HEPARIN
Livestock

Executive Summary

Heparinic acid, or heparin, is highly acidic mucopolysaccharide formed of equal parts of sulfated D-glucosamine and D-glucuronic acid with sulfaminic bridges. Heparin occurs in and is obtained from liver, lung, mast cells, etc., of vertebrates. Its function is unknown, but in humans it is used to prevent blood clotting *in vivo* and *in vitro*, in the form of many different salts. [1]

The subject of the petition is a request for heparin to be approved for use in organic livestock medical treatment. Heparin is used in blood transfusions to prevent the donor's blood from coagulating prior to administration, as well as in animals at risk of thrombosis due to endotoxemia and disseminated intravascular coagulopathy.

Summary of TAP Reviewer Analyses [2]

Synthetic/ Nonsynthetic	***Allow without restrictions?***	***Allow only with restrictions? (See Reviewers' comments for restrictions)***
Synthetic (3)	Yes (1) No (2)	 No (2)

Identification

Chemical names: Heparin, Heparinic acid

Other Names: Calcilean, Calciparine, Hepalean, Heparin Leo, Liquaemin

Bemiparin, CY 216, CY 222, Certoparin, Clexane, Clivarin, Clivarine, Dalteparin, Enoxaparin, Eparina [DCIT], FR 860, Fluxum, Fragmin A, Fragmin B, Fraxiparin, Hed-heparin, Heparin CY 216, Heparin sulfate, Heparina [INN-Spanish], Heparinate, Heparine [INN-French], Heparinum [INN-Latin, Hepathrom, KB 101, Lipo-hepin, Liquemin, Multiparin, Novoheparin, OP 386, OP 622, Pabyrin, Parnaparin, Parvoparin, Pularin, Reviparin, Sandoparin, Sublingula, Thromboliquine, Vetren, Vitrum AB, *alpha*-Heparin, *depo*-Heparin

CAS Number: #9005-49-6

Other numbers:

EINECS #232-681-7
HSDB #3094
NIOSH: MI0700000
RTECS Number : MI0850000

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[1] "Heparin." ChemID Plus. http://toxnet.nlm.nih.gov/cgi-bin/sis/search

[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.*

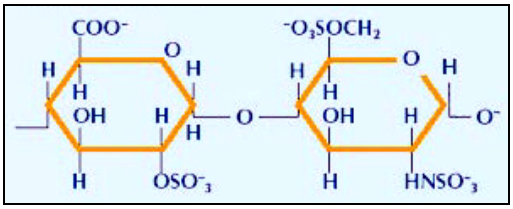
VA Classification: PrimaryBL110

Characterization

Composition/Structure:

Heparin is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans, that has anticoagulant properties. Although other sugars may be present, the main sugars occurring in heparin are:

(1) a-L-iduronic acid 2-sulfate,
(2) 2-deoxy-2-sulfamino-a-D-glucose 6-sulfate,
(3) b-D-glucuronic acid,
(4) 2-acetamido-2-deoxy-a-D-glucose, and
(5) a-L- iduronic acid.



l. Heparin.[3]

These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes. For unfractionated standard heparin, molecular weight ranges from 5,000 to 30,000 Da, and for low molecular weight heparin (LMWH) it ranges from 4,000 to 6,000 Da (Ramos-Sanches et al., 1995). Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups.

Heparin is synthesized endogeneously and stored in the basophilic granules of mast cells, which are found in most tissues of mammalian species. The greatest concentrations are found in the liver, lung and intestines.

In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions. Heparin may also be a salt of calcium.

Heparin Sodium Injection, USP is a sterile solution of heparin sodium derived from porcine intestinal mucosa, standardized for anticoagulant activity, in water for injection. It is administered by an intravenous or deep subcutaneous route. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram. [4, 5]

Properties:

Appearance: White powder.
Odor: Odorless.
Solubility: Soluble in water.
pH: 6.0-7.5 (1% aqueous solution)
% Volatiles by volume @ 21C (70F): 0
Vapor Pressure (mm Hg): 0 @ 20C (68F)
Evaporation Rate (BuAc=1): 0
Stability: Stable under ordinary conditions of use and storage. Hygroscopic.
Hazardous Decomposition Products: Burning may produce carbon monoxide, carbon dioxide, sulfur oxides, and

[3] "Heparin – General Information." BioIberica. http://www.bioiberica.com/eng/mp/heparin.htm
[4] "Heparin – Rx List Monograph." RxList.com http://www.rxlist.com/cgi/generic/heparin.htm
[5] "Heparin Sodium – General Information." BioIberica. http://www.bioiberica.com/eng/mp/heparines.htm

nitrogen oxides.
Hazardous Polymerization: Will not occur.
Incompatibilities: Strong oxidizers.
Conditions to Avoid: Heat, flames, ignition sources and incompatibles. [6]

Protein binding:
Very high; primarily to low-density lipoproteins; also bound to globulins and to fibrinogen.

Biotransformation:
Hepatic; however, the primary route of removal from the circulation is uptake by the reticuloendothelial system.

Half-life:
1 to 6 hours (average 1.5 hours); dose and route dependent and subject to inter- and intrapatient variation. May be increased above the average in patients with renal failure, hepatic function impairment, or obesity. May be decreased in patients with pulmonary embolism, infections, or malignancy.

Onset of action:
Direct intravenous injection - Immediate.
Intravenous infusion - Immediate when infusion is preceded by the recommended intravenous loading dose. If no loading dose is given, the onset of action may depend upon the rate of infusion.
Subcutaneous - Generally within 20 to 60 minutes but subject to interpatient variability.

Elimination:
Renal, usually as metabolites. However, after intravenous administration of high doses, up to 50% of a dose may be excreted unchanged.

In dialysis - Not removed via hemodialysis.[7]

How Made:

Heparin may be derived from porcine intestinal mucosa or bovine intestinal or lung tissue in an extraction process. However, since the outbreak of bovine spongiform encephalopathy (BSE), or mad cow disease, only porcine-derived heparin is allowed in the United States and Europe. Crude heparin is obtained during the extraction phase of the intestinal mucosa, involving a proteolytic treatment of the tissue followed by extraction and complexing with ion pairing reagents. The crude heparin is subjected to fractional precipitation, purification, and chemical treatment to obtain injectable heparin. [8]

The following is general information on biological and natural extraction, from the EPA:

3.4.2.2 Biological and Natural Extraction

Many materials used as pharmaceuticals are derived from such natural sources as the roots and leaves of plants, animal glands, and parasitic fungi. These products have numerous and diverse pharmaceutical applications, ranging from tranquilizers and allergy-relief medications to insulin and morphine. Also included in this group is blood fractionation, which involves the production of plasma and its derivatives.

Despite their diversity, all extractive pharmaceuticals have a common characteristic: they are too complex to synthesize commercially. They are either very large molecules, and/or their synthesis results in the production of several stereoisomers, only one of which has pharmacological value. Extraction is an expensive manufacturing

[6] "Heparin Na – MSDS." Mallinckrodt Baker, Inc. 8 May 2000. http://www.jtbaker.com/msds/h0314.htm
[7] "Heparin Leo: USPDI Professional Information." Drugs.com. http://drugs.com/xq/cfm/pageID_0/xml_001310/type_pros/bn_Heparin%20Leo/qx/index.htm#
[8] "Risk of transmission of new variant Creutzfeldt-Jakob disease: tests developed to guarantee the safety of an injectable medicine, heparin." Institut National de la Recherche Agronomique. September 2001. http://www.inra.fr/presse/sept01/gb/nb1.htm

process which requires collecting and processing large volumes of specialized plant or animal matter to produce small quantities of products. Facilities utilize extraction when there are no other reasonable alternatives for producing a desired active ingredient.

The extraction process consists of a series of operating steps beginning with the processing of a large quantity of natural or biological material containing the desired active ingredient. After almost every step, the volume of material being handled is reduced significantly. In some processes, reductions may be in orders of magnitude, and complex final purification operations may be conducted on quantities of materials only a few thousandths of the volume handled in earlier steps. Neither continuous processing methods nor conventional batch methods are suitable for extraction processing. Therefore, a unique assembly-line, small-scale batch processing method is used. Material is transported in portable containers through the plant in 75- to 100-gallon batches. A continuous line of containers is sent past a series of operating stations. At each station, operators perform specific tasks on each batch in turn. As the volume of material being handled decreases, individual batches are continually combined to maintain reasonable operating volumes, and the line moves more slowly. When the volume is reduced to a very small quantity, the containers also become smaller, with laboratory-size equipment used in many cases. An extraction plant may produce one product for a few weeks; then, by changing the logistical movement of containers and redefining tasks to be conducted at each station, the plant can convert to the manufacture of a different product.

Residual wastes from an extraction plant essentially will be equal to the weight of raw material, since the active ingredients extracted are generally present in the raw materials at very low levels. Solid wastes are the greatest source of the pollutant load; however, solvents used in the processing steps can cause both air and water pollution. Detergents and disinfectants used in equipment cleaning operations are normally found in the wastewater.

Priority pollutants, including methylene chloride, toluene, chloroform, 1,2-dichloroethane, and phenol, were identified as being used in the manufacturing of extractive pharmaceuticals in the Detailed Questionnaire. The cations of lead and zinc are known to be used as precipitating agents. Phenol was identified as a disinfecting chemical. The other priority pollutants found were used as processing solvents. The Detailed Questionnaire identified nonconventional pollutants most often used in the extractive manufacturing process as ethanol, methanol, n-amyl acetate, isopropanol, and acetone. These nonconventional pollutants may be used as processing solvents. Table 3-6 lists solvents used in biological or natural extraction operations.

Solvents are used in two ways in extraction operations. Some solvents are used to remove fats and oils that would contaminate the products. These "defatting" extractions use an organic liquid that dissolves the fat but not the product material. Solvents are also used to extract the product itself. For example, when plant alkaloids are treated with a base, they become soluble in such selected organic solvents as benzene, chloroform, and 1,2-dichloroethane.

Ammonia is used in many extraction operations because it is necessary to control the pH of water solutions from both animal and plant sources to separate valuable components from waste materials. Ammonium salts are used as buffering chemicals, and aqueous or anhydrous ammonia is used as an alkalinizing reagent. The high degree of water solubility of ammonium salts prevents unwanted precipitation of salt, and they do not react chemically with animal or plant tissue. Such basic materials as hydroxides and carbonates of alkali metals do not have these advantages.

The principal sources of wastewater from biological/natural extraction operations are: 1) spent raw materials (e.g., waste plasma fractions, spent media broth, plant residues); 2) floor and equipment wash water; 3) chemical wastes (e.g., spent solvents); and 4) cleanup of spills. Wastewater from extraction plants is generally characterized by low BOD , COD, and TSS 5 concentrations; small flows; and pH values of approximately 6.0 to 8.0.

Table 3-6
Solvents Used in Biological or Natural Extraction Operations

Acetone	Ethylene glycol
Acetonitrile	Formaldehyde
Ammonia (aqueous)	n-Heptane
n-Amyl acetate	n-Hexane
Amyl alcohol	Isopropanol
n-Butyl alcohol	Isopropyl acetate
Chloroform	Isopropyl ether
1,2-Dichloroethane	Methanol
Diethylmine	Methylene chloride
Diethyl ether	Petroleum naphtha
N,N-Dimethylformamide	Phenol
Dimethyl sulfoxide	n-Propanol
1,4-Dioxane	Pyridine
Ethanol	Tetrahydrofuran
Ethyl acetate	Toluene [9]

Specific Uses:

Heparin is used as an anticoagulant in both human and veterinary medicine.

