Zinc Sulfate

Livestock

Identification of Petitioned Substance

Chemical Names:

$ZnSO_4$, O_4SZn, $ZnSO_4 \cdot 7H2O$, $ZnSO_4 \cdot H_2O$, $ZnSO_4 \cdot 6H_2O$, Zinc Sulfate monohydrate, Sulfuric acid; zinc salt (1:1), monohydrate; Zinc sulfate hexahydrate; Zinc sulfate heptahydrate, Zinc sulfate monohydrate

Other Names:

Zinc Sulphate, Zinc Sulfate anhydrous, Sulfate de zinc, Sulfuric acid zinc salt, Zinc (II) sulfate, Zinc (ii) sulphate, Zinksulfat, Sulfate de zinc, sulfato de cinc, Sulfuric acid zinc salt, Sulfuric acid; zinc salt, Sulfuric acid; zinc salt (1:1), Zinc sulfate (1:1), Zinc sulfate (ZnSO4), Zinc sulfate dried, Zinc(II) sulfate, White vitriol

Trade Names:

Complexonat, Bonazen, Medizinc, Biolectra Zink, Bonazen, Bufopto Zinc Sulfate, Honny Fresh 10P, Kreatol, Op-Thal-Zin, Optraex, Solvazinc, Solvezink, Verazinc, Zinc vitriol, Zincaps, Zincate, Zinco, Zincomed, Zinksulfat, Z-Span

CAS Number:

7733-02-0, 7446-19-7, 13986-24-8, 7446-20-0

Other Codes:

InChIKey: WQSRXNAKUYIVET-UHFFFAOYSA-L, AGN-PC-04678T, MolPort-027-837-982, ChemSpider ID: 22833, PubChem ID: 24424, UNII: 0J6Z13X3WO, EC: 231-793-3, UN number: 3077, ChEBI: 35176, ChEMBL: 1200929, RTECS number: ZH5260000, ATC code: A12CBo1, Smiles: [Zn+2][O-]S([O-])(=O)=O

Summary of Petitioned Use

A petition submitted on May 25, 2014, by Vantage Dairy Supplies, L.L.C. of Paul, Idaho (van Tassell, 2014) requests allowance of the synthetic substance, zinc sulfate, for use in organic livestock production as follows:

§205.603 Synthetic substances allowed for use in organic livestock production

(b) As topical treatment, external parasiticide or local anesthetic as applicable.

As required by the Organic Foods Production Act[1], the National Organic Standards Board has the responsibility to review each petition for inclusion of a synthetic substance(s) in the National List. The NOSB has requested a full technical evaluation report for zinc sulfate to support their decision-making.

Characterization of Petitioned Substance

Composition of the Substance:

Zinc sulfate is an inorganic compound: the sulfate salt of zinc and a good source of zinc ions. The molecular formula for zinc sulfate is $ZnSO_4$. A graphic representation of the structure of zinc sulfate is shown in figure 1 (Pubchem, 2014). Zinc sulfate appears geologically as a white crumbly salt efflorescence known as "goslarite." Goslarite, the heptahydrate of zinc sulfate was first extracted from the mines of the Rammelsburg, a mountain south of German town of Goslar, and first characterized chemically in 1845 ($ZnSO_4 \cdot 7H_2O$—Schuiling, 1992; Haidinger, 1845). Goslarite is frequently found near mining sites. Because certain sulfate compounds can

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[1] 7 USC Sec. 6517(d)

substitute metals as they dehydrate, goslarite contributes to the retention and release of heavy metals to the environment (Anderson et al., 2005).

Fig. 1—Zinc Sulfate Structure

Zinc sulfate is produced synthetically by combining zinc ash with aqueous sulfuric acid (Equation 1).

$$\text{Eq. 1) } Zn + H_2SO_4 + 7\,H_2O \rightarrow ZnSO_4{\cdot}(H_2O)_7 + H_2$$

The substance described in this review is an active component of a preparation containing an aqueous solution of zinc sulfate. It is used alone or combined with other substances or excipients such as copper sulfate and lauryl sulfate. The preparation is used as a footbath to prevent and treat bacterial infections (Pedersen, 2012).

Source or Origin of the Substance:

Commercially, zinc sulfate is manufactured from zinc ore mined from underground or open pit mines. Zinc ore deposits are spread widely throughout the world. Zinc ores are extracted in more than 50 countries. China, Australia, Peru, Europe and Canada are the biggest zinc mining countries. Zinc is normally associated with lead, other metals and minerals including barium, bismuth, cadmium, calcium, copper, magnesium, tin, gold and silver. In some areas, zinc is naturally concentrated to much higher levels by geological and geochemical processes (5-15% or 50-150g/kg). Such concentrations, found at the earth's surface and underground, are being excavated as ore bodies. The ore is not usually rich enough to be directly used by smelters. Thus, it is crushed and ground to separate the minerals and concentrate the zinc producing fraction. The zinc containing fraction is roasted or sintered at >900^{o}C to produce zinc ash which is rich in zinc oxide. Roasting zinc ore also produces sulfur dioxide which is recycled to produce the byproduct, sulfuric acid. In the hydrometallurgical process, one of two manufacturing processes for zinc sulfate production, zinc ash is stirred into sulfuric acid that has been diluted to 65-70% with water. During the reaction, hydrogen gas is produced as a byproduct. Zinc dissolves in the sulfuric acid, while impurities such as iron, lead and silver remain partially or undissolved. The remaining zinc sulfate solution is filtered and submitted to electrolysis to harvest metallic zinc or crystallized, processed and packaged for sale and distribution (International Zinc Association, 2011).

In the pyrometallurgical process, zinc ore is smelted with carbon in an "Imperial" smelting furnace. Zinc ash floating on the surface of the molten zinc is extracted by skimming and subsequent treatment with sulfuric acid to form zinc sulfate. The pyrometallurgical method is energy intensive and thus, expensive. Zinc is manufactured using the imperial smelting method in only a few countries including China, India, Japan and Poland. Zinc sulfate is mostly produced hydrometallurgically. Zinc sulfate in bulk is usually packaged in bags in granular or powdered form. Approximately 75% of the zinc consumed worldwide originates from mined ores and 25% from recycled or secondary zinc. Commercially, recycled zinc is processed hydrometallurgically in the manufacture of zinc sulfate (International Zinc Association, 2011).

Properties of the Substance:

Goslarite has been found in US mines at depths up to four hundred feet. It appears on the surface of walls in tufts up to three inches in length associated with copper sulfate and is likely to be a decomposition product of cupriferous zinc blende. Naturally, goslarite appears as long, silky and needle shaped crystals (Pearce, 1885). The crystals, called "Zinkvitriol" when first collected from a mine in Germany were described as orthorhombic prisms (Haidinger, 1845). Mineral forms appearing to have similar characteristics to goslarite have been described that contain iron and copper respectively, ferro-goslarite and cupro-goslarite (Wheeler, 1891; Rogers, 1899).

Zinc holds an ambiguous position on the periodic table of elements, appearing to be a transition element like copper, but actually exhibiting the properties of a main block element like beryllium or magnesium. This is the result of a characteristic flaw inherent to the most recognized form of the periodic table of elements. Table 1 provides a comparison of properties relating to the atomic configuration of both copper and zinc. While copper atoms have a number of different valence electrons available for binding and oxidation states often separated by one unit, zinc has a single oxidation state separated by two units. Zinc does not form colored ions, but copper ions are likely to be green or blue. Furthermore, unlike zinc ions which are prone to be diamagnetic and stereoactive, copper ions are likely to be paramagnetic, but not stereoactive (Jensen, 2003). These properties of zinc and copper are important for both their activities in preventing disease and their influence on the environment when released.

Table 1 Comparison of properties resulting from the atomic configuration of copper (Cu) and zinc (Zn)*

Atom	Valence electrons	Core Configuration	Known Oxidation States	Colored or Paramagnetic Ions
Cu	$3d^{10} 4s^1$	$(1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6)$	I, II, III, IV	Yes
Zn	$4s^2$	$(1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 3d^{10})$	II	No

**from* Jensen, 2003

There are four hydration states associated with zinc sulfate. A summary of their important physical properties is provided in Table 2. Anhydrous zinc sulfate is not found naturally. The product, Boyleite ($ZnSO_4 \cdot 4H_2O$), is not a stable dehydration intermediate (Anderson et al., 2005).

