroxyquinoline is presumed to have antibiotic properties. It may be weakly antibiotic (since FDA considers it bacteriostatic, i.e. it suppresses micro-organism colony growth, as opposed to bacteriocidal, i.e. actually killing micro-organisms). But this only makes the argument against its approval more compelling since if it is only weakly antimicrobial, its effectiveness is doubtful (and if it is not antimicrobial at all, the benefits of bag balm are probably due to other ingredients such as lanolin). Yet, weak antimicrobials are more likely to encourage the development of resistant organisms (Grady, 2000). Moreover, hydroxyquinoline may be chemically related to the fluoroquinolone antibiotics, (Budavari 1996) which are the subject of FDA action to withdraw certain uses of these antibiotics because of concerns for antibiotic resistance and the public health (FDA, 2000b).

As much as we have developed "bright lines" in the review of organic materials for livestock use, the prohibition of the routine use of antibiotic-containing products is one of them.

Advised Recommendation:

Synthetic and prohibited

Conclusion

Hydroxyquinoline sulfate is clearly synthetic and prohibited unless added to the National List. A majority of the TAP reviewers find that the availability of alternatives and uncertainty about safety are sufficient reasons to not recommend its allowance in organic systems. The OFPA prohibits the administration of medicines in the absence of illness (7 USC 6509(d)). One reviewer is concerned that the substance has antibiotic properties, which are also prohibited in subtherapeutic doses under OFPA 6509(d). The NOSB has sufficient reasons to recommend that hydroxyquinoline sulfate not be added to the National List. These reasons include the evidence that the substance is synthetic; that the toxicological properties are not clearly established; that a widely used product containing this substance is considered by FDA to be an unapproved new animal drug; and that there are several alternatives available for producers.

References

Anonymous, 1992. Final Report on the Safety Assessment of Oxyquinoline and Oxyquinoline Sulfate. Journal of the American College of Toxicology, Vol. 11, No. 4, pages 497-507.

Battler, Dr. Neal. 2001 FDA/Center for Veterinary Medicine (HFV-214), Division of Surveillance, 7500 Standish Place, Rockville, MD 20855-2773. (301) 827-0163 e-mail: nbatalle@cvm.fda.gov. Electronic mail communication, dated Feb. 15, 2001.

Budavari, S. ed. 1996. The Merck Index 12th Ed. p. 298 – see carbostyryl; p. 832 - 8-hydroxyquinoline; p. 1388 – quinoline. Merck & Co., Whitehouse Station, NJ.

Bag Balm Ointment, website <http://bagbalm.com/>

BIBRA working group. 1990. Toxicology profile, British Industrial Biological Research Assoc. Year 1990, p. 7.

CGSB – Canadian General Standard Board. 1999. *Organic Agriculture*. Ottawa.

CFR- Code of Federal Regulations, 2000, 21CFR310.545. Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

- de Bairacli Levy, Juliette. 1952. The Complete Herbal Handbook For Farm and Stable. Faber and Faber Limited, 3 Queen Square London WC1N 3AU, p. 198.
- Duke, James. 1997, The Green Pharmacy, St Martin's Press, pp. 392-395.
- FDA, 1994. OTC Drug Review Ingredient Status Report. <http://www.fda.gov/cder/otc/ingred.pdf>
- FDA, 1998. Prescription and Over-the-Counter Drug Product List. - 17th Edition Cumulative Supplement Number 11: Jan '97 - Nov '97 <http://www.fda.gov/cder/da/pdpl1197.htm>
- FDA, Dec 2000 Office of Regulatory Affairs, Inspectional References: Investigations Operations Manual, Appendix A - Food Additive Status List - 4. http://www.fda.gov/ora/inspect_ref/iom/APPENDICES/appa4.html
- FDA, 2000b. NOOH FOR POULTRY FLUOROQUINOLONES -- Background Information. December 7, 2000. <http://www.fda.gov/cvm/antimicrobial/NOOHB.htm>
- FDA 20001 Approved Animal Drug Products (The Green Book On Line) <http://www.fda.gov/cvm/greenbook/greenbook.html>. Updated monthly, information downloaded Feb. 10, 2001.
- Grady, D. June 2, 2000. Disease Spread Is Traced to Many Agents. New York Times. <http://www.nytimes.com>
- Holmes, C.W. , G. F. Wilson et. al. 1987. Milk Production from Pasture. p. 59, 87. Butterworth Agricultural Books, New Zealand.
- Keller, Dr. William, 2001. Director, Division of Compliance, Center for Veterinary Medicine, HFV-200. FDA, Rockville MD 20857. Personal communication Feb. 9, 2000.
- Kirk-Othmer, 4th ed. 1996a. Encyclopedia of Chemical Technology. Vol. 2. Antibiotics (survey) pp 893-905. New York, John Wiley
- Kirk-Othmer, 4th ed. 1996b. Encyclopedia of Chemical Technology. Vol. 20 . Quinolines and Isoquinolines. P 769-799. New York, John Wiley.
- Lipnicki, J. 2001. Fax communication from FDA, Division of OTC Drug Products, Office of Drug Evaluation V, Center for Drug Evaluation and Research. Includes: (a) OTC Active Ingredient Status Report Sept. 01, 1994, pg. 42: (b) Comments from the Federal Register, 56 FR 2572-2573, and (c) 47FR 22880-22881: 8 pages total.
- National Toxicology Program (NTP) of US Department of Health and Human Services, National Institutes of Health's National Institute of Environmental Health Sciences (NIH/NIEHS), Chemical Repository 8-Hydroxyquinoline Sulfate. Downloaded Jan 2001. http://ntp-server.niehs.nih.gov/htdocs/CHEM_H&S/NTP_Chem1/Radian134-31-6.html
- Material Safety Data Sheet, on file with US Department of Labor, Occupational Safety and Health Administration, provided by Dairy Association Co., Inc. Lyndonville, VT 05851.
- Material Safety Data Sheet, on file with the US Department of Labor, Occupational Safety and Health Administration, provided by Napp Technologies, Inc. Saddle Brook, NJ.
- Meister, R.T. 2000. Farm Chemicals Handbook. Vol 86. p. C45, listing for "Beltanol L". Willoughby OH.
- Napp Technologies Inc., 1999. Technical Documentation, Neutral 8-Hydroxyquinoline Sulfate, no. 75-020, Saddle Brook, NJ.
- Peterson, M.S. and A. H. Johnson. 1978. Encyclopedia of Food Science. "Carcinogens Related To Foods", p. 110. Westport CT , AVI Publishing.
- Radostitis, O.M, D.C. Blood, and C.C. Gray. 1994. Veterinary Medicinien, A textbook of the Diseases of Cattle, Sheep, pigs, Goats and Horses. 8th ed. p.407-408. Balliere Tindall, London.
- Taber, C.M. 1981. Taber's Cyclopedic Medical Dictionary, p. 94. F.A. Davis, Philadelphia.

USP Dictionary of USAN and International Drug Names, 2000 ed. US Pharmacopoeia, Rockville MD. p. 870, 2970.

Sax, N.I 1992. Dangerous Properties of Industrial Materials. 8th Ed. R. J. Lewis, editor. Vol. III, p. 2970. Van Nostrand Reinhold. New York.

Webster, John. 1993. Understanding the Dairy Cow. p. 248-249. Blackwell Sci. Publ. London.

Windholz, M. Ed. 1983. The Merck Index. 10th Ed Merck and Co., Rahway NJ. P. 706-707.