In humans, heparin is indicated for:

1. Anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension. Heparin is indicated using a full-dose regimen in the treatment of patients with recent thrombosis or thrombophlebitis of the deep veins to prevent extension and embolization of the thrombus and to reduce the risk of pulmonary embolism or recurrent thrombus formation. In acute pulmonary embolism, full-dose heparin is indicated to decrease the risk of extension, recurrence, or death.
2. Use in a low-dose regimens for prevention of post-operative deep venous thrombosis and pulmonary embolism in patients undergoing major abdomino-thoracic surgery, or who for other reasons are at risk of developing thromboembolic disease. It is indicated in patients requiring prolonged immobilization following surgery, especially if they are 40 years of age or older. Low-dose heparin may be ineffective for this purpose in some patients, especially following hip surgery. [Low-dose heparin prophylaxis is also used to prevent thrombus formation in selected immobilized medical patients who are not at risk of hemorrhage.]
3. Prophylaxis and treatment of pulmonary embolism.
4. Atrial fibrillation with embolization. Heparin is indicated as adjunctive therapy in acute myocardial infarction to reduce the risk of thromboembolic complications, especially in high-risk patients such as those with shock, congestive heart failure, prolonged arrhythmias (especially atrial fibrillation), previous myocardial infarction, or history of venous thrombosis or pulmonary embolism. Also, heparin may be administered to help prevent reocclusion following thrombolytic therapy in patients with acute myocardial infarction. Heparin is also used to prevent catheter-induced thromboembolism during coronary angiography and percutaneous transluminal angioplasty.
5. Diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation).
6. Prevention of clotting in arterial and cardiac surgery. It is administered systemically or by local intra-arterial injection.
7. Prophylaxis and treatment of peripheral arterial embolism. It may prevent further thrombus formation when surgery must be delayed.

[9] "Example Pharmaceutical Products by Manufacturing Process and Classification." U.S. Environmental Protection Agency. http://www.epa.gov/guide/pharm/techdev/tdd.pdf

8. As an anticoagulant in blood transfusions, extracorporeal circulation, dialysis procedures and in blood samples for laboratory purposes. However, heparinized blood should not be used for isoagglutinin, complement, or erythrocyte fragility tests, or for platelet counts. In addition, leukocyte counts should be performed within 2 hours after heparin is added to the blood sample. [10, 11]

Heparin is the anticoagulant of choice when an immediate effect is required. When long-term anticoagulant therapy is required, a coumarin or indandione derivative is usually administered as a follow-up to heparin therapy. However, in some patients (especially pregnant women) long-term anticoagulation with heparin may be desirable.

Prophylactic use of heparin (low-dose or full-dose) is not recommended for patients with bleeding disorders; patients having neurosurgery, ophthalmic surgery, or spinal anesthesia; or patients who are receiving a coumarin- or indandione-derivative anticoagulant or a platelet active agent.

Heparin has also been used to reduce the risk of thrombosis and/or occlusion of the aortocoronary bypass following coronary bypass surgery; however, its efficacy has not been established and this use is controversial. Also, platelet aggregation inhibitors, especially aspirin, are more commonly used for this indication.

Other effects of heparin include reducing the concentration of triglycerides in plasma by releasing the enzyme lipoprotein lipase from tissues and stabilizing the enzyme. The resultant hydrolysis of triglycerides leads to increased blood concentrations of free fatty acids.

Heparin Sodium Injection, USP (porcine) for humans is available as follows:
Each 1,000 Units/mL contains: 1,000 USP Heparin Units (porcine); 9 mg sodium chloride; Water for Injection q.s. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment (5.0-7.5). [12]

In livestock, the petitioned uses of heparin are for use as an anticoagulant in blood transfusions, to prevent blood from coagulating enroute from the donor to the recipient animal; and for use in thrombosis prevention in animals suffering from endotoxemia. When used in blood transfusions, the heparin is added to the container prior to the blood.

The following is an abstract from a research project involving treatment of coagulation disorders in horses.

"Heparin is used for treatment of coagulation disorders associated with severe gastrointestinal disease, septicemia and endotoxemia in horses. Further indications are the prevention of laminitis, intraabdominal adhesions, disseminated intravascular coagulation, venous thrombosis and thrombophlebitis. Unfractioned heparin (UFH) has some undesirable side effects. In horses, a rapid decrease in packed cell volume (PCV), erythrocyte agglutination, thrombocytopenia and hemorrhage are frequently associated with use of unfractioned heparin. Furthermore, unfractioned heparin has unpredictable pharmakokinetic properties and there is marked individual variation of sensitivity to heparin in horses and human beings. Low-molecular-weight heparin (LMWH) is routinely used in human medicine. LMWH has reduced side effects, higher bioavailability, longer half-inactivation time and dose-dependent anticoagulatory effect. However, LMWH has similiar antithrombotic properties as UFH. The purpose of the study is to compare the action and side effects of unfractioned and low-molecular-weigt heparin for prophylaxis of coagulation disorders in gastrointestinal disease in horses." [13]

Some veterinary doses of heparin are as follows:
Cat: 1 mg/kg BW IV (Kinsell, 1986)

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[10] "Heparin – Rx List Monograph." RxList.com http://www.rxlist.com/cgi/generic/heparin.htm
[11] "Heparin Leo: USPDI Professional Information." Drugs.com. http://drugs.com/xq/cfm/pageID_0/xml_001310/type_pros/bn_Heparin%20Leo/qx/index.htm#
[12] "Heparin Leo: USPDI Professional Information." Drugs.com. http://drugs.com/xq/cfm/pageID_0/xml_001310/type_pros/bn_Heparin%20Leo/qx/index.htm#
[13] Schwarzwald, C., Karsten Feige, Ueli Braun, Th. Bombeli. "Comparison of low-molecular-weight heparin and unfractioned heparin for prophylaxis of coagulation disorders in horses – Abstract." Klinik für Wiederkäuer, Departement für Nutztiere. Universitat Zurich. May 2001. http://www.research-projects.unizh.ch/vet/unit50700/area256/p2028.htm

Dog: 1 mg/kg BW IV (Kinsell, 1986)
Guinea pig: 5 mg/kg BW IV (Melby and Altman, 1976)
Mouse: 10 mg/kg BW IV (Melby and Altman, 1976)
NHP: 2 mg/kg BW IV (Meiby and Altman, 1976)
Rat: 10 mg/kg BW IV (Borchard et al., 1990)
Rabbit: 5 mg/kg BW IV (Melby and Altman, 1976)[14]

Action:

Heparin sodium inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both *in vitro* and *in vivo*. Heparin acts indirectly at multiple sites in both the intrinsic and extrinsic blood clotting systems. It works in conjunction with the inhibitory action of antithrombin III (heparin cofactor) on several activated coagulation factors, including thrombin (factor IIa) and factors IXa, Xa, XIa, and XIIa, by forming a complex with and inducing a conformational change in the antithrombin III molecule. Inhibition of activated factor Xa interferes with thrombin generation and thereby inhibits the various actions of thrombin in coagulation. Heparin also accelerates the formation of an antithrombin III-thrombin complex, thereby inactivating thrombin and preventing the conversion of fibrinogen to fibrin; these actions prevent extension of existing thrombi. Heparin also prevents formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor by thrombin. Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

Larger doses of heparin are required to inactivate thrombin than are required to inhibit thrombin formation. Full-dose heparin prolongs partial thromboplastin time, thrombin time, whole blood clotting time, and activated clotting time (ACT). In most cases, clotting time is not measurably affected by low doses of heparin.

Peak plasma levels of heparin sodium are achieved two to four hours following subcutaneous administration, although there are considerable individual variations. Loglinear plots of heparin sodium plasma concentrations with time, for a wide range of dose levels, are linear, which suggests the absence of zero order processes. Liver and the reticulo-endothelial system are the sites of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase ($t_{1/2}$ = 10 minutes) and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin sodium.[15, 16]

An overdose of heparin in humans is treated by administration of the heparin antagonist protamine. One milligram of protamine sulfate will neutralize approximately 100 USP Units of heparin. However, heparin blood concentrations decrease rapidly following intravenous administration; 30 minutes after intravenous administration of heparin, half as much protamine sulfate may be sufficient to neutralize the remaining heparin. In most cases, it is recommended that protamine sulfate be administered intravenously, slowly (over a one- to three-minute period), and in doses not exceeding 50 mg in any ten-minute period. It is strongly recommended that blood coagulation tests be used to determine optimum protamine dosage, especially when neutralizing large doses of heparin given during cardiac or arterial surgery.[17]

Combinations:

In humans, when long-term anticoagulant therapy is required, a coumarin or indandione derivative is usually administered as a follow-up to heparin therapy.[18]

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[14] "Heparin: Drugs and Dosages." Veterinary Clinical Services, Yale University. 17 February 2000. http://info.med.yale.edu/yarc/vcs/miscellaneous2.htm#Heparin
[15] "Heparin – Rx List Monograph." RxList.com http://www.rxlist.com/cgi/generic/heparin.htm
[16] "Heparin Leo: USPDI Professional Information." Drugs.com. http://drugs.com/xq/cfm/pageID_0/xml_001310/type_pros/bn_Heparin%20Leo/qx/index.htm#
[17] "Heparin Leo: USPDI Professional Information." Drugs.com. http://drugs.com/xq/cfm/pageID_0/xml_001310/type_pros/bn_Heparin%20Leo/qx/index.htm#
[18] "Heparin Leo: USPDI Professional Information." Drugs.com. http://drugs.com/xq/cfm/pageID_0/xml_001310/type_pros/bn_Heparin%20Leo/qx/index.htm#

Status

Historic Use by Organic Farmers:

Heparin was discovered in the 1920's by William Henry Howell during aqueous extraction of liver tissue. The isolation of an anticoagulant phospholipid by medical student Jay McLean in 1916 is considered by many to be the first discovery of heparin. In 1936, Charles Best and his team succeeded in purifying large quantities of heparin from cattle lungs. In 1937, these purified extracts obtained were shown to be effective, causing no ill effects in dogs, rabbits, guinea pigs and mice, and subsequently in human patients.[19] By the early 1940's, purified heparin was available for clinical and experimental use. Since WWII, heparin has been a part of routine human medical treatment.[20] Gordon Murray used heparin to prevent postoperative thrombosis in surgery for the first time, and in the late 1950's, he pioneered coronary artery surgery. Heparin became essential for the heart-lung machines needed for effective cardiac surgery. [21] Heparin continues to be used veterinarily.

USDA, FDA, NOP/NOSB Final Rules:

Following documents are shown below:

1. Federal Organic Foods Production Act of 1990: Otherwise prohibited substances may be exempt if they satisfy a list of criteria, shown below. Also listed are specifications on handling materials. Heparin is not specifically mentioned.
2. Title 21 – 21CFR640.4: Guidelines for blood collection, with a mention of heparin.
3. National Organic Program Final Rule 2000/Draft 2002 / NOSB recommendations: Organic livestock guidelines, including administration of medications. Heparin is not specifically mentioned.