Table 2 Molecular hydration states and physical properties of zinc sulfate

Chemical Name	Mineral Name	CAS No.	Molecular Formula	Molecular Weight	Density, g/cm^3	Melting Point, ^{o}C	Boiling Point, ^{o}C	Solubility at 20^{o}C
Zinc sulfate (anhydrous)		7733-02-0	$ZnSO_4$	161.46	3.54	680, decomposes	740	57.7 g/100 mL, water; Soluble in alcohol
Zinc sulfate monohydrate	Gunningite	7446-19-7	$ZnSO_4 \cdot 1H_2O$	179.47		238, decomposes		Insoluble in ethanol
Zinc sulfate hexahydrate	Bianchite	13986-24-8	$ZnSO_4 \cdot 6H_2O$	269.47	2.072	70, decomposes		
Zinc sulfate heptahydrate	Goslarite	7446-20-0	$ZnSO_4 \cdot 7\ H_2O$	287.54		100, decomposes	280, decomposes	54.5 g/100 mL water; Insoluble in alcohol
Zinc/Fe, Cu, Co, Mn Sulfate heptahydrate	Zinc Melanterite		$MSO_4 \cdot 7H_2O$, $M=Zn^{+2}$ (Fe, Cu, Cu, Mn)					
Zinc/Mg, Ni Sulfate heptahydrate	Zinc Epsomite		$MSO_4 \cdot 7H_2O$, $M=Zn^{+2}$, (Mg, Ni)					

Specific Uses of the Substance:

Papillomatous digital dermatitis (PDD—foot rot, infectious pododermatitis) is a dermatosis of the digital skin of cattle, sheep and other ungulates and an important cause of lameness. The etiology of this disease is complicated, but appears to include a combined infection of three or four bacterial species: *Treponema* spp., *Fusobacterium* spp., *Bacteroides* spp. and *Dichelobacter nodosus*. PDD occurs on the hairy skin between the hoof and heel of the hind limb characterized by the appearance of red circumscribed plaques (Slawuta et al., 2006). Generally thought to be contagious, foot rot can progress from digital dermatitis to lesions on the interdigital wall of the hoof and subsequent under-running or separation of the hard horn from the foot (Bennet and Hickford, 2011).

Cost and economic benefit are important considerations in the choice of effective treatments and control procedures for foot rot. Surgical paring of the hoof to expose lesions with subsequent antibacterial treatment such as quaternary ammonium antiseptics, iodine or zinc sulfate has been shown to be effective in sheep and cattle. However, when a large number of animals are involved individual treatment may not be practical. Foot-bathing is a practical alternative. Traditionally copper sulfate and formalin have been used in footbaths for foot rot. More recently a 10% to 20% zinc sulfate solution with 2% sodium lauryl sulfate as an excipient has been shown to be as effective for both sheep and cattle (Kimberling and Ellis, 1990; Blowey, 2005). In some practices, a combination of copper sulfate and zinc sulfate may be used (van Tassell, 2014). Footbaths containing copper and/or zinc sulfate are recycled to the farm lagoon, composting system or manure pile and subsequently distributed on farmland in the form of a soil amendment.

Conventionally, zinc salts are used to control the growth of moss on structures, walkways, patios and lawns in rainy areas, primarily in the Northwestern U.S. Zinc oxide also is an industrial preservative, incorporated into carpet fibers to inhibit bacterial and fungal spoilage, and a bacteriostat, applied as a pressure treatment to preserve cut lumber. Other, more significant, non-pesticidal uses of zinc salts in the U.S. include use in fertilizers, animal feed, dry cell batteries, and as galvanizers. Zinc is an element necessary to all forms of life. It is a normal part of metabolism in all living organisms. Zinc is widely distributed in plants, animals and soils, and is normally present in food (EPA, 1992).

Approved Legal Uses of the Substance:

The US Environmental Protection Agency covers the distribution of sewage sludge on farmland in 40 CFR § 503.13 (a). However, the use of sewage sludge is prohibited in organic farming (7 CFR § 205.105(g)). For zinc the ceiling concentration or maximum concentration permitted for the application of sewage sludge to farmland is 7500 parts per million. The cumulative loading rate for zinc is 2800 kilograms per hectare with an annual loading rate of 140 kilograms per hectare. This is equivalent to a cumulative loading rate of approximately 7700 kilograms of zinc sulfate monohydrate per hectare or an annual loading rate of approximately 390 kilograms. Zinc sulfate is generally recognized by the US Food and Drug Administration as safe when used in accordance with good manufacturing practice (21 CFR § 182.8997).

Action of the Substance:

Footbaths are commonly associated with ideal management of foot problems on dairies, and for range band and farm flocks (Wassink et al., 2010). An advantage of using a footbath is that it can be located at the exit lanes of a milking parlor or on a sheep or goat walk. A 10-20 percent solution of zinc sulfate with the addition of 0.2-2.0% sodium lauryl sulfate as an excipient has been shown to be effective, safe, practical and economical for use in bovine and ovine footbaths (Downing et al., 2010; Kimberling and Ellis, 1990). Papillomatous digital dermatitis (PDD), which causes many of the foot problems in cattle and sheep was first recognized in the late eighteenth century (1791) in France (Mohler and Washburn, 1904; Nuss, 2006; Cheli and Mortellaro, 1974). There is good evidence that PDD is the result of an infection by three bacterial species: *Dichelobacter nodosus*, *Fusobacterium necrophorum* and the spirochaete, *Treponema vincentii*. *Treponema vincentii* is similar to a spirochaete phylotype responsible for human periodontal disease, although other *Treponema* spp have been isolated from PDD infections (Duncan et al., 2014; Hordoff et al., 2008). Administration of zinc salts to rabbits infected with *Treponema palladium* has been shown to effectively eliminate the spirochaete. This response, attributed to an effect of the zinc salt on the spirochaete itself, occurred within three days (Walker, 1927). Zinc, a trace element, is necessary for all living organisms. It plays in a role in many cell regulatory processes, including the innate immune response. Pattern recognition receptors of the innate immune system are stimulated by bacterial infection. Stimulation of the innate immune system causes monocyte derived macrophages to proliferate, but also increases macrophage autophagy to facilitate microbial clearance. Increased autophagy is correlated with increased intracellular zinc transport and subsequent metallothionein production. Thus, increasing zinc concentration close to lesions caused by PDD improves conditions for bacterial clearance from these sites (Lahiri and Abraham, 2014). Stimulation of the innate immune response has been shown to be a primary immune response to progressive PDD (Davenport et al., 2014).

High concentrations of zinc are also toxic to bacteria, because zinc (Zn^{++}) is well-known as a sulfhydryl reactive agent and blocks essential reactions in the bacterial cell by binding to sites normally occupied by Fe^{++} and Mn^{++} (Hantke, 2005; Derosiers et al., 2010). For example, zinc at high concentration is bacteriostatic to bacteria that cause dental caries when used in toothpaste: reversibly inhibiting the F-ATPase of permeabilized cells of *Streptococcus mutans* with a 50% inhibitory concentration of about 1 millimolar for cells in suspensions; reversibly inhibiting the phosphoenolpyruvate—sugar phosphotransferase system with 50% inhibition at about 0.3 millimolar $ZnSO_4$ and inhibiting alkali production from arginine or urea (a potent enzyme inhibitor for arginine deiminase of *S. rattus* FA-1 and for urease of S. salivarius). At higher levels (10–20 millimolar) zinc citrate is weakly bactericidal (Phan et al., 2004). *Dichelobacter nodusus* and the *Treponema* spp., like S. mutans also have zinc uptake regulation genes (Znu and Zur genes) that are sensitive to high zinc concentrations (Myers et al., 2007; Parker et al., 2005). Foot bathing in zinc sulfate can produce a pronounced curative effect against a range of foot rot lesions (Egerton et al., 2000).

