NTP NOMINATION FOR USNIC ACID AND USNEA BARBATA HERB.

Submitted by the Food and Drug Administration, Division of Dietary Supplement Programs

Usnic Acid (labeling name) and Usnea Barbata (botanical supplement name)

Plant Name(s)/Source(s): Most notably in Usnea sp., but also in other genera of lichens, including Alectoria, Cladonia, Lecanora, Ramalina and Evernia.
Ingredient Name(s): Usnic acid, sodium usniate or sodium usnate
Labeling Name(s): Usnic acid, sodium usniate, usnea lichen or extract, usnea barbata

What is it?
• Usnic acid is a complex polycyclic chemical compound produced naturally by certain lichens species.¹
• Lichens containing usnic acid have been used as traditional medicines and crude drugs in other countries.¹
• Usnic acid as a pure substance has been formulated in creams, toothpaste, mouthwash, deodorants and sunscreen products, either as an active principle or a preservative. FDA has not received any certification from industry on the safety or use of this substance in cosmetic products.
• In recent years, usnic acid and its salt form, sodium usniate, have been marketed in the US as an ingredient in dietary supplement products (mostly with claims as weight-loss aides, though some as antimicrobial agents).

Regulatory History
Usnic acid a complex polycyclic phenolic compound is one of the most abundant characteristic secondary metabolite of lichens. This commercially available product has been extensively used as a preservative or active ingredient in medicinal products,
perfumery, creams, toothpaste, mouthwash, deodorants and sunscreens. In recent years, the compound has also been used in health food supplements promoted as weight reduction remedies. However, to date, no sound non-clinical or clinical data have been presented to support any such claims.

**Uses of Usnic Acid or Sodium Usniate:**
This product is primarily marketed as a dietary supplement to promote weight loss and to raise the body’s metabolic rate. The most common source is the lichen Usnea barbata and related species that is promoted for its antibacterial and antifungal properties in complementary and alternative medicine practices. It is also promoted for consumption as a brewed tea for its effects as a natural metabolic stimulant.

These ingredients are also used in deodorants, cosmetic products, lotions, balms and air fresheners based on their antibacterial and antifungal properties. U.S. patents exist for usnic acid in these types of products. It is unknown what the exposure level or risk may be associated with the use of these common products.

**New Dietary Ingredient Notification:**
Although the herb Usnea has a long history of pre-1994 use, we are unaware of any evidence that Usnic Acid was marketed before 10/15/94. FDA has not received any applications for Usnic Acid as a new dietary ingredient for which a premarket notification pursuant to 21 USC 50b(a)(2) is required.

**Adverse Events:**
FDA has received at least 21 Adverse Event Reports in which LipoKinetix (containing Sodium Usneate) is reported to have been associated with the adverse event, including one death, one liver transplant, 7 cases of liver failure, 10 cases of chemical hepatitis, and four cases of mild hepatic toxicity. Of these, 6 Adverse Event Reports were clinically confirmed from the product label as associated with LipoKinetix/Sodium Usniate, including one case of liver failure, 3 cases of chemical hepatitis, and two cases of mild hepatic toxicity.

A Medwatch report dated 1/15/2003 reported the need for a liver transplant in a 28 year old healthy female who developed fulminant liver failure after approximately two weeks of using a product with Pure Usnic Acid taken per the label’s recommended dosing. A second containing Usnic Acid has also been associated with liver failure and is currently under further investigation by CFSAN/FDA.

Based on the adverse events first reported by Medwatch in November 2001, the FDA on November 20, 2001 warned consumers against use of LipoKinetix, and also strongly recommended to the manufacturer Syntrax Innovations Inc. to withdraw the product from the market (USFDA: Letter to Distributor on Hazardous Dietary Supplement LipoKinetix, November 19,20001).