FEDERAL ORGANIC FOODS PRODUCTION ACT OF 1990

6509 ANIMAL PRODUCTION PRACTICES AND MATERIALS.

(a) **In General**. Any livestock that is to be slaughtered and sold or labeled as organically produced shall be raised in accordance with this chapter.

(d) **Health Care**.

(1) **Prohibited Practices**. For a farm to be certified under this chapter as an organic farm with respect to the livestock produced by such farm, producers on such farm shall not

(A) use subtherapeutic doses of antibiotics;

(B) use synthetic internal paraciticides on a routine basis; or

(C) administer medication, other than vaccinations, in the absence of illness.

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[19] Starr A & Edwards M (1961) *Ann Surg* **154**, 726

[20] Marcum, James A. "Origin of the Dispute over the Discovery of Heparin." *Journal of the History of Medicine*. Vol. 55, January 2000. pp. 37-66. http://www3.oup.co.uk/jalsci/hdb/Volume_55/Issue_01/freepdfs/550037.pdf

[21] Warren, P. "MH 13: The Surgical Treatment of Pulmonary and Cardiac Disease." *Hippocrates on the Web: History of Medicine*, Faculty of Medicine, University of Manitoba. http://www.umanitoba.ca/faculties/medicine/history/notes/surgery/

(2) **Standards**. The National Organic Standards Board shall recommend to the Secretary standards in addition to those in paragraph (1) for the care of livestock to ensure that such livestock is organically produced.

6517 NATIONAL LIST.

(a) **In General**. The Secretary shall establish a National List of approved and prohibited substances that shall be included in the standards for organic production and handling established under this chapter in order for such products to be sold or labeled as organically produced under this chapter.

(b) **Content of List**. The list established under subsection (a) of this section shall contain an itemization, by specific use or application, of each synthetic substance permitted under subsection (c) (1) of this section or each natural substance prohibited under subsection (c)(2) of this section.

(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;

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

(iii) is consistent with organic farming and handling;

(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;

(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

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

(C) the specific exemption is developed using the procedures described in subsection (d) of this section. [22]

6510 HANDLING.

(a) In General. For a handling operation to be certified under this chapter, each person on such handling operation shall not, with respect to any agricultural product covered by this chapter

(1) add any synthetic ingredient during the processing or any post harvest handling of the product;

[22] Federal Organic Foods Production Act of 1990. http://www.ams.usda.gov/nop/orgact.htm

(2) add any ingredient known to contain levels of nitrates, heavy metals, or toxic residues in excess of those permitted by the applicable organic certification program;

(3) add any sulfites, nitrates, or nitrites;

(4) add any ingredients that are not organically produced in accordance with this chapter and the applicable organic certification program, unless such ingredients are included on the National List and represent not more than 5 percent of the weight of the total finished product (excluding salt and water);

(5) use any packaging materials, storage containers or bins that contain synthetic fungicides, preservatives, or fumigants;

(6) use any bag or container that had previously been in contact with any substance in such a manner as to compromise the organic quality of such product; or

(7) use, in such product water that does not meet all Safe Drinking Water Act [42 U.S.C.A. 300f et seq.] requirements.

(b) Meat. For a farm or handling operation to be organically certified under this chapter, producers on such farm or persons on such handling operation shall ensure that organically produced meat does not come in contact with nonorganically produced meat.

CODE OF FEDERAL REGULATIONS
Title 21, Volume 7
Revised as of April 1, 2002

21CFR640.4

TITLE 21--FOOD AND DRUGS

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

PART 640--ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Subpart A--Whole Blood

Sec. 640.4 Collection of the blood.

(a) Supervision. Blood shall be drawn from the donor by a qualified physician or under his supervision by assistants trained in the procedure. A physician shall be present on the premises when blood is being collected, except that blood may be collected when a physician is not present on the premises, provided the establishment

(1) maintains on the premises, and files with the Center for Biologics Evaluation and Research, a manual of standard procedures and methods, approved by the Director of the Center for Biologics Evaluation and Research, that shall be followed by employees who collect blood, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who collect blood when a physician is not present on the premises.

(b) The donor center. The pertinent requirements of Secs. 600.10 and 600.11 of this chapter shall apply at both the blood establishment and at any other place where the bleeding is performed.

(c) Blood containers. Blood containers and donor sets shall be pyrogen-free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized. In addition, all container and donor set surfaces that come in contact with blood used in the processing

of Heparin Whole Blood shall be water repellent.

(d) The anticoagulant solution. The anticoagulant solution shall be sterile and pyrogen-free. Anticoagulant solutions shall be compounded and used according to a formula approved by the Director, Center for Biologics Evaluation and Research.

(e) Donor identification. Each unit of blood shall be so marked or identified by number or other symbol as to relate it to the individual donor whose identity shall be established to the extent necessary for compliance with Sec. 640.3.

(f) Prevention of contamination of the blood. The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected by aseptic methods in a sterile system which may be closed or may be vented if the vent protects the blood against contamination.

(g) Samples and segments for laboratory tests. Samples and segments for laboratory tests shall meet the following standards:

(1) One or more segments shall be provided with each unit of blood when issued or reissued except as provided in Sec. 640.2(c)(2) and all segments shall be from the donor who is the source of the unit of blood.
(2) All samples for laboratory tests performed by the manufacturer and all segments accompanying a unit of blood shall be collected at the time of filling the original blood container.
(3) All containers for all samples shall bear the donor's identification before collecting the samples.
(4) All segments accompanying a unit of blood shall be attached to the whole blood container before blood collection, in a tamperproof manner that will conspicuously indicate removal and reattachment.
(5) Segments for compatibility testing shall contain blood mixed with the appropriate anticoagulant.

(h) Storage. Immediately after collection, unless the blood is to be used as a source for Platelets, it shall be placed in storage at a temperature between 1 and 6 deg.C unless it must be transported from the donor clinic to the processing laboratory. In the latter case, the blood shall be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a range between 1 and 6 deg.C until it arrives at the processing laboratory, where it shall be stored at a temperature between 1 and 6 deg.C. Blood from which Platelets is to be prepared shall be held in an environment maintained at a temperature range 20 to 24 deg.C until the platelets are separated. The red blood cells shall be placed in storage at a temperature between 1 and 6 deg.C immediately after the platelets are separated.

[38 FR 32089, Nov. 20, 1973, as amended at 42 FR 59878, Nov. 22, 1977; 43 FR 34460, Aug. 4, 1978; 49 FR 23834, June 8, 1984; 50 FR 4138, Jan. 29, 1985; 55 FR 11013, Mar. 26, 1990; 64 FR 45372, Aug. 19, 1999; 66 FR 1836, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001][23]

NOP:

DEPARTMENT OF AGRICULTURE
Agricultural Marketing Service
7 CFR Part 205
[Docket Number: TMD-00-02-FR]
RIN: 0581-AA40

NATIONAL ORGANIC PROGRAM

AGENCY: Agricultural Marketing Service, USDA.
ACTION: Final Rule with request for comments.

[23] 21CFR640.4. 1 April 2002. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?FR=640.4

SUMMARY: This final rule establishes the National Organic Program (NOP or program) under the direction of the Agricultural Marketing Service (AMS), an arm of the United States Department of Agriculture (USDA). This national program will facilitate domestic and international marketing of fresh and processed food that is organically produced and assure consumers that such products meet consistent, uniform standards. This program establishes national standards for the production and handling of organically produced products, including a National List of substances approved for and prohibited from use in organic production and handling. This final rule establishes a national-level accreditation program to be administered by AMS for State officials and private persons who want to be accredited as certifying agents. Under the program, certifying agents will certify production and handling operations in compliance with the requirements of this regulation and initiate compliance actions to enforce program requirements. The final rule includes requirements for labeling products as organic and containing organic ingredients. This final rule also provides for importation of organic agricultural products from foreign programs determined to have equivalent organic program requirements. This program is authorized under the Organic Foods Production Act of 1990, as amended.

National Organic Program Overview

Subpart A – Definitions

Description of Regulations

This subpart defines various terms used in this part. These definitions are intended to enhance conformance with the regulatory requirements through a clear understanding of the meaning of key terms.

We have amended terms and definitions carried over from the proposed rule where necessary to make their wording consistent with the language used in this final rule. We have revised the definitions of the following words for greater clarity: person, practice standard, inert ingredient, processing, tolerance. We have removed the definitions for the following terms because the terms are not used in this final rule or have been determined to be unnecessary: accredited laboratory, estimated national mean, system of organic production and handling. We received comments on some of these definitions that have been deleted. We have not addressed those comments here because the relevant definitions have been deleted.

Subpart C - Organic Crop, Wild Crop, Livestock, and Handling Requirements

Description of Regulations

General Requirements
This subpart sets forth the requirements with which production and handling operations must comply in order to sell, label, or represent agricultural products as "100 percent organic," "organic," or "made with organic (specified ingredients or food group(s))." The producer or handler of an organic production or handling operation must comply with all applicable provisions of subpart C. Any production practice implemented in accordance with this subpart must maintain or improve the natural resources, including soil and water quality, of the operation. Production and handling operations which sell, label, or represent agricultural products as organic in any manner and which are exempt or excluded from certification must comply with the requirements of this subpart, except for the development of an organic system plan.

Livestock Production

Any livestock product to be sold, labeled, or represented as organic must be maintained under continuous organic management from the last third of gestation or hatching with three exceptions. Poultry or edible poultry products must be from animals that have been under continuous organic management beginning no later than the second day of life. Milk or milk products must be from animals that have been under continuous organic management beginning no later than 1 year prior to the production of such products, except for the conversion of an entire, distinct herd to organic production. For the first 9 months of the year of conversion, the producer may provide the herd with a minimum of 80-percent feed that is either organic or produced from land included in the organic system plan and managed in compliance with organic crop requirements. During the final 3 months of the year of conversion, the producer must provide the herd feed in compliance with section 205.237. Once the herd has been converted to

organic production, all dairy animals shall be under organic management from the last third of gestation. Livestock used as breeder stock may be brought from a nonorganic operation into an organic operation at any time, provided that, if such livestock are gestating and the offspring are to be organically raised from birth, the breeder stock must be brought into the organic operation prior to the last third of gestation.

Should an animal be brought into an organic operation pursuant to this section and subsequently moved to a nonorganic operation, neither the animal nor any products derived from it may be sold, labeled, or represented as organic. Breeder or dairy stock that has not been under continuous organic management from the last third of gestation may not be sold, labeled, or represented as organic slaughter stock. The producer of an organic livestock operation must maintain records sufficient to preserve the identity of all organically managed livestock and all edible and nonedible organic livestock products produced on his or her operation.

Except for nonsynthetic substances and synthetic substances included on the National List that may be used as feed supplements and additives, the total feed ration for livestock managed in an organic operation must be composed of agricultural products, including pasture and forage, that are organically produced. Any portion of the feed ration that is handled must comply with organic handling requirements. The producer must not use animal drugs, including hormones, to promote growth in an animal or provide feed supplements or additives in amounts above those needed for adequate growth and health maintenance for the species at its specific stage of life. The producer must not feed animals under organic management plastic pellets for roughage or formulas containing urea or manure. The feeding of mammalian and poultry slaughter by-products to mammals or poultry is prohibited. The producer must not supply animal feed, feed additives, or feed supplements in violation of the Federal Food, Drug, and Cosmetic Act.