Combinations of the Substance:

In addition to zinc sulfate, copper sulfate and formalin have also been used alone or in combination with zinc sulfate for treatment and prevention of PDD. Sodium lauryl sulfate (sodium dodecyl sulfate) is used as a surfactant or excipient to improve penetration of zinc sulfate into the claw (Murnane, 1933; Kimberling and Ellis, 1990). Copper sulfate is allowed for use in footbaths as a topical treatment, external parasiticide in the production of organic livestock (7 CFR §205.603(b)(1)). Sodium lauryl sulfate is generally regarded as safe by the US Food and Drug Administration and approved as a food additive (EPA, 1993; 21 CFR §172.822). Excipients, such as sodium lauryl sulfate, are allowed for use in the manufacture of drugs for treatment of organic livestock if they are identified as generally recognized as safe by the FDA or approved by the FDA as a food additive (7 CFR §205.603(f)). A study carried out in Japan, has shown efficacy of a sodium molybdate, citrate, potassium nitrate, tartaric acid, sodium hypochlorite and zinc sulfate solution (Baek et al., 2006). Peracetic acid foam has also been used in combination with footbaths (Blowey, 2005). Peracetic acid is allowed for use in disinfecting equipment, seed and asexually propagated planting material (§205.601(a)(6)); and to control fire blight bacteria in plants (§205.601(i)(8)).

Status

Historic Use:

Footbaths for the treatment and control of footrot were described as early as 1904 and considered extremely important (Mohler and Washburn, 1904; Murnane, 1933).). Copper sulfate and formalin, alone or in combination were predominantly used as active components (Gregory, 1939). Topical treatment of footrot with zinc sulfate solution was first reported as an effective therapy in 1941(Beveridge, 1941). It was subsequently shown that the addition of sodium lauryl sulfate as an excipient improved the efficacy of zinc sulfate treatment (Cross, 1978).

Organic Foods Production Act, USDA Final Rule:

Zinc sulfate is allowed for use in organic livestock by the US Department of Agriculture, National Organic Program production as a synthetic feed additive in the form of a trace mineral, used for enrichment or fortification (7 CFR §205.603(d)(2)). Sodium lauryl sulfate is often used as an excipient for administration of zinc sulfate in footbaths. Sodium lauryl sulfate as an excipient or wetting agent is allowed for use as an excipient in manufactured products used for treatment of livestock (7 CFR §205.603(f)). Zinc sulfate is allowed for use in organic crop production as a plant or soil amendment in the form of a micronutrient (7 CFR §205.601(j)(6)(ii)). An important provision for the use of micronutrients is that their use does not contribute to contamination of crops, soil, or water.

International

Canada —Operators of organic livestock production facilities must establish a provision for prompt treatment for animals with detectable disease, lesions, lameness, injury and other physical ailments. Where preventive practices and vaccines are inadequate to prevent sickness or injury and where disease and health problems require treatment, the use of biological, cultural, and physical treatments and practices is permitted, in accordance with CAN/CGSB-32.311, Organic Production Systems — Permitted Substances Lists, but maybe relaxed under veterinary supervision if listed substances fail to work. Products from sick animals or those undergoing treatment with restricted substances shall not be organic or fed to organic livestock (CGSB, 2011a). Sulfates of zinc may be used only to correct for deficiencies determined by soil or plant tissue testing. Sulfates produced using sulfuric acid are prohibited. Zinc sulfate may be used to correct a documented zinc deficiency (CGSB, 2011b).

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL-32-1999) — Where specific disease occurs, and no management practice exists, therapeutic use of veterinary drugs is permitted; Zinc can be used as a trace element supplement when the need is recognized by the certification body or authority. The use of zinc sulfate for control of footrot in cattle sheep and goats has not been specifically addressed (Codex, 2007).

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008 —Disease shall be treated immediately to avoid suffering to the animal; chemically synthesized allopathic veterinary medicinal products may be used where necessary and under strict conditions, when the use of phytotherapeutic, homeopathic and other products is inappropriate. Restrictions with respect to courses of treatment and withdrawal periods are defined (EU, 2007); Animal health is based on prevention of disease, but treated livestock may not be sold as organic products if treatment involves an unapproved medication. Treated livestock must be submitted to the defined conversion periods. Zinc sulfate may be used as a trace element in the production of organic livestock. The maximum concentration for zinc in composted or fermented household waste to be used as fertilizer or soil conditioner is 200 milligrams per kilogram (EU, 2008).

Japan Agricultural Standard (JAS) for Organic Production—Veterinary Drugs specified by Article 1. 1 of the Ministerial Ordinance for Handling by the Ministry of Health, Labor and Welfare (No.4 of 1961) are permitted. Zinc sulfate use is limited to the case where livestock is unable to grow normally because of its shortage as a trace element (MAFF, 2012).

International Federation of Organic Agriculture Movements (IFOAM) – Organic animal management systems follow the principle of positive health, which consist of a graduated approach of prevention (including vaccinations and anti-parasite treatments only when essential), then natural medicines and treatment, and finally if unavoidable, treatment with allopathic chemical drugs. Organic animal management never withholds medical treatment considered necessary for the welfare of an animal in order to maintain the organic status of the animal (IFOAM, 2014).

Evaluation Questions for Substances to be used in Organic Crop or Livestock Production

Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including

netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?

The National List does not currently provide for the use of zinc sulfate (7 CFR § 205.105(a)) in footbaths for the prevention and treatment of papillomatous digital dermatitis in cattle, sheep and goats. It is a sulfur containing compound, not derived from refinement of a fossil fuel and not classified by the environmental protection agency as an inert of toxicological concern. Zinc salts as pesticides have no food uses. The Food and Drug Administration lists zinc salts as "generally recognized as safe" for use in food as dietary supplements and as nutrients. Zinc sulfate is unlikely to cause unreasonable adverse effects in people or the environment, and is eligible for reregistration (EPA, 1992).

Evaluation Question #2: Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

Zinc sulfate is manufactured in conjunction with processes for manufacturing other zinc products. It is produced by treating mineral ores, zinc ashes and recycled products containing zinc metal or zinc oxide with sulfuric acid, followed by filtration, crystallization, grinding and bagging (International Zinc Association, 2011; USPTO, 1924).

Since the introduction of zinc sulfate as a treatment for ovine and bovine footrot in 1941, many different formulations have been tested (Beveridge, 1941). Footbaths containing copper sulfate or formalin were shown to be effective in footrot treatment for sheep as early as 1933: however, subsequent data clearly indicated that topical application of 10% aqueous zinc sulfate alone produced results as good or better than eleven other treatments including chloramphenicol in 70% ethanol, 70% ethanol, 10% copper sulfate in vinegar, vinegar, copper sulfate and pine tar, copper sulfate in water, formalin in water, dichlorophenol plus hexachlorophene, pine tar plus creosote in kerosene and creosote (Murnane, 1933; Cross, 1978; Cross and Parker, 1981). The efficacy of zinc sulfate in footbaths for sheep was subsequently shown to improve with the addition of the anionic surfactant sodium lauryl sulfate (Sodium Dodecyl Sulfate—SDS) as an excipient. This excipient appeared to promote penetration of zinc sulfate into the ovine hoof. Sixteen pounds of fertilizer grade zinc sulfate were mixed with twenty gallons of water and two thirds of a cup of SDS (Kimberling and Ellis, 1990). It was later determined that other commercially prepared anionic detergents could be substituted for SDS which was relatively expensive, e.g. Teepol (Skerman et al., 1983). A study carried out in Japan has shown efficacy of a sodium molybdate, citrate, potassium nitrate, tartaric acid, sodium hypochlorite and zinc sulfate solution (Baek et al., 2006).