**Adverse Event Reports Associated with Dietary Supplements Containing Usnic Acid or Sodium Usniate – Results by Gender**
The FDA has received 21 adverse event reports of consumers who developed hepatotoxicity after ingesting dietary supplements containing usnic acid or sodium usniate (the salt form of usnic acid). Of these 21 cases, liver failure reportedly occurred in 7 patients.

Stratifying the results by gender, it appears that females made up 57% of the total number of hepatotoxicity cases (i.e. 12 of the 21 liver toxicity adverse events occurred in female consumers). Among those who had liver failure, all but one was female (i.e. 6 of the 7 liver failure cases involved female consumers).

The age of these 6 women who developed liver failure ranged from 19 to 36 years old. Their clinical outcomes were as follows: three underwent successful liver transplant; one died from liver failure complications before having a transplant; one was managed successfully without requiring a transplant; records were not available for one patient to see if transplant ever took place.

**Background:**
Usnic acid a prominent secondary lichen metabolite was first isolated by Knop in 1844. The globally distributed consortium of lichens is developed through symbiosis between the green algae and or cyanobacteria (photobionts), which produce carbohydrates by photosynthesis for themselves and for their dominant fungal partners (mycobionts), which in exchange provides physical protection, water and minerals. Lichens can colonize on rocks to foliose (crustose lichens) or on tree trunks, soil or several other diversified substrata (fruticose lichens). It is estimated that lichens covers approximately 8% of the earth’s surface (Cocchietto 2002). Over the history of mankind out of more than 20,000 known species of lichens, a number of them have been used for diversified purposes such as dyeing, pollution monitoring, perfumery, floral decoration, and as therapeutic agents (Romagni et al. 2000, Ingolfsdottir 2002).

The crude extracts of usnic acid rich lichens (e.g. Usnea species) have been used throughout the world to treat various ailments such as pulmonary tuberculosis, pain, fever, wounds, athlete foot, other dermal lesions; it has also been used as an expectorant, in antibiotic salves, deodorants, and herbal tinctures (Shibata et al. 1948, Vartia, 1973, Okuyama et al. 1995, Correche et al.., 1998). Usnea species have been used in contemporary homeopathic medicines, and traditional medicines in China, Pacific Islands, and New Zealand. Reportedly, Hippocrates used some of these lichens to treat urinary conditions (Ingolfsdottir 2002). Many other lichens have been used as medicines, and it is estimated that approximately 50% of all lichen species possess antibiotic properties.

Active research to develop pharmaceuticals from lichens continues, especially in Japan. Over the long evolutionary period, lichens have developed a great capacity to survive under the extreme and harsh environmental conditions. This ability is achieved by attaining a dormant state, through slow metabolism, and most importantly by producing excretory bioactive metabolites (e.g. usnic acid), which provide chemical protection from the invading viral spectrum, bacterial and protozoan parasites, and against animal
predators such as insects and nematodes and against competitor plants. These secondary metabolites also provided defense against ultraviolet rays and excessive dryness. For defense purposes, these phytoorganics are deposited on the surface of the hyphae, not inside the organism. By nature of their defensive functions, these compounds are external excretory toxicants, and their anti growth, antimicrobial, and antiderbivoral properties have been employed in the traditional medicine to treat diversified medical conditions.

Reportedly, lichens produce over 800 secondary metabolites comprising many classes of compounds including amino acid derivatives, sugar alcohols, aliphatic acids, macrolytic lactones, monyclic aromatic compounds, quinines, chromones, xanthones, dibenzofurans, depsides, depsidones, depsones, terpenoids, steroids, carotenoids, and diphenyl ethers (Huneck 1999, Huneck and Yoshimura 1996, Fiedler et al 1986). Of all the secondary lichen metabolites, usnic acid is the most studied and used compound. It is abundantly distributed in species of Cladonia, Usnea, Lecanora, Ramalina, Evemia, Parmelia and Alectoria. The species of Alectoria are known to contain up to 6% usnic acid. Usnea leaves from the Venezuelan Andes contained 2.7% usnic acid in the thallus (Marcano et al. 1999).