The producer of an organic livestock operation must establish and maintain preventive animal health care practices. The producer must select species and types of livestock with regard to suitability for site-specific conditions and resistance to prevalent diseases and parasites. The producer must provide a feed ration including vitamins, minerals, protein, and/or amino acids, fatty acids, energy sources, and, for ruminants, fiber. The producer must establish appropriate housing, pasture conditions, and sanitation practices to minimize the occurrence and spread of diseases and parasites. Animals in an organic livestock operation must be maintained under conditions which provide for exercise, freedom of movement, and reduction of stress appropriate to the species. Additionally, all physical alterations performed on animals in an organic livestock operation must be conducted to promote the animals' welfare and in a manner that minimizes stress and pain.

The producer of an organic livestock operation must administer vaccines and other veterinary biologics as needed to protect the well-being of animals in his or her care. When preventive practices and veterinary biologics are inadequate to prevent sickness, the producer may administer medications included on the National List of synthetic substances allowed for use in livestock operations. The producer may not administer synthetic parasiticides to breeder stock during the last third of gestation or during lactation if the progeny is to be sold, labeled, or represented as organically produced. After administering synthetic parasiticides to dairy stock, the producer must observe a 90-day withdrawal period before selling the milk or milk products produced from the treated animal as organically produced. Every use of a synthetic medication or parasiticide must be incorporated into the livestock operation's organic system plan subject to approval by the certifying agent.

The producer of an organic livestock operation must not treat an animal in that operation with antibiotics, any synthetic substance not included on the National List of synthetic substances allowed for use in livestock production, or any substance that contains a nonsynthetic substance included on the National List of nonsynthetic substances prohibited for use in organic livestock production. The producer must not administer any animal drug, other than vaccinations, in the absence of illness. The use of hormones for growth promotion is prohibited in organic livestock production, as is the use of synthetic parasiticides on a routine basis. The producer must not administer synthetic parasiticides to slaughter stock or administer any animal drug in violation of the Federal Food, Drug, and Cosmetic Act. The producer must not withhold medical treatment from a sick animal to maintain its organic status. All appropriate medications and treatments must be used to restore an animal to health when methods acceptable to organic production standards fail. Livestock that are treated with prohibited materials must be clearly identified and shall not be sold, labeled, or represented as organic.

A livestock producer must document in his or her organic system plan the preventative measures he or she has in place to deter illness, the allowed practices he or she will employ if illness occurs, and his or her protocol for

determining when a sick animal must receive a prohibited animal drug. These standards will not allow an organic system plan that envisions an acceptable level of chronic illness or proposes to deal with disease by sending infected animals to slaughter. The organic system plan must reflect a proactive approach to health management, drawing upon allowable practices and materials. Animals with conditions that do not respond to this approach must be treated appropriately and diverted to nonorganic markets.

The producer of an organic livestock operation must establish and maintain livestock living conditions for the animals under his or her care which accommodate the health and natural behavior of the livestock. The producer must provide access to the outdoors, shade, shelter, exercise areas, fresh air, and direct sunlight suitable to the species, its stage of production, the climate, and the environment. This requirement includes access to pasture for ruminant animals. The producer must also provide appropriate clean, dry bedding, and, if the bedding is typically consumed by the species, it must comply with applicable organic feed requirements. The producer must provide shelter designed to allow for the natural maintenance, comfort level, and opportunity to exercise appropriate to the species. The shelter must also provide the temperature level, ventilation, and air circulation suitable to the species and reduce the potential for livestock injury. The producer may provide temporary confinement of an animal because of inclement weather; the animal's stage of production; conditions under which the health, safety, or well-being of the animal could be jeopardized; or risk to soil or water quality. The producer of an organic livestock operation is required to manage manure in a manner that does not contribute to contamination of crops, soil, or water by plant nutrients, heavy metals, or pathogenic organisms and optimizes nutrient recycling. [24]

NOSB:
The NOSB will be reviewing heparin for use in livestock in September 2002.[25]

Regulatory: EPA/Other Sources:

EPA: None. [26]

OSHA: None. [27]

ACGIH: None.

IARC: Not listed.

NTP: Not listed. Two-year carcinogenicity studies conducted by NTP demonstrated no evidence of carcinogenicity in mice and rats. [28]

TSCA: Listed substance.

Status Among U.S. Certifiers

State Organic Certifiers:
Minnesota: Follows USDA suggested guidelines.
Oregon: Follows USDA suggested guidelines.
Pennsylvania: Follows OMRI suggested guidelines.

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[24] *Final Rule, 2002*. NOP. http://www.ams.usda.gov/nop/nop2000/nop2/finalrulepages/entirerule2.htm 2002.
[25] *Materials to Review*. NOSB. http://www.ams.usda.gov/nop/materialsmay2002.pdf 2002.
[26] U.S. Environmental Protection Agency website. http://www.epa.gov/
[27] "Heparin Sodium Injection USP – Porcine Intestinal Mucosa Origin – MSDS." American Pharmaceutical Partners, Inc. 6 August 1996. http://www.appdrugs.com/MSDSSheets/heparin_pork.pdf
[28] "Heparin Sodium Injection – MSDS." Eli Lilly and Company. http://www.ehs.lilly.com/msds/msds_heparin_sodium_injection.html

International

IFOAM: In the 2000 final rule[29] and in the 2002 final draft, there is no specific mention of heparin as permissible. Pertinent excerpts regarding the use of veterinary medicines in organic production follow.

INTERNATIONAL FEDERATION OF ORGANIC AGRICULTURE MOVEMENTS
Basic Standards for Organic Production and Processing
Final Draft 2002

To be voted on at the general assembly
Victoria, August 26-28, 2002

5.7. Veterinary Medicine

General Principle

Organic management practices promote and maintain the health and well-being of animals through balanced organic nutrition, stress-free living conditions and breed selection for resistance to diseases, parasites and infections.

Recommendations

Operators should maintain animal health and practice disease prevention through the following techniques:

- Selection of appropriate breeds or strains of animals
- Adoption of animal husbandry practices appropriate to the requirements of each species, such as regular exercise and access to pasture and/or open-air runs, to encourage the natural immunological defence of animal to stimulate natural immunity and tolerance to diseases
- Provision of good quality organic feed
- Appropriate stocking densities
- Grazing rotation and management

Operators should use natural medicines and treatments, including homeopathy, ayurvedic medicine and acupuncture whenever appropriate.

When illness does occur an operator should determine the cause and prevent future outbreaks by adopting appropriate management practices.

Standards shall require that:

5.7.1.
The operator shall take all practical measures to ensure the health and well-being of the animals through preventative animal husbandry practices.

5.7.2.
If an animal becomes sick or injured despite preventative measures that animal shall be treated promptly and adequately, if necessary in isolation and in suitable housing. Producers shall not withhold medication where it will result in unnecessary suffering of the livestock, even if the use of such medication will cause the animal to lose its organic status.

An operator may use chemical allopathic veterinary drugs or antibiotics only if:
- preventive and alternative practises are unlikely to be effective to cure sickness or injury

[29] "IFOAM Basic Standards for Organic Production and Processing, Final 2000." International Federation of Organic Agriculture Movements. http://www.ifoam.org/standard/basics.html

- they are used under the supervision of a veterinarian, and
- withholding periods shall be not less than double of that required by legislation, or a minimum of 48 hours, whichever is longer.

5.7.3.
Substances of synthetic origin used to stimulate production or suppress natural growth are prohibited

5.7.4.
Vaccinations are allowed with the following limitations:
- when an endemic disease is known or expected to be a problem in the region of the farm and where this diseases cannot be controlled by other management techniques; or
- when a vaccination is legally required, and
- the vaccine is not genetically engineered. [30]

CODEX:
There is no mention of heparin.[31]

EEC/UK:
In general, "heparin and salts" are permitted in the EU as a veterinary medicine in food animals (Annex II; Regulation amending Annex of Regulation 2377/90: Reg. 2796/95) [32]

The following guidelines are with regard to veterinary treatment of organic livestock in the EU. There is no specific mention or approval of heparin in this document. An addition in the UK version of organic standards calls for an "allow[ance] for the evolution of a farming system progressively less dependent on allopathic veterinary medicinal products." [33]

ANNEXES I-VIII TO COUNCIL REGULATION (EEC) No. 2092/91
June 24, 1991

5. **Disease prevention and veterinary treatment**

5.1. Disease prevention in organic livestock production shall be based on the following principles:

(a) the selection of appropriate breeds or strains of animals as detailed in Section 3;

(b) the application of animal husbandry practices appropriate to the requirements of each species, encouraging strong resistance to disease and the prevention of infections;

(c) the use of high quality feed, together, with regular exercise and access to pasturage, having the effect of encouraging the natural immunological defence of the animal;

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[30] "IFOAM Basic Standards for Organic Production and Processing: Final Draft 2002." International Federation of Organic Agriculture Movements. http://www.ifoam.org/standard/ibs_final02.html
[31] "Guidelines for the Production, Processing, Labelling, and Marketing of Organically Produced Food: Proposed Draft Amendments." Codex Alimentarius Commission. http://www.hc-sc.gc.ca/food-aliment/friia-raaii/ip-pi/codex/pdf/e_cl01_48e.pdf December 2001.
[32] "Status of MRL Procedures: MRL assessments in the context of Council Regulation (EEC) 2377/90." European Agency for the Evaluation of Medicinal Products. 12 July 2002. http://www.emea.eu.int/pdfs/vet/srwp/076599en.pdf
[33] "Standards for Organic Food Production." UK Register of Organic Foods Standards. February/November 2001. http://www.defra.gov.uk/farm/organic/ukrofs/standard.pdf

(d) ensuring an appropriate density of livestock, thus avoiding overstocking and any resulting animal health problems.

5.2. The principles set out above, should limit animal-health problems so that they can be controlled mainly by prevention.

5.3. If, despite all of the above preventive measures, an animal becomes sick or injured, it must be treated immediately, if necessary in isolation, and in suitable housing.

5.4. The use of veterinary medicinal products in organic farming shall comply with the following principles:

(a) Phytotherapeutic (e.g. plant extracts (excluding antibiotics), essences, etc.), homeopathic products (e.g. plant, animal or mineral substances) and trace elements and products listed in Part C, section 3 of Annex II, shall be used in preference to chemically-synthesised allopathic veterinary medicinal products or antibiotics, provided that their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended;

(b) If the use of the above products should not prove, or is unlikely to be, effective in combating illness or injury, and treatment is essential to avoid suffering or distress to the animal, chemically-synthesised allopathic veterinary medicinal products or antibiotics may be used under the responsibility of a veterinarian;

(c) The use of chemically synthesised allopathic veterinary medicinal products or antibiotics for preventive treatments is prohibited;

5.5. In addition to the above principles, the following rules shall apply:

(a) the use of substances to promote growth or production, (including antibiotics, coccidiostatics and other artificial aids for growth promotion purposes) and the use of hormones or similar substances to control reproduction (e.g. induction or synchronisation of oestrus), or for other purposes, is prohibited. Nevertheless, hormones may be administered to an individual animal, as a form of therapeutic veterinary treatment;

(b) veterinary treatments to animals, or treatments to buildings, equipment and facilities, which are compulsory under national or Community legislation shall be authorised, including the use of immunological veterinary medicinal products when a disease has been recognised as present in a specific area in which the production unit is located.