Evaluation Question #3: Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

Zinc sulfate is produced from ore mined in both underground and open pit mines. The ore is ground and heated to a high temperature forming an ash containing a high concentration of zinc oxide. Hydrogen sulfide produced during heating is used to make sulfuric acid. Zinc sulfate is produced by dissolving the zinc oxide containing ash in sulfuric acid. Zinc sulfate monohydrate is available as a fertilizer or pesticide grade product. Certificates of analysis generally provide 36.5% zinc and 17% sulfur, with arsenic, cadmium, lead and mercury contamination levels respectively 10 parts per million (PPM), 20 PPM, 20 PPM and 1 PPM.

Naturally, zinc sulfate appears in four variably hydrated mineral forms: goslarite ($ZnSO_4{\cdot}7H_2O$), bianchite ($ZnSO_4{\cdot}6H_2O$), gunningite ($ZnSO_4{\cdot}H_2O$) and boyleite ($ZnSO_4{\cdot}4H_2O$); these show reversible hydration/dehydration phase changes forming a geological $ZnSO_4{\cdot}H_2O$ system. The $ZnSO_4$ system further interacts with transition and non-transition metals, interchangeably substituting one for the other depending upon mineral-soil hydration state and metal ion concentration (Anderson et al., 2005). This is very important because sulfates precipitate and dissolve in response to changing climactic conditions and contribute to the release or retention of metals to the environment.

Goslarite appears as incrustations on soil and mineral surfaces and in stalactite form on the walls of mines. It contains about five percent ferrous sulfate and one to two percent copper sulfate and manganese sulfate. Goslarite is also found in and associated with the drainage of mines. It occurs as a result of zinc sulfide leaching, oxidation and crystallization and dry climactic conditions (Wheeler, 1891; Colorado Scientific Society, 1885). It is described as "zinkvitriol" and found to form white prism shaped crystals (Haidinger, 1845).

Formation of natural goslarite occurs through the action of sulfur-oxidizing bacteria on sphalerite (zinc or ferrous sulfide), zinc hydroxides; hydrous zinc silicates and zinc carbonates found in rock and soil. Oxidation of the sulfides produces sulfuric acid which solubilizes zinc to produce zinc sulfate. During rainy and humid weather, metal laden solutions wick up to the soil or rock surface. The solutions evaporate during dry weather to form crystalline encrustations of goslarite (Schuiling, 1992).

<u>Evaluation Question #4:</u> Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518 (m) (2)).

Using zinc sulfate in livestock footbaths for the treatment and prevention of papillomatous digital dermatitis includes flushing the spent zinc sulfate containing solution into the farm's sewage lagoon or dairy manure handling system and ultimately onto fields (Van Tassel, 2014). In a study where soil samples from dairy farms in Oregon using zinc sulfate footbaths were chemically analyzed for zinc, concentrations ranged from 0.6 to 41.8 parts per million (PPM) with an average of 10.1±9.3 ppm. While, manure levels from the same farms ranged from two to twenty-five PPM with an average of 4.2±6 PPM (Downing et al., 2010). The field measurements were taken at a depth of 15 inches. Cumulative zinc concentrations represented ranges from 1.8 to 556 kilograms per hectare. Although, nearly five-fold less than the EPA cumulative loading limit for zinc in soil (2800 kilograms/hectare), soil concentrations of zinc at the these dairy farms were much higher than trace element requirements for zinc in crop production. Crops grown on land where footbath tailings are discarded can potentially sequester additional zinc that may be introduced into the livestock food supply.

Zinc is not very mobile and is strongly adsorbed to soils at pH 5 or greater. Only a fraction of the zinc in soil that is soluble is also bioavailable (Evans, 1989; Blume, 1991; Christensen, 1996). Zinc distribution in soils takes one of three forms: 1) free ions (Zn^{2+}) and organo-zinc complexes in soil solution; 2) adsorbed and exchangeable zinc in the colloidal fraction of the soil and 3) secondary minerals and insoluble complexes in the solid phase of the soil. The distribution of zinc among these forms depends on the concentration of Zn^{2+} and other ions in the solution, the kind and amount of adsorption sites associated with the solid phase of the soil, the concentration of all ligands capable of forming organo-zinc complexes, pH and redox potential of soil. Normally, concentrations of bioavailable zinc in soil solution are low relative to total zinc content of soils. The bioavailability of zinc in soils is also influenced by total zinc content, organic matter, microbial activity, moisture, and interactions with other macro and micronutrients (EPA, 2007).

In addition to being found on farms treating livestock for PDD using footbaths, hydrous zinc sulfates are commonly found associated with mine drainage. In the mine scenario, the cycle of dehydration, hydration, dissolution and recrystallization varies seasonally with temperature and rainfall. The structure of the hydrocolloid metal sulfates has been elucidated at the atomic level disclosing a complex system of interaction not only between the soil and zinc ions, but also between additional ions of magnesium, nickel, iron, copper, cobalt, and manganese. This newly described structure begins to explain the persistence and increased zinc levels in soils used for the disposal of zinc sulfate footbath tailings. Figure 2 shows the hydration/dehydration pattern of the heptahydrate epsomite mineral, goslarite and a closely related mineral group, the melanterites (Anderson et al., 2005; 2007). Minerals in the epsomite group of orthorhombic heptahydrate sulfates and their products of dehydration all have the general formula $M^{2+}SO_4 \bullet nH_2O$; M^{2+} = Mg, Zn, Ni. The melanterite group of monoclinic heptahydrate sulfates has the general formula $M^{2+}SO_4 \bullet 7H2O$; M^{2+} = Fe, Cu, Co, Mg, Mn. While Fe, Cu, Co, Mg, Mn are true transition metals, Mg, Zn, Ni are not (Jensen, 2003). As a result, even though many of the products of hydration/dehydration shown in Fig. 2 are isostructural, which allows Zn^{+2} to readily exchange with other

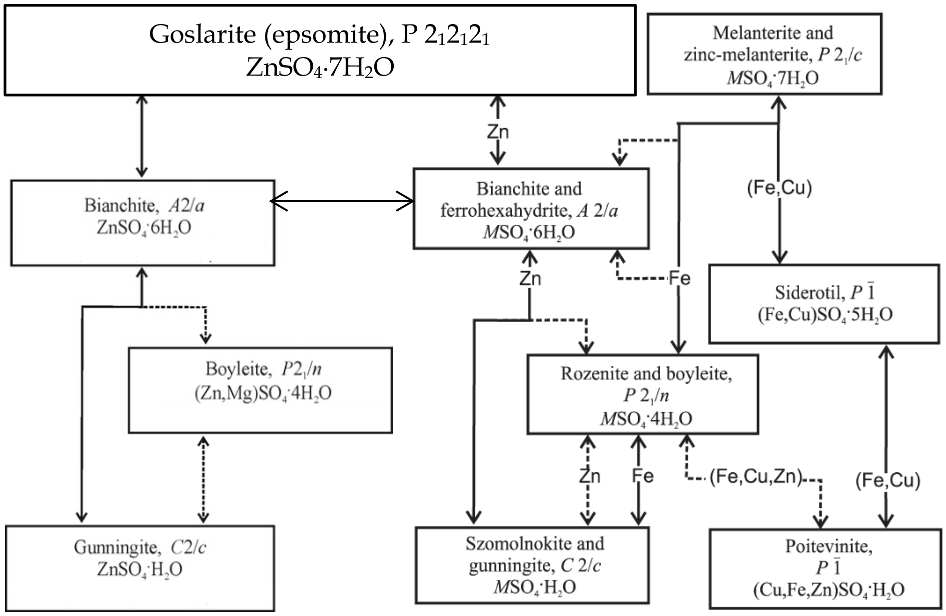

Fig. 2. Schematic diagram showing reversible hydration/dehydration phase changes that occur in the $ZnSO_4{\cdot}H_2O$ system and $(Fe,Cu)SO_4{\cdot}H_2O$ systems. Crystallographic space group notation is provided to the right of the mineral name. Solid arrows represent well documented phase changes and dashed lines indicate phase changes that may only occur in metal-substituted material or produce metastable phases (adapted from Anderson et al., 2005).

metals, the epsomite and melanterite groups are not isostructural, having distinct chemical and crystallographic properties (Anderson et al., 2007). Goslarite and metal substituted melanterite are complex molecules with a clear structure present in soil. The structures of goslarite and melanterite are distinct. Furthermore, recent neutron and x-ray diffraction studies have shown that, goslarite is intolerant of metal substitution and in conflict with early findings of ferro-goslarite or cupro-goslarite. Instead, data suggests that ferro-goslarite and cupro-goslarite are likely to be mixtures of goslarite and metal substituted melanterite resulting from the hydration/dehydration cycle. Thus, goslarite ($ZnSO_4{\cdot}7H_20$) added to soils, in the presence of Fe^{+2} or Cu^{+2} and subject to seasonal cycles of hydration and dehydration is likely to transform to bianchite, or other melanterite isostructural forms permiting incorporation of other metals both transition and non-transition into melanterites present in soil, stabilizing the metals and further decreasing zinc bioavailability (Carmona et al., 2009). Humus is also responsible for retaining and stabilizing zinc in the soil, since its colloidal nature is in part due to the structure of multimetallic complexes, making it difficult to accurately determine relative toxicity or environmental impact of metals stabilized in soil (Evans, 1989; OECD, 2012a).