It is generally believed that the production of usnic acid is exclusively restricted to lichens (Ingolfsdottir, 2002, Correche et al, 1998). However, usnic acid has also been found in Kombucha mushroom, which in fact is not a mushroom (Perron et al 1995). In a few unconfirmed isolated cases, this compound was also reported in non-lichens ascomycetes and isolated mycobionts (Bondarenko et al. 1969, Komiya and Shibata 1969). In addition, closely related compounds such as phytotoxin mycousnine, cercosporamide and usnic acid amide are found in non-lichen fungi (Sassa and Igarashi and 1990, Conover et al 1992).

**CHEMISTRY:**
Usnic acid is a dibenzofuran derivative Fig 1. It occurs as a (+or d-usnic) and a (- or 1-usnic) enantiomer, indicating a or P projection of the angular -CH3 group at the chiral 9b position, respectively. In addition, two other natural isomers, (+) and (-) isousnic acids are also found in lichens. They differ from usnic acid in the substitution of ring A.
Commercial availability and use: A highly purified form of usnic acid isolated from genus Usnea is commercially available. It is also prepared in tissue culture using tiny segments of thalli from Usnea and Ramalina species. In its purified form, usnic acid has been formulated into creams, toothpaste, mouthwash, deodorants, antibiotic ointments and sunscreen products. Usnea barbata, usnic acid, and copper usnate have been produced as antimicrobial preparations. In Germany, lichen extracts used in cosmetics and pharmaceuticals are marketed under trade names Omnigran a, Granobil, and Usnagren A and T (Reynolds 2000). In Italy, usnic acid has been used in vaginal creams, foot creams, powders, and hair shampoo (Rafanelli et al. 1995). In Argentina, "Barba della Piedra (Usnea densirostra) has been sold to treat many ailments (Correch et al. 1998). In these preparations, usnic acid is employed as an active agent as well as a preservative. The extracts of lichens rich in usnic acid have been utilized in pharmaceuticals, perfumery, cosmetics, and in ecological applications. It has also been indicated that usnic acid could also be used as a biomarker to assess pollution, as its concentration in lichens increases with the increased exposure to toxicants. In recent years, usnic acid containing health food supplements have been promoted as weight reduction products.

BIOLOGY:
A number of biological roles such as antibiotic, antifungal, antifeedent, phytotoxic, photobiont regulator, and UV filter etc. have been linked to usnic acid lichens rich in usnic acid. However, it must be mentioned that neither of these effects have been substantiated nor formally attributed to usnic acid. These indications have simply served as a guide for pharmacological studies of these substances. The compound probably does not have a single major biological role, but can play different species-specific roles. Furthermore, both the enantiomers have been known to exhibit different biological activities. For instance, (-) usnic acid specifically inhibits the activities of arginase and urease, whereas (+) form was found to be a more effective antimicrobial agent (Proska et al, 1996, Lauterwein et al, 1995, Ghione et al, 1988). Even usnic acid's well known toxic...
effect allergic contact dermatitis is also enantioiner-specific. For instance, both forms of
usnic acid sensitized lichen pickers, while only its d- form sensitized lumberjacks
(Benezra 1987). In an acute study in larvae of a herbivorous insect, the (-) usnic acid
proved to be 10 times more toxic than its (+)-enantiomer (Emmerich et al. 1993).

Traditional Chinese Medicine (TCM) of Usnea herb “Song Lo”
Song Lo was first recorded in “Sheng Nong Ben Cao Jing” (Other names: The Herbal
Classic of Divine Plowman or Sheng Nung’s Herbal), approximately 101 BC. Song Lo as
one of the few Usnea plants, have also been recorded in other classic TCM books.
Despite its long history, Song Lo is a rarely used herb in TCM (among >6000 herbs, only
~ 500 commonly used). Song Lo tea or decoction for internal and external use has been
recorded (for detoxication of liver, treatment of malaria, wounds, snake bite, cough, etc).
The powder of the plant has also been used for burns/wounds.