5.6. Whenever veterinary medicinal products are to be used the type of product must be recorded clearly, (including an indication of the active pharmacological substances involved) together with details of the diagnosis; the posology; the method of administration; the duration of the treatment, and the legal withdrawal period. This information is to be declared to the inspection authority or body before the livestock or livestock products are marketed as organically produced. Livestock treated must be clearly identified, individually in the case of large animals; individually or by batch, in the case of poultry and small animals.

5.7. The withdrawal period between the last administration of an allopathic veterinary medicinal product to an animal under normal conditions of use, and the production of organically produced foodstuffs from such animals, is to be twice the legal withdrawal period or, in a case in which this period is not specified, 48 hours.

5.8. With the exception of vaccinations, treatments for parasites and any compulsory eradication schemes established by Member States, where an animal or group of animals receive more than two or a maximum of three courses of treatments with chemically-synthesised allopathic veterinary medicinal products or antibiotics within one year (or more than one course of treatment if their productive lifecycle is less than one year) the lifestock concerned, or produce derived from them, may not be sold as being products produced in accordance with this Regulation, and the livestock must undergo the conversion periods laid down in Section 2 of this Annex, subject to the agreement of the inspection authority or body.[34]

[34] "Annexes I-VIII to Council Regulation (EEC) No 2092/91 of 24 June 1991." European Union. February 2002. http://www.defra.gov.uk/farm/organic/reg2092annex.pdf

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Canadian General Standards:
Heparin is not listed on the list of approved livestock materials. The following concerns veterinary medicines as used in organic livestock production.

National Standard of Canada
Organic Agriculture
June 1999

7. **LIVESTOCK PRODUCTION**

7.2 **Feed**

7.2.3 The following products shall under no circumstances be included or added to a livestock animal's diet: feed medications, including all hormones and antibiotics used to promote growth, synthetic appetence modifiers, preservation agents (subject to par. 7.2.5), colouring agents, urea, animal by-products (slaughterhouse waste), dung, droppings or other animal waste, medicated feeds, genetically engineered and/or modified organisms (GEO/GMO) or their products, feeds that have been defattened using solvents (hexane, etc.), chemically-extracted feeds (soy-canola or other meals) or feeds to which other chemicals or prohibited substances have been added.

7.4 **Health**

7.4.1 In cases where disease and health problems require treatment, the use of biological, cultural and physical treatments and/or practices are recommended. If no alternative treatment or management practice exists, substances for veterinary use, as described in A ppendix B, section B2, are permitted. If a veterinary drug treatment is used the withdrawal period shall be at least double the permitted federal withdrawal period allowed for veterinary drugs. The withholding of necessary veterinary treatments in order to maintain the organic status of the affected animal is not permitted.

7.4.2 Vaccination of livestock and therapeutic use of veterinary drugs are permitted only when it has been documented that the targeted diseases are communicable to livestock on the enterprise and cannot be combated by other means.

7.4.3 Allopathic treatments (see Appendix B, section B2), shall be used only as a last resort and are to be aimed at preventing the needless suffering of livestock. If an allopathic treatment is used, the withdrawal period shall be at least double the permitted federal withdrawal period allowed for veterinary drugs.

7.4.4 No products from livestock treated with synthetic antibiotics, parasitides, or other synthetic veterinary compounds not permitted in this standard, with the exception of vaccines, shall be labeled or marketed as certified organic, in accordance with this standard, until an interval of time that is at least double the permitted federal withdrawal period allowed for such veterinary compounds has been exceeded for the treated animal.

7.4.5 All treatments of diseased livestock shall be recorded and individual animals clearly identified. This record shall contain details concerning all treatments, including, but not limited to, the duration of treatment and trade names of the drugs used. Records of all treatments should be kept along with adequate animal/flock/colony identification at all stages of production, transportation, distribution, slaughter, and processing. The operator shall record the method of disposal of milk, waste, or other products from treated livestock. Shipping of diseased livestock to slaughter for human consumption is not permitted.

7.4.6 The use of any synthetic compound to stimulate or retard growth and/or production is prohibited (see Appendix B, section B2). [35]

Heparin is not listed on the Certified Organic Associations of British Columbia (COABC) Livestock materials list. [36]

Japan Agricultural Standards for Organic Agricultural Products and Their Processed Foods:
Heparin is not mentioned. [37]

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.*

No information has been found regarding any detrimental interactions of heparin with other organic farming materials.

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.*

Heparin is stable under normal conditions of use and storage. However, it must not be burned, as the decomposition products include carbon monoxide, carbon dioxide, sulfur oxides, and nitrogen oxides.

No information has been found regarding environmental fate and toxicity.

The following is information regarding the possible animal toxicity of heparin sodium.

Animal Toxicity Data - Single Exposure
Oral: Mouse, median lethal dose greater than 5000 mg/kg.
Skin: No applicable information found.
Inhalation: No applicable information found.
Intravenous: Heparin sodium - Mouse, median lethal dose 2800 mg/kg.
Skin Contact: No applicable information found.
Eye Contact: 30% Heparin solution - Rabbit, slight irritant
5% Heparin sodium solution - Rabbit, nonirritant

Animal Toxicity Data - Repeat Exposure
Target Organ Effects: Heparin - Blood effects (decreased red blood cell count, decreased hemoglobin).
Reproduction: Heparin - Rats administered subcutaneous doses up to 10 mg/kg/day demonstrated no effects on conception or pregnancy or on teratogenicity, implantation sites, or fetal weight (when administered during organogenesis).
Mutagenicity: Heparin - Negative in Ames assay. No increase in chromosome aberrations in human lymphocytes in vitro. Negative in rate bone marrow micronucleus test in vivo.

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[35] "National Standard for Organic Agriculture." Canadian General Standards Board Sales Centre Public Works and Government Services Canada, Hull, Quebec, K1A 1G6. June 1999.
[36] "Certified Organic Management Standards." Certified Organic Associations of British Columbia. http://www.certifiedorganic.bc.ca/Standards/Bk2_COABC_Organic_Management_Standards_Version4-03-02.pdf
[37] Japanese Agricultural Standards. http://www.fas.usda.gov/gainfiles/200004/25647377.pdf

Information on the human health effects from exposure to heparin is limited. It is not an NTP known or anticipated carcinogen, and it is not listed as a carcinogen by the IARC. However, it should still be handled as a possible human health hazard. The following information concerns routes of exposure:

Inhalation: No information found, but the compound should be handled as a potential health hazard. It may cause irritation to the respiratory tract. Symptoms may include coughing, sore throat, labored breathing, and chest pain.

No airborne exposure limits have been set.

Ingestion: No information found, but the compound should be handled as a potential health hazard. It may cause irritation to the gastrointestinal tract. Symptoms may include nausea, vomiting and diarrhea.

Skin Contact: No information found, but the compound should be handled as a potential health hazard. It may cause irritation with redness and pain, and be absorbed through the skin with possible systemic effects.

Eye Contact: No information found, but the compound should be handled as a potential health hazard. It may cause irritation, redness and pain.

Chronic Exposure: No information found.

Aggravation of Pre-existing Conditions: No information found.[38]

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

During the manufacturing process of extraction, sources of environmental contamination include waste water. This water contains raw materials (e.g., waste plasma fractions, spent media broth); 2) floor and equipment wash water; 3) chemical wastes (e.g., spent solvents); and 4) cleanup of spills. Wastewater from extraction plants is generally characterized by low BOD, COD, and TSS 5 concentrations; small flows; and pH values of approximately 6.0 to 8.0.

Heparin is stable under normal conditions of use and storage. However, it must not be burned, as the decomposition products include carbon monoxide, carbon dioxide, sulfur oxides, and nitrogen oxides.

No information has been found regarding environmental fate and toxicity. The following is also written in the Mallinckrodt-Baker MSDS for heparin sodium:

Handling and Storage
Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Isolate from incompatible substances. Containers of this material may be hazardous when empty since they retain product residues (dust, solids); observe all warnings and precautions listed for the product.

Disposal Considerations
Whatever cannot be saved for recovery or recycling should be managed in an appropriate and approved waste disposal facility. Processing, use or contamination of this product may change the waste management options. State and local disposal regulations may differ from federal disposal regulations. Dispose of container and unused contents in accordance with federal, state and local requirements.

The transportation of heparin is unregulated. [39]

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

[38] "Heparin Na – MSDS." Mallinckrodt Baker, Inc. 8 May 2000. http://www.jtbaker.com/msds/h0314.htm
[39] "Heparin Na – MSDS." Mallinckrodt Baker, Inc. 8 May 2000. http://www.jtbaker.com/msds/h0314.htm

(See Criterion 2, *Toxicity*)

These are the effects of heparin on humans when administered during human medical treatment.

Possible issues to consider:

1. Cross-sensitivity and/or related problems:
Patients with a history of allergies, especially those who are allergic to swine, beef, or other animal proteins, may be allergic to this medication also (depending on heparin source).

2. Pregnancy:
Heparin does not cross the placenta and is the anticoagulant of choice for use during pregnancy because it does not affect blood clotting mechanisms in the fetus. Although heparin has not been reported to cause birth defects, use during pregnancy has been reported to increase the risk of stillbirth or prematurity. However, the underlying condition, rather than heparin itself, may have been responsible. Also, the reported incidence (13 to 22%) of these complications is lower than that reported with coumarin-derivative anticoagulants (31%). In addition, caution is recommended when heparin is used during the last trimester of pregnancy or during the postpartum period because of the increased risk of maternal bleeding.

Especially careful monitoring of the patient and attention to dosage are recommended during pregnancy. Heparin requirements increase, because of expansion of the patient's blood volume, as pregnancy progresses . Readjustment of heparin dosage may be needed following delivery .

3. Breast-feeding:
Heparin is not distributed into breast milk. However, administration to lactating women has rarely been reported to cause rapid (within 2 to 4 weeks) development of severe osteoporosis and vertebral collapse.

4. Pediatrics:
Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of heparin in children. However, heparin injections that contain benzyl alcohol should not be administered to premature neonates because the preservative has been associated with a fatal “gasping syndrome ” in these patients.

5. Geriatrics:
Patients 60 years of age or older, especially females, may be more susceptible to hemorrhaging during heparin therapy. Also, elderly patients are more likely to have age-related renal function impairment, which may increase the risk of bleeding in patients receiving anticoagulants.

6. Drug interactions and/or related problems:

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate) - not necessarily inclusive (» = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication. Interactions listed below may not apply to short-term use of heparin followed by protamine reversal, as in cardiovascular surgery.