<u>Evaluation Question #5:</u> Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).

Zinc is an essential element for a number of biological process. It is a cofactor for over 300 enzymes, and is found in all tissues. Zinc sulfate is registered by the US Environmental Protection Agency as a pesticide and used as an herbicide for moss growing on structures, walkways, patios and lawns in rainy areas (EPA, 1992). The EPA has not found zinc sulfate to pose an unreasonable risk through the use of currently registered pesticides. It does however require labelling for ecotoxicity:

> "This pesticide is toxic to fish and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or public waters unless this product is specifically identified and addressed in a National Pollutant Discharge Elimination System (NPDES) permit. Do not discharge this product into sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of U.S. EPA."

Sheep and calves receiving in excess of 1000 milligrams (mg) per kilogram (kg) of zinc and calves receiving 500 to 900 mg/kg in their daily rations over the course of several weeks show clinical signs of zinc toxicity. There is a correlation between loss or appetite, weight loss, diarrhea, weakness, subcutaneous edema, jaundice and dehydration in ruminants and the microscopic pathology in the kidney and gastro-intestinal tract of toxicity from zinc (Allen et al., 1983).

Many of the most pronounced clinical symptoms in humans are associated with chronically severe or moderate deficiency, rather than toxic exposure (EPA, 2005). An Organization for Economic Cooperation and Development (OECD) Screening information dataset (SIDS) initial assessment profile suggests that zinc sulfate is one of six compounds with similar toxicological hazards because it dissociates leading to the formation of a zinc cation (Zn^{+2}) responsible for hazardous effects including acute toxicity after ingesting large quantities, i.e., Lethal Dose $(LD)_{50}$ < 2000 milligrams (mg)/kilogram (kg) bodyweight (bw), and severe irritation to the eyes at high concentrations (OECD, 2012b). In repeated dose toxicity studies with rats and mice, oral zinc exposure resulted in copper deficiency and pathological changes in the pancreas and the spleen as the most sensitive effects, with a no-observed-adverse-effect-level (NOAEL) of 13.3 mg Zn^{2+}/kg bw/day. In studies with human volunteers, women appeared to be more sensitive than men to the effects of repeated zinc supplementation. In women, supplementation at a level of 150 mg Zn^{2+}/day (2.5 mg/kg bw/day), based on a bodyweight of 60 kg; lowest-observed-adverse-effect-level (LOAEL) resulted in clinical signs such as headache, nausea and gastric discomfort, and in indications for disturbance of copper homeostasis. The NOAEL in women supplemented with zinc was 50 mg Zn^{2+}/day (0.83 mg/kg bw/day). The background intake of zinc via food is approximately 10 mg/day (OECD, 2012b).

Zinc cations naturally bind to a family of low-molecular-mass cysteine-rich proteins called metallothioneins. Metallothioneins have the ability to bind mono- and divalent transition and non-transition metal ions forming metal-thiolate clusters (Carpene et al., 2007; Margoshees and Valee., 1957). Metallothioneins have a role in the homeostasis of essential Zn(II) and Cu(I) ions. Cd(II), and other environmental toxic heavy metals such as silver, platinum and mercury also bind to certain metallothioneins, but this maybe as part of metallothionein's role in protecting the cell from heavy metals detoxification (Coyle et al., 2002; Takahashi, 2012; Friesinger and Vasak, 2013). Metallothionein production appears to be up-regulated by extra- and intracellular zinc cations. Metallothionein also regulates proliferation of cells involved in the immune response.

<u>Evaluation Question #6:</u> Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).

Zinc mining and zinc sulfate manufacturing are in many ways linked because zinc sulfate is an intermediate in the zinc production process. Zinc is the third most widely used non-ferrous metal in the world, after aluminum and copper. Respectively, mine production, metal production and metal usage for 2013 were 13,201,000; 12,891,000 and 12,985,000 metric tons (ILZSG, 2014). Zinc is produced from ores containing 85% zinc sulfide (by weight—sphalerite) and 8–10 % iron sulfide, with the total zinc concentration about 50%. The ores also contain metal sulfides such as lead, cobalt, copper, silver, cadmium and arsenic sulfide. Ores are roasted with air producing zinc oxide, sulfur oxide and ferrous zinc blend. Chlorine and fluorine are removed from the combustion gas and the sulfur oxide is converted catalytically into sulfuric acid. Roasted ores are leached in sulfuric acid. In subsequent processing, pure zinc sulfate is separated from the iron containing component and many impurities are removed by precipitation. Metallic zinc is electrolytically purified from zinc sulfate or the zinc sulfate is crystallized and packaged (EMEP/EEA air pollution emission inventory guidebook, 2013).

Emissions from zinc and zinc sulfate production include sulfur dioxide and other gases (sulfur oxides (SO_x), nitrogen oxides (NO_x), volatile organic gaseous compounds (non-methane volatile organic compounds and methane (CH_4)), carbon monoxide (CO), carbon dioxide (CO_2), nitrous oxide (N_2O), and ammonia (NH_3)., particulate matter, and heavy metals such as cadmium and zinc. Environmental release of contaminants is dependent upon the technology used to prevent emission. Typical estimates for unabated air pollution from primary production of pure zinc sulfate per thousand grams of zinc produced are 210 grams of total suspended particles; 35 grams of lead; 5 grams of cadmium; 5 grams of mercury; 80 grams of zinc; 0.9 grams polychlorinated biphenyls and 5 micrograms of the toxic equivalence component of emitted polychlorinated dibenzodioxins. In the best case and using state of the art fabric filters pollution from primary zinc production can be reduced per thousand grams of zinc produced to 0.02 grams of total suspended particles; 0.0035 grams of lead; 0.0005 grams of cadmium; 4.5 grams of mercury; 0.0082 grams of zinc; 0.9 grams polychlorinated biphenyls and 5 micrograms of the toxic equivalence component of emitted polychlorinated dibenzodioxins. Secondary zinc production emissions are slightly higher, but the reduction with state of the art abatement methodology is similar in magnitude (EMEP/EEA air pollution emission inventory guidebook, 2013). In developed countries, pollution abatement is mandatory, regulated and expensive to implement. Many developing countries still lack policy instruments for pollution control and have not established or strengthened regulations to prevent high emission levels of toxic materials as new technologies have become available. Thus, the cost of zinc sulfate from developing countries or countries without strong pollution control regulations may be lower, but pollution abatement in these developing countries may be primitive or even absent (Eskeland and Jimenez, 1992).

Evaluation Question #7: Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).

Zinc sulfate is often used in footbaths for livestock alone or with other chemicals including: copper sulfate, formalin, sodium lauryl sulfate, peracetic acid, zinc chloride and chemicals used to adjust pH. Although, most cattle producers use copper sulfate or formalin in their footbaths, there is no single standard for footbaths to treat and prevent footrot. Livestock is generally led to and walked through the footbath which should be long enough to allow effective contact of feet with the footbath solution (Abbott and Lewis, 2005). Although zinc sulfate has a high efficacy relative to other footbath treatments, the method of administration, the frequency of footbathing and the cleanliness of the environment play important roles in the effectiveness of treatment independent of bovine or ovine treatment (Blowey, 2005).One study optimized the length of footbaths for dairy cattle to ensure that cows dip their feet at least two times with a 95% confidence. An example of an optimized footbath for treatment and prevention of footrot in cattle with this improvement is shown in Fig. 4. Soaking solutions are removed and replaced for every 100-300 cows (Cook et al., 2012).