There are about dozen Usnea plants. Usnea longissima Ach, U. florida (L.) Wigg. And
U. diffracta Vain are the three listed for medicinal use in TCM (Encyclopedia of Chinese
Materia Medica and Modern Chinese Materia Medica).

Usnic acid, diffractic acid, and lichenin (polysaccharide) and essential oils have been
reported from Song Lo. The usnic acid concentrations in different Usnea plant species
could vary, but may as high as 1-2% or more. For crude herb (dried plant), the common
TCM doses are 6-9 grams, which is about 60-120 mg usnic acid per day. One thing to
be considered is that TCM rarely uses only one herb for a long term to treat a disease.
However, between the late 50’s and early 70’s, some herbs including Song Lo have been
tested in humans at relatively high doses (e.g., 30 g of Song Lo/day as reported below).

Partially purified usnic acid from Song Lo has been tested in China for TB and chronic
bronchitis (in the 50’s-70’s, Encyclopedia of Chinese Materia Medica). For TB, usnic
acid (tablets) 90 mg/day (or 1.5 mg/kg/day). Thirty patients were treated for an average
of 71 days. Side effects reported including stomachache and elevated liver enzymes.
Some required suspension of usnic acid treatment for a week after taking the usnic acid
tablets for 3 about months. For bronchitis, 91 patients were treated by one of the four
preparations (2 x 100 ml decoction of 30 g Song Lo/day; Crude crystalline material of
Song Lo, Sodium Usniate, and Unspecified partially purified Song Lo extract, at some
doses of each time 30 mg and three times per day). Ten days was considered a treatment
period. Side effects, dry mouth, dizzy, and nausea, were reported.

No information on the “no observed adverse effect level” of usnic acid is available. For
dietary supplement use (potential long term and unsupervised use), doses lower than the
common TCM use (e.g., 2-3 g of the herb equal to > 30 mg/day Usnic acid) would seem
to be without serious effects.

CLINICAL PHARMACOLOGY:
Antimicrobial activity: Prior to the discovery of penicillin, usnic acid was under active
investigation for its broad spectrum antibiotic activities. In fact, between the ends of
World War II until the end of 1950s, most of the 64 research publications on usnic acid

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were related to its antimicrobial activity. After 1980s, interest in usnic acid was renewed because of increasing experience of multi-drug resistance caused by overuse of synthetic antibiotics (Cocchietto et al, 2002).

Earlier it was demonstrated that both the optical antipodes of usnic acid were active against Gram positive bacteria and mycobacterium (Shibata et al., 19948; Stroll et al., 1950). In recent years, the antibacterial properties of usnic acid have been confirmed by several researchers. In preliminary clinical trials, a mouthwash containing 1 % (+) usnic acid was administered to volunteers, and at regular intervals the samples of oral bacterial flora were examined. It was revealed that the growth of Streptococcus mutans involved in the etiology of dental caries, was selectively suppressed (Ghione et al., 1988). Currently, a number of usnic acid (+) containing preparations are marketed (Cocchietto et al., 2002) Using standardized assays, the in vitro susceptibility of pathogenic Gram positive and anaerobic bacteria towards usnic acid has been confirmed (Ingolfsdottir 2002). Usnic acid has been shown to suppress the growth of Gram positive organisms mainly responsible for body odor. Ethoxydiglycol extracts of lichens containing 10% usnic acid on wet weight basis have been demonstrated to have preservative potential in moisturizing cream (Scifert and Bertram, 1955).

Usnic acid was found to be effective against Mycobacterium aureum (Ingolfsdottir et al. 1998). In vitro assays, usnic acid and its salt inhibited the growth of Mycobacterium tuberculosis at relatively low concentrations (Krishna and Venkataramana, 1992).