In addition to the documented interactions listed below, the possibility should be considered that multiple effects leading to further impairment of blood clotting and/or increased risk of bleeding may occur if heparin is administered to a patient receiving any medication having a significant potential for causing hypoprothrombinemia, thrombocytopenia, or gastrointestinal ulceration or hemorrhage.

a. Acid citrate dextrose (ACD)-converted blood:

Blood collected in heparin and later converted to ACD blood. Heparin anticoagulant activity lasts for up to 22 days after conversion to ACD blood when refrigerated; thus, use of ACD blood in heparin-treated patients may increase the risk of hemorrhage.

b. Adrenocorticoids, Glucocorticoids, or Corticotropin:
Especially applicable to chronic therapeutic use, ethacrynic acid, or nonacetylated salicylates. The potential occurrence of gastrointestinal ulceration or hemorrhage during therapy with these medications may cause increased risk of bleeding in patients receiving anticoagulant therapy. Large [antirheumatic] doses of salicylates may cause hypoprothrombinemia, which may increase the risk of bleeding in patients receiving anticoagulant therapy.

c. Anticoagulants, coumarin- or indandione-derivative:
Although these medications are commonly used concurrently with heparin, the fact that concurrent use may lead to a severe deficiency of vitamin K-dependent procoagulant factors, and thus an increased risk of bleeding, must be considered. Heparin may prolong the prothrombin time used for dosage adjustments of these agents.

d. Antihistamines, Digitalis glycosides, Nicotine, or Tetracyclines:
These medications may partially counteract the anticoagulant effect of heparin; heparin dosage adjustment may be required during and following concurrent use.

e. Anti-inflammatory drugs, nonsteroidal (NSAIDs), or »Platelet aggregation inhibitors, especially: »Aspirin and »Sulfinpyrazone:
Inhibition of platelet function by these agents may lead to hemorrhage because it impairs a hemostatic mechanism on which heparin-treated patients depend to prevent bleeding. Hypoprothrombinemia induced by large [antirheumatic] doses of aspirin, and the potential occurrence of gastrointestinal ulceration or hemorrhage during therapy with NSAIDs, aspirin, or sulfinpyrazone, may also cause increased risk of bleeding in patients receiving heparin therapy.

f. »Cefamandole or »Cefoperazone or »Cefotetan or »Plicamycin or »Valproic acid:
These medications may cause hypoprothrombinemia; in addition, plicamycin or valproic acid may inhibit platelet aggregation; concurrent use with heparin may increase the risk of hemorrhage and is not recommended.

g. Chloroquine or Hydroxychloroquine:
These agents may cause thrombocytopenia, which may increase the risk of hemorrhage because heparin-treated patients depend on platelet aggregation to prevent bleeding.

h. »Methimazole or »Propylthiouracil:
These medications may cause hypoprothrombinemia, which may enhance the anticoagulant effect of heparin and increase the risk of bleeding)

i. Nitroglycerin, intravenous:
The anticoagulant effect of heparin may be decreased in patients receiving nitroglycerin via intravenous infusion; adjustment of heparin dosage may be required to maintain the desired degree of anticoagulation during and following administration of a nitroglycerin infusion.

j. »Probenecid:
Probenecid may increase and prolong the anticoagulant effect of heparin.

k. »Thrombolytic agents, such as: »Alteplase (tissue-type plasminogen activator, recombinant), »Anistreplase (anisoylated plasminogen-streptokinase activator complex; APSAC), »Streptokinase, or »Urokinase:
Concurrent or sequential use with heparin increases the risk of bleeding complications; although heparin is sometimes given before, and is usually given to decrease the risk of reocclusion following, thrombolytic therapy. Caution and especially careful monitoring of the patient are recommended.

7. Medical considerations/Contraindications:

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate) - not necessarily inclusive (» = major clinical significance).

Risk-benefit should be considered when the following medical problems exist:

a. Allergic reaction to heparin, history of, and Allergy or asthma, history of:
Increased risk of allergic reactions because heparin is derived from animal tissue.

b. Any medical or dental procedure or condition in which the risk of bleeding or hemorrhage is present, such as: »Anesthesia, regional or lumbar block, »Blood dyscrasias, hemorrhagic, especially thrombocytopenia or hemophilia; or other hemorrhagic tendency, »Childbirth, recent Diabetes, severe »Endocarditis, subacute bacterial Gastrointestinal ulceration, history of use of an Intrauterine contraceptive device, »Neurosurgery, recent or contemplated, »Ophthalmic surgery, recent or contemplated, »Pericarditis or pericardial effusion, Radiation therapy, recent Renal function impairment, mild to moderate, »Renal function impairment, severe »Spinal puncture, recent » major Surgery, recent or wounds resulting in large open surfaces, »Trauma, severe, especially to the central nervous system (CNS), Tuberculosis, active »Ulceration or other lesions of the gastrointestinal, respiratory, or urinary tract, active »Vasculitis,
c. Severe hepatic function impairment, mild to moderate, or »Hepatic function impairment
d. Severe Hypertension, mild to moderate:
Increased risk of cerebral hemorrhage.
e. »Caution in use is also recommended for lactating women, who may develop severe osteoporosis after only 2 to 4 weeks of heparin therapy; and geriatric patients, who may be at increased risk of heparin-induced hemorrhage.

8. Side/Adverse Effects:

Note: The occurrence of hemorrhage (especially in the gastrointestinal tract) during heparin therapy, especially if blood coagulation tests are within the therapeutic range, may indicate the presence of an underlying occult lesion such as a tumor or ulcer.

Two forms of reversible thrombocytopenia related to heparin therapy have been identified, either of which may occur in up to 30% of patients receiving the medication. A mild form may occur on the second to fourth day of heparin therapy and may improve despite continuing heparin usage. This condition is characterized by a moderate decrease in platelet count and by the absence of thrombotic or hemorrhagic complications; it may occur more frequently with bovine lung heparin than with porcine mucosal heparin. A severe form of thrombocytopenia, associated with the development of heparin-dependent antiplatelet antibodies resulting in greatly increased platelet aggregation, has also been reported. This condition usually occurs after the eighth day of therapy, although it has occurred within as little as 2 days in some patients, and is characterized by reduction of platelet count to as low as 5000 per cu. mm. and by increased resistance to heparin therapy. Continued use of heparin may lead to the " white clot syndrome," i.e., the formation of new thrombi composed primarily of fibrin platelet aggregates, which may cause thrombotic complications including organ infarction, skin necrosis, gangrene of the extremities, pulmonary embolism, and stroke. Rarely, hemorrhage may occur. This severe form of thrombocytopenia is independent of the source of heparin, dosage, or route of administration; however, patients who have recently received a prior course of heparin therapy may be at greater risk of developing this complication. Heparin should be discontinued immediately if severe thrombocytopenia occurs or is suspected. Severe thrombocytopenia may recur if heparin is administered to the patient within several months following the development of this complication.

Adrenal hemorrhage resulting in acute adrenal insufficiency has been reported to occur rarely during anticoagulant therapy. Diagnosis may be difficult because the initial symptoms (abdominal pain, apprehension, diarrhea, dizziness or fainting, headache, loss of appetite, nausea or vomiting, and weakness) are nonspecific and variable. If acute adrenal insufficiency is suspected, anticoagulant therapy must be discontinued and high-dose adrenocorticoid therapy (preferably with hydrocortisone, since other glucocorticoids do not provide sufficient sodium retention) instituted immediately. Delay of treatment while laboratory confirmation of the diagnosis is awaited may prove fatal to the patient. It has been proposed that abdominal computerized axial tomographic (CAT) scanning may be of use in diagnosing this condition more rapidly.

Heparin may suppress aldosterone synthesis. Rarely, with prolonged use, inhibition of renal function, hyperkalemia, and metabolic acidosis may result.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate) - not necessarily inclusive:

Those indicating need for medical attention:

Incidence less frequent or rare:

a. Allergic reaction:
Fever with or without chills, runny nose, headache, nausea with or without vomiting, shortness of breath, troubled breathing, wheezing, or tightness in chest, skin rash, itching, or hives, tearing of eyes.

b. Anaphylactoid reaction, possibly including anaphylactic shock:
Changes in facial skin color skin rash, hives, and/or itching fast or irregular breathing puffiness or swelling of the eyelids or around the eyes, shortness of breath, troubled breathing, tightness in chest, and/or wheezing, sudden, severe decrease in blood pressure and collapse, chest pain frequent or persistent erection, itching and burning feeling, especially on the plantar site of the feet, pain, coldness, and blue color of skin of arms or legs, peripheral neuropathy (numbness or tingling in hands or feet).
Note: Signs and symptoms suggestive of ischemia may occur in one or more limbs approximately 6 to 10 days following initiation of therapy. If heparin therapy is continued, progression of the reaction may lead to cyanosis, tachypnea, and headache. Protamine sulfate will not reverse these effects, which in the past have been attributed to an allergic vasospastic reaction. Whether these effects are actually identical to complications associated with heparin-induced thrombocytopenia has not been determined. [40]

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.*

If used in the manner proposed, there is no evidence of significant biological and chemical interactions in the agroecosystem.

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

Sodium citrate, acid citrate dextrose (ACD), citrate phosphate dextrose (CPD), and citrate phosphate dextrose adenine (CPDA-1) solutions are other anticoagulants that may be used in blood preservation for transfusions.

FDA recommendations for blood storage:

ACD Whole Blood:
21 days from date of collection, providing labeling. Recommends storage between 1 and 6 °C.
CPD Whole Blood:
21 days from date of collection, providing labeling. Recommends storage between 1 and 6 °C.
CPDA-1 Whole blood:
35 days from date of collection, providing labeling. Recommends storage between 1 and 6 °C. [41]

[40] "Heparin Leo: USPDI Professional Information." Drugs.com. http://drugs.com/xq/cfm/pageID_0/xml_001310/type_pros/bn_Heparin%20Leo/qx/index.htm#

[41] "Guidance for Industry: Use of Sterile Connecting Devices in Blood Bank Practices." U.S. Department of Health and Human Services. Food and Drug Administration. November 2000. http://www.fda.gov/cber/gdlns/bbconn.pdf

CPDA-1 solution (100 mL) contains:	
Citric acid (anhydrous) USP:	0.299 g
Sodium citrate (dehydrate) USP:	2.63 g
Monobasic Sodium phosphate (monohydrate) USP:	0.222 g
Dextrose (anhydrous) USP	2.9 g
Adenine (anhydrous) USP:	0.0275 g
Water for injection USP	100 mL [42]

Sodium citrate has been approved in to the National List (§ 205.605) as a synthetic "nonagricultural (nonorganic) substance allowed as an ingredient in or on processed products labeled as "organic" or "made with organic (specified ingredients)."" It is allowable in meat products by IFOAM. Thus, it is has previously been ruled compatible with an organic system of agriculture.

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

Although the tissue for the making of heparin may be of organic livestock origin, the extraction process to obtain the heparin may use toxic chemical solvents for defattening, etc. Manufacturing may also lead to environmental contamination by waste water. This is not compatible with a system of sustainable agriculture, which suggests the presence of an environmentally-friendly farming system.

TAP Reviewers' Discussion

Reviewer 1 *[Ph.D, Food Biochemistry; Assistant Professor, Food Science and Technology. Southeast U.S.]*

Observations/OFPA Criteria Evaluation

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

- Although there are not many possibilities for contact and reaction of heparin and materials used in organic farming system prior to heparin application, it should be kept in mind that heparin-cation interactions *in vivo* are biologically important. Heparin strongly binds calcium, magnesium, cupric, and zinc ions via its carboxylic and sulfamino groups (Mattai and Kwak, 1988; Ling and Chakrabarti, 1982). If trace minerals are used for diet enrichment (including cooper sulfate and magnesium sulfate; 205.603 (14)(d)) possibilities of interaction *in vivo* and alteration in minerals' metabolism/availability may occur with prolonged intravenous administrating of high doses of heparin.