There is developing concern that disposal of spent contents of livestock footbaths and its long term environmental consequences needs consideration. Particularly, if spent material is improperly remediated prior to dumping into a farm lagoon or onto manure (Downing et al., 2010, Anderson et al., 2005). Zinc sulfate retention in soils is complex, because it is retained by precipitation reactions leading to the formation of new secondary mineral phases, such as melanterite and goslarite (Evans, 1989). Zinc changes from one form to another, sometimes reversibly, in numerous chemical reactions that proceed under a wide range of common environmental conditions (USPHS, 2005). Humic substances also contain a highly complex mixture of functional groups whose metal-complexing abilities may be expected to vary considerably.

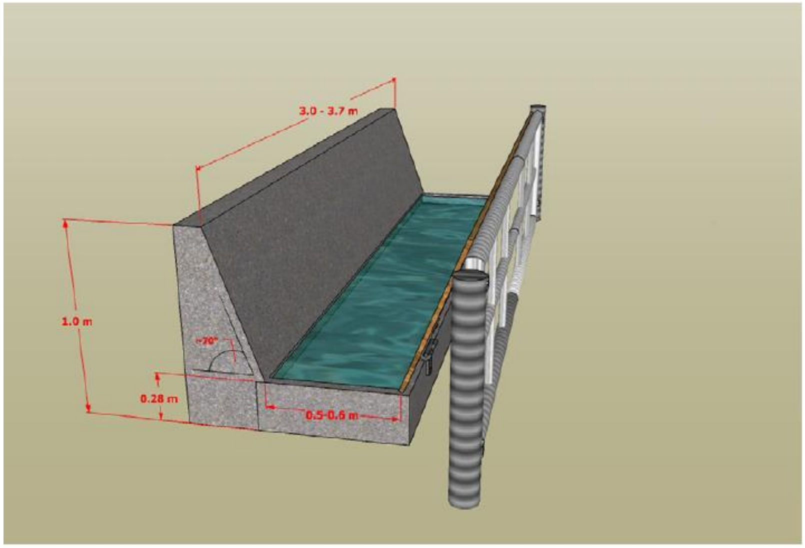

Fig. 4 Footbath designed to optimize cow flow and the number of foot immersions per cow, while minimizing bath volume (Cook et al., 2012)

Zinc sulfate monohydrate is a safe source of zinc for all animal species, the maximum contents for total zinc in feeding stuffs has been established in several nations including the United States and Europe. In Europe, safe concentrations of zinc in water for animals to drink can be applied only in feeding regimes where feed is supplement with zinc. Levels for drinking water are: milk replacers: 20 mg/L, pigs: 30 mg/L, poultry: 40 mg/L, pets: 100 mg/L; maximum daily amount of zinc administered via water for cattle: 500 mg, and dairy cows: 2000 mg (EFSA, 2012). In organic farming antibiotics are not allowed in feeds. In the US, livestock producers, drug companies, and veterinarians have also begun to curb the use of antibiotics to promote growth in food-producing animals. Drug resistant bacteria resulting from intense antibiotic selection in agriculture now challenge the efficacy of human disease treatment with antibiotics. As an alternative to antibiotics used to promote growth, high levels of zinc are substituted for antibiotics to inhibit bacterial growth especially in poultry and swine (Nielsen, 2012). Zinc has been shown to inhibit the induction nuclear factor kappa light chain enhancer (NF-κβ) in immune system cells responding to pathogens in the gut of pigs. Inhibition of NF-κβ expression in intestinal immune cells and less inflammation from the innate immune response results in reduced tissue damage and less impact from bacterial infection. The action of high zinc levels in the diet to reduce inflammation results in improved maintenance of normal gut function (Sargeant, et al, 2011).

High levels of zinc or the lack of iron can induce iron chlorosis in plants (Fontes and Cox, 2008). High zinc concentrations have been shown to induce chlorosis in blueberries, particularly, because the blueberry requires low pH soil for best growth and production. Zinc bioavailability, and free ionic concentration increase as pH decreases (Gupton and Spiers, 1996). Chlorosis resulting from high concentration of bioavailable zinc may result from spurious up-regulation of iron sufficiency regulatory proteins in non-graminaceous plants, such as the blueberry. Plant sensors utilizing a ratio of bound iron and zinc as a signal to regulate iron uptake, inappropriately sense sufficient iron and down regulate iron metabolism (Kobayahi et al., 2013). Zinc sulfate interacts with the soil to which it is added. Its toxicity is dependent on its bioavailability. Bioavailability depends on soil type and aging, which further depend on pH, cation exchange capacity and leaching (Smolders, 2009). Soil biochemistry influences the predicted no effect concentration (PNEC) and ecological soil screening level (Eco-SSL) for zinc sulfate, however; zinc soil concentrations protective of wildlife and the environment have not entirely been resolved (Ford and Beyer, 2014; EPA, 2007).

Soils harbor large numbers of protists (typically 10^4–10^7 active individuals per gram) that are important components of biogeochemical cycles. These organisms are affected by zinc sulfate fixation (Bates et al, 2012). In addition, to the protists there are also unicellular algae and bacteria in soils that can be affected by zinc sulfate fixation. Microorganisms play a role humus formation and in the zinc aging process, because zinc sulfate affects them and their biogeography. The zinc aging process in the soil may take longer when zinc sulfate is added to compost or directly to soil. Sulfate has an effect on the salinization of soil. Although, large quantities of zinc sulfate are required, high sulfate can interfere with plant calcium uptake (Allison et al., 1954).

Evaluation Question #8: Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).

Lameness in livestock is a serious global problem with many etiologies. It is important that the problem be diagnosed correctly and treated quickly to minimize economic loss (Griffin, 2011).

Footrot is a significant cause of lameness in sheep, goats and cattle caused by the interaction of three bacterial species, one of which is *Dichelobacter nodosus*, a gram negative anaerobe. Virulence of this bacterium is associated with type IV fimbriae that permit movement into the lesion and a tissue degradative extracellular protease that digests digital tissue providing a source of bacterial nutrition. A mutation in genes encoding the type IV fimbriae or the protease renders the bacteria non-virulent. Tests are available that detect the virulent and non-virulent subtypes and determine their origin. For example, the virulent bacterium responsible for the first outbreak of footrot in Norwegian sheep in over sixty years was traced to a single location where a virulent strain was introduced after the importation of sheep. The virulent strain was differentiated at the molecular level from the non-virulent background strain by a single amino acid difference in the tissue degradative subtilisin-like serine protease (Kennan et al., 2014; Gilhuus et al., 2014).

Bacterial type IV fimbriae are hair-like appendages essential for *Dichelobacter nodosus* virulence. They facilitate *Dichelobacter nodosus* colonization of the interdigital skin, penetration of the stratum corneum and serine protease secretion (Kennan et al., 2001; Craig et al., 2004). Excess zinc inhibits virulence in a closely related organism, Shiga-toxigenic *Eshcherichia coli*, by interfering with type IV fimbriae dependent bacterial attachment to the intestinal wall (Crane et al., 2011). Ribonucleic acid (RNA) transcription of genes responsible for fimbrial production and attachment is differentially regulated by a zinc sensitive alternate RNA polymerase. Expression of this RNA polymerase is inhibited by excess zinc (≥0.8 millimolar—Parker et al., 2006; Dupont et al., 1994; Niyogi et al., 1981). In practice the zinc concentration in a zinc sulfate footbath is much higher (≥75 millimolar). Work in several labs continues to focus on elucidating the link between excess zinc and inhibition of the expression pattern of virulence genes in *Dichelobacter nodosus* (Kennan et al., 2014).