**Antimycotic activity:** During a short-term treatment with usnic acid salt, 65 patients with Tinea pedis exhibited a significant improvement in clinical condition (De Battisti et al. 1991).

**Antiprotozoal activity:** Usnic acid (-) exhibited significant inhibitory effect against the pathogenic protozoan Trichomonas vagina/is at comparatively lower concentrations than metronidazole (Wu et al, 1995). The compound also showed leishmanicidal properties both in vitro and in vivo studies; intralesional administration produced a reduction in lesion weight as well as in body burden of parasite (Fourner et al, 1997).

**Antiviral activity:** In a cancer chemoprevention assay, (+) usnic acid isolated from Usna longissima was found to be significantly effective against tumor-promoter- induced Epstein-Barr virus with an ED50 of 1.0 µg/mL (Yamamoto et al, 1995). (+) usnic acid also inhibited the cytopathic effects of Herpes simplex type 1 and polio type 1 viruses in the infected kidney cells of African green monkey (Perry et al. 1999). In a clinical trial, the effect of an intravaginal formulation containing usnic acid and zinc sulfate as an adjuvant therapy to radio surgical treatment was evaluated in 100 females infected with genital human papilloma virus. The treatment significantly improved the time of reepithilization one month after the radio surgery (Scrippa et al. 1999).

**Antiproliferative activity:** Usnic acid caused moderate inhibition in the murine P388 leukemia assay, and also exhibited cytotoxic activity against cultured L1210 cells; it was inferred that p-triketone moiety was essential for the optimum activity (Takai et al. 1979). On the other hand, (+) usnic acid (50µg/mL) reduced the cell counts of leukemic (K-562)
and endometrial carcinoma cell culture (Ishikawa HEC- 50) (Cardarelli et al. 1997; Kristmundsdottir et al. 2002). (+) usnic acid exhibited cytotoxic activity against human keratinocyte cell cultures (Kumar and Muller 1999).

**Anti-inflammatory activity:** In an acute rat paw edema and a chronic rat cotton pellet assays at 100mg/Kg oral dose level, the anti-inflammatory action of (+) usnic acid was comparable to ibuprofen at the same dose level (Vijayakumar et al. 2000).

**Analgesic and antipyretic activity:** In two mice studies, the analgesic and antipyretic effects of usnic acid were evaluated (Okuyama et al. 1995). At 100 mg/kg oral dose level, usnic acid exhibited a significant analgesic effect as indicated in acetic acid-induced writhing- and tail pressure tests. At oral dose levels up to 300mg/kg, usnic acid also expressed significant antipyretic activity determined through lipopolysaccharide-induced hyperthermia.

**TOXICOLOGY:** Irrespective of a long history of usnic acid containing products, only a few animal studies were conducted to evaluate the clinical safety of usnic acid. There is a total lack of systemic sub chronic and chronic general toxicity studies. The conduct and quality of the some of the available studies is also questionable.

**Non-clinical: Usnic Acid Studies**

**Acute toxicity studies:** (Martindale- The complete drug reference-Monographs 1982-2003)
- Mouse: LD50 oral = 838mg/kg
- LD50 intravenous = 25mg/kg
- LD50 subcutaneous = 75mg/kg
- Rabbit: LD50 oral = >500mg/kg

In an acute study where larvae of a herbivore insect (*Spodoptera litoralis*) received injections of both enantiomers of usnic acid in the hemolymph, (-)-form was found to be 10 times more toxic than its (+)-form (LD50 8.6 versus 90.8 µmol). (Emmerich et al. 1993).