(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 agree with the provided information.

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

- I agree with the provided information.

(4) the effect of the substance on human health;

- NTP Chemical Repository (www.ntp-server.niehs.nih.gov) includes heparin on the list of pharmaceutical incompatibilities for antibiotic gentamycin sulfate (1405-41-0) and sedative chlorpromazine hydrochloride (69-09-0).

[42] "Blood Bag Systems." SURU International. http://www.suru.com/bloodbag.htm

- More importantly, as it is stated in TAP Review, "heparin does not cross placenta", "does not affect blood clotting mechanism in the fetus", and "is not distributed into breast milk". Thus, I believe that application of heparin in animal blood transfusions would have no effect on human health.

(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 same comments as under the criterion (1).

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

- Citric acid and sodium citrate are already on the National list and could be used as alternatives for heparin in blood preservation for transfusions. However, citrate phosphate dextrose (CPD) and citrate phosphate dextrose adenine (CPDA) solutions contain components that are not on the National list and, thus, only ACD (acid citrate dextrose) solution should be considered as an alternative with already approved ingredients.
- Antithrombin III is a natural plasma protein. It also acts as an anticoagulant and several studies have been conducted applying antithrombin as an anticoagulating factor in treating cats, dogs and horses. Although is commercially available it is far less used than heparin or ACD and should not be considered as a reasonable alternative for petitioned applications.

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

- I agree with the provided information.

Reviewer 1 Conclusions

"In livestock, the petitioned uses of heparin are for use as an anticoagulant in blood transfusions, to prevent blood from coagulating enroute from the donor to the recipient animal; and for use in thrombosis prevention in animals suffering from endotoxemia. When used in blood transfusions, the heparin is added to the container prior to the blood."

Although I do not have experience in veterinary medicine, I understand that endotoxemia is a serious clinical problem in livestock and treatment for this condition often includes antibiotics and other therapeutic measures under supervision of veterinarian. Application of antibiotics per se is not allowed in organic livestock operation (205.238 (c)(1); (7)) and use of heparin in thrombosis prevention in animals suffering from endotoxemia would not cure the disease. Suffering animal should be adequately treated and withhold from organic operation for the withdrawal period recommended for allopathic veterinary medical products or antibiotics applied in endotoxemia treatment.

Application of heparin in blood transfusion would not present health problem to humans. However, alternative anticoagulants for this purpose exist and are already approved for organic livestock operations.

Reviewer 1 Recommendations Advised to the NOSB

The substance is Synthetic.

For Livestock, the substance should be Excluded from the National List.

Reviewer 2 [*Ph.D, Reproductive Physiology. Research, consulting, professor of animal sciences with activities related to animal production. Southeast U.S.]*

Observations

The following includes excerpts from the report.

In humans, heparin is indicated for:

1. Anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension.
2. Use in a low-dose regimens for prevention of post-operative deep venous thrombosis and pulmonary embolism in patients undergoing major abdomino-thoracic surgery, or who for other reasons are at risk of developing thromboembolic disease
3. Prophylaxis and treatment of pulmonary embolism.
4. Atrial fibrillation with embolization.
5. Diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation).
6. Prevention of clotting in arterial and cardiac surgery.
7. Prophylaxis and treatment of peripheral arterial embolism.
8. As an anticoagulant in blood transfusions, extracorporeal circulation, dialysis procedures and in blood samples for laboratory purposes.

Heparin is the anticoagulant of choice when an immediate effect is required.

Prophylactic use of heparin (low-dose or full-dose) is not recommended for patients with bleeding disorders; patients having neurosurgery, ophthalmic surgery, or spinal anesthesia; or patients who are receiving a coumarin- or indandione-derivative anticoagulant or a platelet active agent.

Heparin has also been used to reduce the risk of thrombosis and/or occlusion of the aortocoronary bypass following coronary bypass surgery; however, **its efficacy has not been established and this use is controversial**. Also, platelet aggregation inhibitors, especially aspirin, are more commonly used for this indication.

Other effects of heparin include **reducing the concentration of triglycerides** in plasma by releasing the enzyme lipoprotein lipase from tissues and stabilizing the enzyme. The resultant hydrolysis of triglycerides leads to increased blood concentrations of free fatty acids.

In livestock, the petitioned uses of heparin are for use as an anticoagulant in blood transfusions, to prevent blood from coagulating enroute from the donor to the recipient animal; and for use in thrombosis prevention in animals suffering from endotoxemia. When used in blood transfusions, the heparin is added to the container prior to the blood.

Some veterinary doses of heparin are as follows:
Cat: 1 mg/kg BW IV (Kinsell, 1986)
Dog: 1 mg/kg BW IV (Kinsell, 1986)
Guinea pig: 5 mg/kg BW IV (Melby and Altman, 1976)
Mouse: 10 mg/kg BW IV (Melby and Altman, 1976)
NHP: 2 mg/kg BW IV (Meiby and Altman, 1976)
Rat: 10 mg/kg BW IV (Borchard et al., 1990)
Rabbit: 5 mg/kg BW IV (Melby and Altman, 1976)

The doses of heparin used for livestock species have not been presented to evaluate efficacy as well as residual carryover into livestock products.

Subpart C - Organic Crop, Wild Crop, Livestock, and Handling Requirements

Description of Regulations

General Requirements
This subpart sets forth the requirements with which production and handling operations must comply in order to sell, label, or represent agricultural products as "100 percent organic," "organic," or "made with organic (specified ingredients or food group(s))." The producer or handler of an organic production or handling operation must comply with all applicable provisions of subpart C....

..... The producer must not withhold medical treatment from a sick animal to maintain its organic status. All appropriate medications and treatments must be used to restore an animal to health when methods acceptable to organic production standards fail. Livestock that are treated with prohibited materials must be clearly identified and shall not be sold, labeled, or represented as organic. .....

..... (c) The producer of an organic livestock operation must not:

(1) Sell, label, or represent as organic any animal or edible product derived from any animal treated with antibiotics, any substance that contains a synthetic substance not allowed under § 205.603, or any substance that contains a nonsynthetic substance prohibited in § 205.604.
(2) Administer any animal drug, other than vaccinations, in the absence of illness;
(3) Administer hormones for growth promotion;
(4) Administer synthetic parasiticides on a routine basis;
(5) Administer synthetic parasiticides to slaughter stock;
(6) Administer animal drugs in violation of the Federal Food, Drug, and Cosmetic Act; or
(7) Withhold medical treatment from a sick animal in an effort to preserve its organic status. All appropriate medications must be used to restore an animal to health when methods acceptable to organic production fail. Livestock treated with a prohibited substance must be clearly identified and shall not be sold, labeled, or represented as organically produced.....

International

IFOAM: In the Basic Standards for Organic Production and Processing, Final Draft 2002, IFOAM **does not** list heparin as permissible, and therefore they are not allowed.

CODEX:
There is no mention of heparin.

EEC/UK:
In general, "heparin and salts" are permitted in the EU as a veterinary medicine in food animals (Annex II; Regulation amending Annex of Regulation 2377/90: Reg. 2796/95)

With regard to veterinary treatment of organic livestock in the EU, there is **no specific mention or approval** of heparin. An addition in the UK version of organic standards calls for an "allow[ance] for the evolution of a farming system progressively less dependent on allopathic veterinary medicinal products."

Canadian General Standards:
Heparin **is not listed** on the list of approved livestock materials.

Heparin is not listed on the Certified Organic Associations of British Columbia (COABC) Livestock materials list.

Japan Agricultural Standards for Organic Agricultural Products and Their Processed Foods:
Heparin **is not mentioned**.

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

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

No information has been found regarding any detrimental interactions of **heparin** with other organic farming materials.

9. 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.

Heparin is stable under normal conditions of use and storage. However, it **must not be burned**, as the decomposition products include carbon monoxide, carbon dioxide, sulfur oxides, and nitrogen oxides.

No information has been found regarding environmental fate and toxicity.

The following is information regarding the possible **animal toxicity of heparin** sodium.

Animal Toxicity Data - Single Exposure
Oral: Mouse, median lethal dose greater than 5000 mg/kg.
Skin: No applicable information found.
Inhalation: No applicable information found.
Intravenous: Heparin sodium - Mouse, median lethal dose 2800 mg/kg.
Skin Contact: No applicable information found.
Eye Contact: 30% Heparin solution - Rabbit, slight irritant
5% Heparin sodium solution - Rabbit, nonirritant

Animal Toxicity Data - Repeat Exposure
Target Organ Effects: Heparin - Blood effects (decreased red blood cell count, decreased hemoglobin).
Reproduction: Heparin - Rats administered subcutaneous doses up to 10 mg/kg/day demonstrated no effects on conception or pregnancy or on teratogenicity, implantation sites, or fetal weight (when administered during organogenesis).
Mutagenicity: Heparin - Negative in Ames assay. No increase in chromosome aberrations in human lymphocytes in vitro. Negative in rate bone marrow micronucleus test in vivo.
Information on the human health effects from exposure to heparin is limited. It is not an NTP known or anticipated carcinogen, and it is not listed as a carcinogen by the IARC. However, it should still be handled as a possible human health hazard. The following information concerns routes of exposure:

Inhalation: **No information found**, but the compound should be handled as a potential health hazard. It may cause irritation to the respiratory tract. Symptoms may include coughing, sore throat, labored breathing, and chest pain.

No airborne exposure limits have been set.

Ingestion: **No information found**, but the compound should be handled as a potential health hazard. It may cause irritation to the gastrointestinal tract. Symptoms may include nausea, vomiting and diarrhea.

Skin Contact: **No information found**, but the compound should be handled as a potential health hazard. It may cause irritation with redness and pain, and be absorbed through the skin with possible systemic effects.

Eye Contact: **No information found**, but the compound should be handled as a potential health hazard. It may cause irritation, redness and pain.

Chronic Exposure: **No information found**.

Aggravation of Pre-existing Conditions: **No information found**.

There have been no reports of toxicity in livestock species.

10. Its compatibility with a system of sustainable agriculture.

Although the tissue for the making of heparin may be of organic livestock origin, the extraction process to obtain the heparin **may use toxic chemical solvents** for defattening, etc. Manufacturing **may also lead to** environmental contamination by waste water. This is **not compatible** with a system of sustainable agriculture, which suggests the presence of an environmentally-friendly farming system.

The following reports raise concerns with the potential toxicity of the compound in question.

The antithrombotic drug heparin is administered parenterally and believed not effective orally. Oral heparin would be most suitable for long term administration, often required for the prevention of thrombosis. Following parenteral administration, heparin is taken up by endothelial cells. Heparin is similarly taken up by endothelium following oral administration, despite low plasma heparin concentrations. In a 24 hour period, endothelial heparin concentrations are greatest within 15 minutes of oral dosing although plasma levels never exceed one percent of dose. Endothelial uptake accounts for a considerable amount of absorption if the total body endothelium is considered. In support of oral heparin absorption, a dose-dependent decrease in thrombosis incidence was demonstrated in a rat jugular vein model following single oral doses of unfractionated heparins (bovine and porcine) or low molecular weight heparins (reviparin, logiparin and ardeparin). Low molecular weight heparins were effective at lower doses than unfractionated heparins where a 50% reduction in thrombosis was observed with 0.025 mg/kg reviparin, 0.1 mg/kg logiparin, versus 7.5 mg/kg bovine unfractionated heparin show measurable systemic changes following oral heparin administration and suggest that **heparin may be effective when administered by the oral route**. It also indicates that the presence of heparin in plasma likely reflects a much greater amount associated with endothelium[a].