Public concern about the environment grew during the 1960-70s when adverse effects of heavy metal emission from metal smelters on surrounding ecosystems were observed. In fact, extreme metal contamination in the vicinity of smelters caused clearly visible effects such as accumulation of deep layers of organic matter on the soil surface through inhibition of the activity of soil microorganisms and soil fauna. Regulatory measures to limit loading rates were subsequently introduced by developed countries to protect against negative effects on soil microorganisms associated with elevated heavy metal concentrations. Soil microorganisms and soil microbial processes are disrupted by elevated metal concentrations, sometimes resulting in severe ecosystem disturbance, however; science based estimates of safe or critical soil metal loading concentrations for soil microorganism protection vary widely between the laboratories providing them. The disparity is likely due to factors such as the distinction between short term acute response and long term chronic toxicity, which in the case of zinc sulfate can be cyclic and dependent on soil type, soil moisture content and soil pH. The response of diverse microorganism populations to zinc sulfate addition to soil is variable and complex. Models developed to explain zinc sulfate effects or lack of effect in field experiments have been difficult to verify, because initial soil respiration responses to metal addition are often not related to long-term effects (Giller et al., 1998). For example, the effect of applying zinc sulfate contaminated pig slurry to soils was followed for seventeen years. Across the entire range of applications of contaminated slurry provided in the study, no statistically significant relationship was observed between the initial response in soil respiration to metal addition and the response 17 years later (Christie and Beattie, 1989). Zinc soil toxicity for resident soil organisms including bacteria, and earthworms is affected by the behavior of particular ions in soil, leaching and type of soil examined. Meta-data derived predicted-no effect concentrations (PNEC) for zinc were developed from several hundred international diagnostic studies. The outcome of this analysis was equivocal with a highly variable PNEC ranging over several logs of concentration (Smolders et al., 2009). Addition of up to 128 millimoles/kilogram of zinc sulfate to forest soils resulted in a short term increase of fungal growth and decrease in bacterial population. This outcome was attributed to the death and ultimate ingestion of bacteria by fungi. Long term both populations returned to starting numbers. Although, the change in the long term bacterial species distribution was not evaluated (Rajapaksha et al., 2004).

Ecological Soil Screening Levels (Eco-SSLs) are concentrations of contaminants in soil that are protective of ecological receptors that commonly come into contact with and/or consume biota that live in or on soil. Eco-SSLs are derived separately for four groups of ecological receptors: plants, soil invertebrates, birds, and mammals. Eco-SSL values were developed by a multi-stakeholder group consisting of federal, state, consulting, industry, and academic participants led by the U.S. EPA Office of Solid Waste and Emergency. Eco-SSL values are meta-values derived from hundreds of eco-toxicological studies (EPA, 2007). The Eco SSL is the geometric mean of the maximum acceptable zinc concentration for three independent species under different test conditions (pH and %organic matter). Eco-SSL values are given in Table 3.

Table 3 Zinc Eco-SSLs (milligram/kilogram dry weight)

Plants	Soil Invertebrates	Wildlife	
		Avian	Mammalian
160	120	46	79

The wildlife soil criteria (WSC) for zinc is the soil concentration of zinc at which wildlife will begin to show signs of impaired health from exposure. At concentrations below the WSC wildlife may show increased tissue concentrations and biochemical signs of increased exposure (Ford and Boyer, 2013). The WSC is meant to serve as alternative to the Eco-SSL. Its decreased conservatism compared to the Eco-SSL results from the choice of a lower total number of receptors. Values for the WSC are 10 fold higher than comparable Eco-SSL values, even for the morning dove, which is its most sensitive receptor. The study suggests that the higher sensitivity of the Eco-SSL results primarily from the inclusion of receptors that eat earthworms since earthworms concentrate zinc from contaminated soil (Ford and Beyer, 2013; Spurgeon and Hopkin, 1999).

Vegetable mould production by earthworms remains as an important indicator of the soil and humus health (Sykes, 1949). Charles Darwin proposed that worms were in fact capable of changing the composition of the soil (Darwin, 1838). Darwin described the abilities of earthworms and fungi to chemically rework mineral soil into humus (Feller et al., 2003). Earthworms can live in soils with zinc levels over 3500 milligrams/kilogram depending on the pH of the soil and its ability to exchange cations, as would be the case for humus. At lower pH levels, earthworms do not survive well in contaminated soil, however, as pH increases so does both earthworm survival and fecundity. Earthworms accumulate zinc by increasing production of metallothioneins that bind zinc. Zinc binding to earthworm metallothionein allows earthworms to safely carry zinc until it is excreted facilitating transfer of zinc from the contaminated site (Spurgeon et al., 2006). Improved survival of earthworms in zinc contaminated soils may result from zinc incorporation in goslarite or melanterite at pH above 5.5.

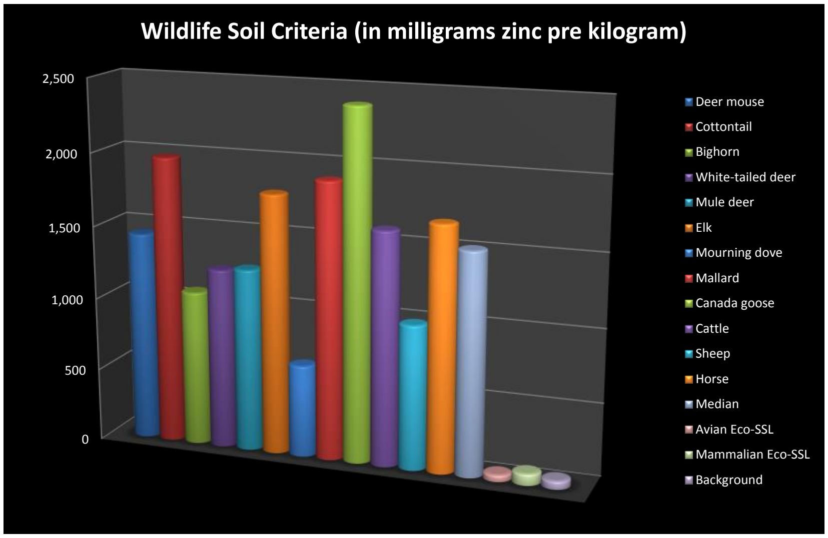

Fig. 5 Wildlife Soil Criteria (Ford and Beyer, 2013)

Data (milligrams zinc per kilogram soil (dry weight)): Deer mouse: 1,437, Cottontail: 1,973, Bighorn: 1,066, White-tailed deer: 1,238, Mule deer: 1,256, Elk: 1,780, Mourning dove: 634, Mallard: 1,896, Canada goose: 2,393, Cattle: 1,600, Sheep: 992, Horse: 1,674, Median: 1,518, Avian Eco-SSL: 46, Mammalian Eco-SSL: 79, Background: 56.5

Evaluation Question #9: Discuss and summarize findings on whether the use of the petitioned substance may be harmful to the environment (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).

Contamination to the environment by zinc tailings from mines and emissions from zinc smelting operations is still significant and prevalent in both developed and developing countries, because regulations for the implementation of appropriate controls have not been established, implemented or enforced (EMEP/EEA air pollution emission inventory guidebook, 2013; Eskeland and Jimenez, 1992). Zinc deposits in the soil resulting from zinc sulfate footbaths do not represent the same magnitude of zinc salts deposited compared to unregulated mining and smelting, but are perceived to have a potential for environmental disruption (Downing et al., 2010). Current guidance for potential disruption of the environment as a result of zinc contamination is not clear. Efforts to quantitate zinc in the soil have been confounded by a number of factors including the different forms that zinc takes when introduced to the soil and by the availability of documented evidence of the effects each of the zinc mineral forms has on soil resident organisms. Terrestrial risk assessment (Eco-SSL) focused on protection of vegetation, invertebrates, and vertebrates, but changes in microbial processes were not included in consequences to plant and animal populations or communities. While protecting higher-order organisms (plants, soil invertebrates, and wildlife) was considered important, too much uncertainty was found in the actual significance and relevance of soil microbial toxicity test data for it to be included in EPA's guidance assessment. It was considered exceedingly difficult to relate specific microbial activities with indications of adverse and unacceptable environmental conditions (EPA, 2007; Kuperman et al., 2014; Mayfield and Fairbrother, 2012; Ford and Beyer, 2013).