**Sub chronic toxicity studies:** No subchronic animal studies were found in the literature.

**Chronic toxicity studies:** The extensive library search did not provide any information about such studies.

**Reproductive and developmental toxicity studies:** In a 35-day oral study in 5-6 weeks old male Swiss mice, no adverse effects of 200mg/kg/day of (+) usnic acid on the number, motility and structure of epididymal spermatozoa, were observed. Additionally, no quantitative differences in the content of testicular protein, RNA and DNA were recorded (AI-Bekaiir et al. 1991).
Elk Herd Toxicity
Early in 2004, Wyoming State officials reported that lichen (Parmelia spp) was responsible for the deaths of nearly 300 elk due to muscle wasting. The lichen is abundant in desert soils around the state. These lichens are not normally a major food source for the elk but have become the major food source because of severe draught conditions.

Tests revealed that the lichen was indeed the cause of the strange affliction that had taken down the elk. Scientists found Parmelia in the stomachs of afflicted elk, and when captive elk where put on a diet of Parmelia they went down with the same muscle wasting symptoms as the elk in the wild.

Although usnic acid had not been specifically reported in Parmelia spp., the symptoms were similar to those expected from usnic acid exposure. Samples of Parmelia spp. were sent to FDA for usnic acid analysis. Usnic acid was identified in the Parmelia spp. at levels that were comparable to the levels found in the lichen Usnea Barbata. This suggests that the usnic acid in the Parmelia spp. was probably the cause of the muscle wasting disease and the usnic acid may be more widespread in lichen species than had previously been known.

Usnic acid and mitochondrial function
Several studies, using well-established methods, have studied the effects of usnic acid on mitochondrial function in vitro. Johnson and colleagues (Johnson, Feldott, and Lardy, 1950) studied the affect of usnic acid on rat kidney and liver homogenates. They reported that usnic acid at low concentrations (1 μM) stimulated oxygen consumption in the presence of several substrates, suggesting uncoupling of oxidative phosphorylation. Uncoupling of oxidative phosphorylation by usnic acid was confirmed by showing a decrease in the ratio of phosphate consumed (used to make ATP) to oxygen consumed (P/O ratio). This uncoupling occurred at concentrations of usnic acid that did not interfere with rates of oxygen consumption. At concentrations of 50 μM or higher, usnic acid inhibited oxygen consumption in the presence of a wide range of substrates, suggesting inhibition of the ETC or other key mitochondrial function. The uncoupling effects of usnic acid were confirmed by the same group in subsequent studies (Lardy, Connelly, and Johnson, 1964)

Uncoupling of oxidative phosphorylation by usnic acid was confirmed in mouse liver mitochondria by Abo-Khatwa et al. (1996). Concentrations as low as 0.75 μM usnic acid decreased the P/O ratio dramatically, without inhibition of oxygen consumption. Stimulation of oxygen consumption by usnic acid was observed in the presence of the ATP synthase inhibitor oligomycin, confirming that usnic acid was acting to uncouple oxidative phosphorylation. Interestingly, concentrations of the classic uncoupler, 2,4-dinitrophenol of 50μM were required to reproduce the uncoupling associated with usnic acid exposure. In observations similar to those of Johnson et al(1950), Abo-Khatwa reported inhibition of mitochondrial oxygen consumption at usnic acid concentrations above 1 μM, again suggesting adverse effects on mitochondrial function not limited to
uncoupling. Abo-Khatwa et al. (1996) noted that usnic acid possessed physical properties like that of a “membrane disruptor”, consistent with its uncoupling actions.

Usnic acid has been suggested to have antimicrobial properties (Lauterwein et al. 1995), and the ability of the compound to interfere with trans-membrane ion gradients and mitochondria function may contribute to these actions. Low concentrations of usnic acid (0.1 µg/ml, or approximately 0.3 µM) stimulated oxygen consumption by the mitochondria-containing fungus *Saccharomyces cerevisiae*, while concentrations above 100 µM inhibited oxygen consumption (Cardarelli et al. 1997). This is strikingly similar to the bi-phasic concentration-response to usnic acid observed in mammalian tissue homogenates and mitochondria.