Because it appears that heparin can be used orally, and may be used in livestock species, there is concern that blood derived products from ruminants can transmit transmissible spongiform encephalopathy's. The following citations present areas of concern for heparin use in livestock species.

As a consequence of the outbreak of bovine spongiform encephalopathy (BSE), ruminant materials have been generally banned from the production of heparin. Immunochemical methods have been recently developed for the control of the raw materials used by manufacturers of materials such as porcine mucosa and for the detection of bovine crude heparins. To certify the porcine origin of crude porcine heparins and to exclude ovine or caprine materials, new ELISAs were developed. Rabbit antisera were produced against species-specific antigenic contaminants present in crude heparins or in eluted materials (EM) from the chromatographic step of the purification process. When analysed by line immunoelectrophoresis, these antisera revealed **five to eleven antigenic contaminants** in the EMs, the major one being the most anodic and predominant antigen in crude heparins. Using the best antisera, competitive indirect ELISAs were optimised. They allowed the detection of porcine, ovine and caprine crude heparins down to a dilution of 0.6 to 1.5 parts per 1000, with CVs ranging from 3 to 12%. These ELISAs complete the set of immunological techniques which can be routinely used by heparin manufacturers to secure their supply chain[b].

This type of testing and the following report shall be necessary to assure that heparin sources used for humans and not only animals are free of ruminant sources.

Heparin is a potent anticoagulant polysaccharide purified for decades from ruminants or porcine tissues. However, with the emergence of bovine spongiform encephalopathy (BSE), the source of pharmaceutical heparin is currently restricted to porcine intestinal mucosa. A major species-specific contaminant, called Ag1, has recently been identified in bovine crude heparin and used to develop an enzyme-linked immunosorbent assay (ELISA) for the species origin control of crude heparins. We describe the different investigations, which were carried out to identify Ag1. This antigen was first localised by immunohistological studies essentially in the connective tissue of the bovine small intestine. After extraction from an intestinal extract by immuno-affinity chromatography, Ag1 was isolated as a single band by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE). Ag1 was then partly sequenced and identified as an aprotinin/heparin complex. Aprotinin, also known as the bovine pancreatic trypsin inhibitor (BPTI), is **present with heparin** in mast cells, and is very resistant to heat, pH, chemical treatments and proteolytic digestion. The stability of Ag1 towards the different treatments performed during heparin extraction process allows this protein to remain in sufficient amounts in crude heparin and makes it an ideal target for the immunochemical control of the absence of bovine material in crude heparins[c].

Several lines of evidence have shown glycosaminoglycans (GAGs) to be physiological ligands of the prion protein (PrP), but the molecular and regulatory aspects of the interaction remain unknown. Using full-length recombinant prion protein and low molecular mass heparin and heparan sulfate as glycosaminoglycans, we have found that the interaction occurs with the formation of oligomeric complexes. Within the protein-glycosaminoglycan complexes, PrP exhibited an enhanced fluorescence emission and a reduced solvent exposure. The pH and ionic strength-dependence of the interaction reveals His residues as the main binding sites at acid pH. A synthetic peptide consisting of four octarepeats is able to reproduce the His-dependent binding of the protein, thus demonstrating the role of the octarepeats in the GAG interaction. Alternatively, **PrP can bind GAGs through His-bound Cu(II)**. These Cu(II) bridges promote a tighter interaction, as shown by the increased resistance to ionic strength, to protease action, and to pH-induced cation release. Inspection of other cations shows that Zn(II) but not Ni(II) shares the interaction trend. Taken together, our data suggest that the octarepeat region constitutes a novel GAG-binding sequence and that His-bound Cu(II) may act as a cofactor for intermolecular recognition reactions, allowing the formation of PrP-Cu(II)-glycosaminoglycan assemblies that may be crucial entities in the PrP metabolism[d].

Several clinical interactions may be involved with heparin that suggests further animal testing is warranted.

Observations are reported of two **heparin-allergic** patients (in one case, urticaria and in the other urticaria and asthma). These two patients show a curious association of the pork/cat syndrome, previously described, that is an association of sensitivity to cat epithelia and pork meat. Since the heparins used nowadays are of porcine origin, the question is raised of a possible causal link that may exist between these 2 allergies. It seems that the possibility of association of these two allergies is much more likely than chance encounter[e].

4-Chloro-m-cresol (4-CmC) induces marked contractures in skeletal muscle specimens from individuals susceptible to malignant hyperthermia (MHS). In contrast, 4-CmC induces only small contractures in specimens from normal (MHN) patients. 4-CmC is a preservative within a large number of commercially available drug-preparations (e.g., insulin, **heparin**, succinylcholine), and it has been suggested that 4-CmC might trigger malignant hyperthermia. This study was designed to investigate the effects of 4-CmC in vivo and in vitro in the same animals. Six Pietrain MHS and six control (MHN) swine were anesthetized with azaperone 4 mg/kg i.m. and metomidate 10 mg/kg i.p. After endotracheal intubation, lungs were mechanically ventilated (inspired oxygen fraction 0.3) and anesthesia was maintained with etomidate 2.5 mg x kg(-1) x h(-1) and fentanyl 50 µg x kg(-1) x h(-1). Animals were surgically prepared with arterial and central venous catheters for measurement of hemodynamic parameters and to obtain blood samples. Before exposure to 4-CmC in vivo, muscle specimens were excised for in vitro contracture tests with 4-CmC in concentrations of 75 and 200 µM. Subsequently, pigs were exposed to cumulative administration of 3, 6, 12, 24, and 48 mg/kg 4-CmC i.v. If an unequivocal episode of malignant hyperthermia occurred, as indicated by venous carbon dioxide concentration > or = 70 mmHg, pH < or = 7.25, and an increase of temperature > or = 2 degrees C, the animals were treated with dantrolene, 3.5 mg/kg. All MHS swine developed malignant hyperthermia after administration of 4-CmC in doses of 12 or 24 mg/kg. Venous carbon dioxide concentration significantly increased and pH significantly decreased. Temperature increased in all MHS animals more than 2 degrees C. Blood lactate concentrations and creatine kinase levels were significantly elevated. All MHS swine were treated successfully with dantrolene. In contrast, no MHN swine developed signs of malignant hyperthermia. After receiving 4-CmC in a concentration of 48 mg/kg, however, all MHN animals died by ventricular fibrillation. The in vitro experiments showed that both concentrations of 4-CmC produced significantly greater contractures in MHS than in MHN specimens. 4-CmC is in vivo a trigger of malignant hyperthermia in swine[f].

These concerns should be addressed by clear guidelines for uses that restrict applications in 'organic animal production'.

Reviewer 2 Conclusions

Heparin should not be allowed in organic animal production systems. The therapeutic use of this product in organic livestock production can not be allowed in order to satisfy requirements for 'organic animal' production.

Reviewer 2 Recommendations Advised to the NOSB

The substance is Synthetic.

For Livestock, the substance should be Excluded from the National List.

References

[a]Hiebert LM. 2002. Oral heparins. Clin Lab 48:111-6.

[b]Levieux A, Rivera V, Levieux D. 2002. Immunochemical control of the species origin of porcine crude heparin and detection of ovine and caprine materials. J Pharm Biomed Anal 27 :305-13.

[c]Rivera V, Levieux A, Levieux D. 2002. Characterisation of Ag1, the major species-specific contaminant of bovine crude heparin, and its identification as an aprotinin/heparin complex. J Pharm Biomed Anal 29 :443-58

[d]Gonzalez-Iglesias R, Pajares MA, Ocal C, Espinosa JC, Oesch B, Gasset M. 2002. Prion protein interaction with glycosaminoglycan occurs with the formation of oligomeric complexes stabilized by Cu(II) bridges. J Mol Biol 319 :527-40.

[e]Drouet M, Le Sellin J, Sabbah A. 1997. Does the pork/cat syndrome constitute a predisposition to heparin allergy? Allerg Immunol (Paris) 29 :43-5.

[f]Wappler F, Scholz J, Fiege M, Kolodzie K, Kudlik C, Weisshorn R, Schulte am Esch J. 1999. 4-chloro-m-cresol is a trigger of malignant hyperthermia in susceptible swine. Anesthesiology 90 :1733-40.

Reviewer 3 *[Ph.D, Biological and Agricultural Engineering. Associate Professor, Department of Agricultural and Biosystems Engineering. Southwest U.S.]*

Observations

1. Heparin is derived from natural sources, i.e., it is synthesized endogenously and stored in tissue cells of most mammalian species. The greatest concentrations are found in the liver, lung and intestines. Since the outbreak of bovine spongiform encephalopathy (BSE), or mad cow disease, only porcine-derived heparin is allowed in the United States and Europe.
2. It has a half-life of 1 to 6 hours.
3. Heparin is used as an anticoagulant in both human and veterinary medicine.
4. Heparin is the anticoagulant of choice when an immediate effect is required. When long-term anticoagulant therapy is required, a coumarin or indandione derivative is usually administered as a follow-up to heparin therapy.
5. In livestock, the petitioned uses of heparin are for use as an anticoagulant in blood transfusions, to prevent blood from coagulating en route from the donor to the recipient animal; and for use in thrombosis prevention in animals suffering from endotoxemia. When used in blood transfusions, the heparin is added to the container prior to the blood.
6. Since WWII, heparin has been a part of routine human medical treatment. It also continues to be used veterinarily.
7. In general, "heparin and salts" are permitted in the European Union as a veterinary medicine in food animals. Also, homeopathic products (e.g. plant, animal or mineral substances) are use in preference to chemically-synthesized allopathic veterinary medicinal products or antibiotics, provided that their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended.

8. Potential concerns that were raised include the fact that, although the tissue for the making of heparin may be of organic livestock origin, the extraction process to obtain the heparin may use toxic chemical solvents for defattening, etc. Also, manufacturing of heparin may lead to environmental contamination by wastewater. This is not compatible with a system of sustainable agriculture, which suggests the presence of an environmentally-friendly farming system. [Crude heparin is obtained during extraction and complexing with ion pairing reagents. The crude heparin is subjected to fractional precipitation, purification, and chemical treatment to obtain injectable heparin.] It should be noted, however, that the manufacturing of heparin will -- in all probability – continue to take place outside of the farm (i.e., not part of the farming system), making the concern moot. Also, heparin is already currently and is anticipated to continue to be manufactured for human and veterinary use.
9. If used in the manner proposed, there is no evidence of heparin having adverse biological and chemical interactions in the agroecosystem. Disposal of container and unused contents should be done in accordance with federal, state and local requirements.

Reviewer 3 Conclusions

I recommend, based on the above salient facts, that Heparin be INCLUDED on the National List.

Reviewer 3 Recommendations Advised to the NOSB

The substance is Synthetic.

For Livestock, the substance should be Added to the National List.

TAP Conclusion

Of the three reviewers, two recommended that heparin be excluded from the National List and from organic livestock production, while one recommended that it be added without restriction. All agreed that heparin is a synthetic material. Concerns included the extraction process of heparin and the presence of alternative materials in organic livestock production.

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