Because composting to produce humus depends on microorganisms, both the correct raw materials and sustainable production conditions must be provided 1) to ensure conversion of waste into humus and 2) to prevent zinc soil toxicity (Sykes, 1959). Zinc soil toxicity is most effectively modelled using pH and cation exchange capacity (CEC) as quantifiers for "free zinc." Furthermore, in natural soils, each of these parameters is functionally dependent on humus content. pH is a measure of acidity. At low pH (<5.5), zinc sulfate is present in the soil solution as dissociated Zn^{+2} cations and SO_4^{-2} anions. This is the bioavailable form of zinc and is also the form that is toxic in soil at high concentration. CEC defines the ability of soil or humus to bind ions such as Zn^{+2}. At least two different molecular frameworks are involved, including minerals such as goslarite and melanterite, and biological ligands, such as metallothioniens and phytochelatins, which are zinc binding proteins in bacteria, fungi, protozoans, worms, insects, plants and higher animals resident in the soil ecosystem (Heemsbergen et al., 2010; Cobbett, 2002).

Applied zinc concentrations causing a 50% reduction in grain yield ranged from 263 mg/kg to 4789 mg/kg, where the farm experiencing 50% loss at 265 mg/kg zinc had the lowest pH and CEC. It was the same farm in both cases. The range of error for this study was very large: as much as ten-fold, but showed that soil characteristics were vitally important in the toxicity pattern for zinc (Warne et al., 2008).

Phytoextraction is a remediation technology using plants to remove heavy metals from soil. Excess zinc can be successfully removed from soil by planting sunflower (*Helianthus annuus*) and canola (*Brassica napus*). Sunflowers and canola can absorb respectively in excess of 1250 and 668 milligrams per kilogram of zinc into their shoots and roots (Mahmoud et al., 2005).

Evaluation Question #10: Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4)).

Gastrointestinal disturbances have been reported mostly in children after ingestion of zinc sulfate including: vomiting, abdominal cramps, and diarrhea, in several cases with blood, have been observed. Anemia has also been observed during medical treatment after administration of 2.6 milligrams (mg) zinc sulfate per kilogram (kg) per day. Pregnant women receiving capsules containing 0.3 mg zinc/kg per day as zinc sulfate during the last two trimesters did not exhibit any reproductive effects (no changes in maternal body weight gain, blood pressure, postpartum hemorrhage, or infection—Roney et al., 2006).

Powdered zinc sulfate may cause eye, skin, respiratory tract and digestive tract irritation. Appropriate personal protective equipment is required for handling. There is no evidence available to suggest human health hazards associated with excess zinc in meat or dairy products resulting from treatment of livestock with zinc sulfate footbaths.

Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

The petitioned use for zinc sulfate is limited to footbaths for the treatment and prevention of footrot. Since the first identification of footrot in sheep, cattle and goats several substances have been used for treatment with varying degrees of efficacy including ethanol, copper sulfate, formalin, pine tar, cresol, and hexachlorophene (Cross, 1954). They vary in side effects and cost. However, most of the substances that are used are neither non-synthetic or are not included in the National List. Among these copper sulfate, formalin and zinc sulfate are the most accepted treatments and are comparable in efficacy (Skerman et al., 1983). Formaldehyde is harmful, carcinogenic and is considered a toxic waste. Copper sulfate is listed in the National List: § 205.603, synthetic substances allowed for use in organic livestock production, (b) As topical treatment, external parasiticide or local anesthetic as applicable, (1) copper sulfate. Copper sulfate is currently used in a number of veterinary products for the treatment of footrot in cattle, sheep and goats. One product containing acidified ionized copper sulfate has been shown to be more effective in prevention compare to untreated copper sulfate (Holzauer et al., 2012). Predominant issues with the use of copper sulfate are its toxicity, and its characteristic blue or green color which can potentially stain wool. Copper sulfate like zinc sulfate has a complex interaction with soil: its toxicity in soil depends on a number of factors. It is less stable in soil than zinc. Peracetic acid and hydrogen peroxide foams are also used in the treatment and control of footrot, although the efficacy of these treatments is controversial (Bergstein et al., 2006). It is important to note that antibiotics are increasingly used in treatment of pododermatitis, due to the bacterial nature of its etiology. However, good evidence is available for increased microbial antibiotic resistance in *Dichelobacter nodosus* and other bacteria present during infection (Lorenzo, et al., 2012). Antibiotics are prohibited in organic livestock production (7CFR §205.237, §205.238).These same bacteria have not demonstrated resistance to zinc sulfate treatment.

Attempts have been made to develop scoring systems to evaluate phenotypic resistance to footrot in sheep. One such system was based on foot lesion severity (Conington et al., 2008). Although statistically sound, significant differences could not be directly correlated genetically.

Some vaccines have been shown to be effective in treating footrot. Because several bacteria are involved in the infection and these are represented by multiple serogroups, the effectiveness of using a monovalent vaccine in treating another serogroup is likely to be limited. Programs are ongoing to address vaccination, but a completely vaccine has not yet been described for footrot in cattle or sheep (Bennett and Hickford, 2010).

Aspirin (Salicylic Acid) is allowed for use in organic livestock production for health care use to reduce inflammation. Salicylic acid has also been shown to be effective in treatment of digital dermatitis in dairy cattle (§ 205.603, Schultz and Capion, 2013). A combination of Australian Tea Tree Oil, Jojoba oil, Benzathonium Chloride, water, propylene glycol and emulsifiers (Hoofmate™) as a topical application has been used with some success in treating digital dermatitis (Schivera, 2014).

<u>Evaluation Question #12:</u> Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

Foot rot is a contagious disease of cattle, sheep and goats that is transmitted by *Dichelobacter nodosus,* an anaerobic rod shaped bacterium. Temperature and moisture play an important role in the transmission and invasion of this organism. Most outbreaks occur in seasons with high rainfall, warm temperatures and lush pasture growth. Infectious material may be transferred directly from the soil to animals. Inflammation of the interdigital skin is a clear sign of infection. This is usually followed by more severe clinical signs (Kimberling and Ellis, 1990).

One of the first steps to be taken in the treatment of flocks and herds affected with footrot is to separate the diseased animals from healthy animals (Mohler and Washburn, 1904). Meticulous surgical paring of the hoof to expose lesions followed by topically applied agents, e.g., copper sulfate, zinc sulfate and formalin, is an effective treatment (Kimberling and Ellis, 1990). However, foot trimming can be painful for animals and if not properly done can exacerbate or complicate existing conditions (Winter, 2009). Foot-bathing with chemicals, such as formalin and copper sulfate is also effective for large numbers of animals. Vaccination against foot rot is a good alternative; however, vaccines for foot rot are still in developmental stages. The development of long term immunity against *Dichelobacter nodosus* has been difficult to establish in ungulates (Winter, 2009). In addition to foot bathing establishing hygienic conditions on the farm, maintaining clean feet and promptly diagnosing and treating affected animals has been successful for preventing foot rot (Pedersen, 2012; Nuss, 2006).

Evaluation of risk factors for digital dermatitis has led to recommendations to provide dairy cows with full access to pasture during the summer, housing with flooring that is dry (e.g. automatic scraped slatted floor, during the dry period, separation from the lactating herd before calving), long and wide cubicles and increased lying time for heifers. Cows that are raised within the dairy cows' accommodation also were at lower risk for developing lesions of digital dermatitis. First-parity cows and lactating cows were at higher risk. Management routines such as a rapid increase in concentrate amount after calving, rough handling, feeding by-products, feeding high starch rations and herd trimming at long intervals also increased the risk of infection (Blowey, 2005; Somers et al., 2005).

A good diet rich in zinc appears to have an effect on foot health and claw integrity (Siciliano-Jones et al., 2008).

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