Little information is known about the toxicology of usnic acid in animals or humans, and thus how the in vitro defined actions of the compound on mitochondrial function extrapolate to potential in vivo toxicity cannot be defined. Usnic acid does affect intact cells in culture, and may be cytotoxic (Kumar and Muller, 1999). Single doses of 5-20 mg/kg appear to be tolerated in animals (Krishna and Venkataramana, 1994). No human clinical toxicology is available for usnic acid. Recently, a case series of hepatotoxicity associated with an usnic acid-containing product was reported (Favreau, et al. 2002) It is interesting to note that other mitochondrial toxins have been associated with hepatotoxicity in humans (Pessayre, et al.1999; Krahenbuhl, 2001), and this case series is consistent with this pattern of adverse effects.

Thus, in vitro studies document that usnic acid acts to uncouple mitochondrial oxidative phosphorylation, similar to the actions of 2,4-dinitrophenol. Additionally, higher concentrations of usnic acid inhibit oxygen consumption by mitochondria. The mechanism of this inhibition of respiration is unknown, but it is qualitatively similar to the effects of ETC inhibitors on mitochondrial function.

**Toxicity Information Needs:**

Over 20 serious adverse events have been reported for usnic acid containing dietary supplements adverse, including one death, one liver transplant, 4 cases of liver failure, 10 cases of chemical hepatitis, and four cases of mild hepatic toxicity. [Put in something about rashes following oral exposure]. There is inadequate information to provide the public with a level of usnic acid exposure that does not present a significant or unreasonable risk of illness or injury.

In several short-term *in vivo* and *in vitro* animal studies, usnic acid has been shown to be an uncoupler of oxidative phosphorylation. Cumulative ingestion of usnic acid may produce hepatotoxicity due to the formation of dysfunctional mitochondria. Since mitochondria play multiple critical roles in tissue homeostasis, toxicity in this organelle may produce a diverse spectrum of clinical syndromes. The development of ataxia in sheep and cattle leading to paralysis of the extremities was attributed to the consumption of usnic acid from lichen *Paramelia molliscula*. In cats, intravenously administered sodium usniate led to an increased rate of metabolism, followed by hyperventilation, increased oxygen consumption, and rise in body temperature. Relatively low LD50
values were recorded in other animals (mice, rats, rabbits, and dogs). In guinea pigs, usnic acid tested as a potent sensitizer.

At present, no scientifically sound data are available to support the safe oral use of usnic acid products.

We propose that a complete battery of short term and long term toxicity and pharmacokinetic studies be completed with special emphasis on the hepatotoxic potential (through uncoupling of mitochondrial oxidative phosphorylation) of usnic acid or sodium usnate compared to ingestion of Usnea herb containing an equivalent amount of usnic acid. Secondary studies could examine the issue of toxicity of usnic acid in the context of consumption of Usnea herb and the dermal toxicity of orally administered usnic acid. Given that lichen products of the Usnea family have been consumed as herbal and TCM remedies without any reports of systemic toxicity, some levels of usnic acid are assumed to be safe. Whether-or- not usnic acid in herbal preparations would act the same as purified usnic acid is an unknown. It would be interesting to evaluate an equal dose of usnic acid in the purified and herbal form to see if the herbal form has other agents that modify the effect of the pure usnic acid. There may also be pharmacokinetic differences in how usnic acid and sodium usnate are handled that would affect toxicity. Since usnic acid appears to be an uncoupler of oxidative phosphorylation, a comparison with a known oxidative uncoupler which has had extensive animal and human evaluation would be most interesting.

Another priority would be information on the genotoxic, developmental, and reproductive toxicity potential of usnic acid and Usnea herb is also needed. This is of lower priority since the most immediate concern is the life threatening hepatotoxicity seen in humans consuming usnic acid and sodium usnate. We are nevertheless concerned that women may be more sensitive to the effects of usnic acid based on the apparent increased incidence of liver failure noted in women taking the supplement.

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