



Memorandum

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Date: _____
From: Consumer Safety Officer, Division of Dietary Supplement Programs, Office of
Nutritional Products, Labeling and Dietary Supplements, HFS-810
Subject: 75-Day Premarket Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

Subject of the Notification: Humifulvate

Firm: Humet

Date Received by FDA: January 30, 2003

90-Day Date: April 30, 2003

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Victoria Roberts

95S-0316

RPT 169



APR 15 2003

Mr. Paul D. Rubin
Counsel to Humet
Patton Boggs LLP
2550 M Street, NW
Washington, DC 20037-1350

Dear Mr. Rubin:

This letter acknowledges receipt of your new dietary ingredient notification dated December 20, 2002, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413 of the Federal Food, Drug, and Cosmetic Act (the Act)) and 21 CFR 190.6). On January 29, 2003, you submitted copies of five references to FDA. Your notification notified FDA of your intent to market Humifulvate, a product derived from a peat bog in Hungary; a substance that you assert is a new dietary ingredient.

In accordance with 21 C.F.R. 190.6 (c), this letter is to acknowledge receipt of your notification for a new dietary ingredient. For 75 days after the filing date, your client must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains Humifulvate.

Please note that acceptance of this notification for filing is a procedural matter and does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342.

We note that the new information contains a description of a six month dog study in which mild pathology (fatty infiltration) was noted in most animals in both the liver and kidney at the high dose group. Myocardial necrosis was also noted in two of the dogs. Vomiting and diarrhea occurred frequently. Additionally, in the three week clinical study of 40 subjects, nausea and vomiting were reported by five subjects at some point during the course. Other studies in the notification also report subjects with mild diarrhea, gastrointestinal discomfort, and abdominal complaints. These data raise the issue of gastrointestinal side effects.

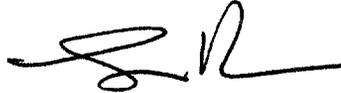
It is the manufacturer's or distributor's responsibility to ensure that any dietary ingredient or a dietary supplement marketed in the United States is safe and complies with all applicable requirements of the Federal Food, Drug and Cosmetic Act and implementing regulations in 21 CFR as well as any other applicable Federal laws and regulations.

Page 2 - Mr. Paul D. Rubin

Your submission will be kept confidential for 90 days from the date of receipt, and after April 30, 2003, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

If you have questions concerning this matter, please contact Victoria Lutwak at (301) 436-1775.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'S. Walker', with a long horizontal stroke extending to the right.

Susan J. Walker, M.D.
Acting Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
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and Applied Nutrition



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December 20, 2002

Paul D. Rubin
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VIA COURIER

Ms. Felicia B. Satchell
Director, Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: Humet Plc. - New Dietary Ingredient Notification for Humifulvate – Six Month Intended Use

Dear Ms. Satchell:

On behalf of Humet Plc. (“Humet”), I hereby submit the attached new dietary ingredient notification for humifulvate. Please note that Humet is the official submitter of this notification, and is also the manufacturer of the humifulvate referenced in the attachments. Accordingly, Humet should be identified (after the 90 day non-disclosure period has lapsed) on FDA’s website as the manufacturer of the new dietary ingredient subject to this notification. If you have any questions regarding this notification, however, please feel free to contact me as the United States contact.

As stated in the attached notification, the humifulvate referenced in this notification is the exact same dietary ingredient referenced in the new dietary ingredient notification submitted by Corvina Natural Products, Inc. (“Corvina”) on November 28, 2000 (i.e., Humet was the manufacturer of the humifulvate described in Corvina’s notification). The Corvina notification, however, contained an intended use of the humifulvate dietary supplement product for only up to two months. This notification therefore differs from



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Ms. Felicia Satchell
December 20, 2002
Page 2

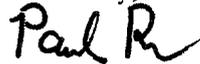
the Corvina notification in that the intended use in this notification, based upon new scientific data that has been developed by Humet, is for up to six months.¹

As per my discussions with Ms. Rhonda Kane in the FDA's Center for Food Safety and Applied Nutrition ("CFSAN"), the agency has requested that the same materials included in the original Corvina notification be resubmitted (including the three binders of attachments) in order to ensure appropriate review of this notification. Accordingly, this notification contains the same data and information included in the original Corvina notification, and also includes: (1) information regarding the continued safe use of the humifulvate dietary supplement product since the submission of the Corvina notification; and (2) data from new safety studies that further support the safe use of humifulvate for the intended use of up to six months.

In addition, as per my discussions with Ms. Rhonda Kane, I was also informed that the agency would appreciate (but not require) the submission of five copies of the notification and attachments. Accordingly, as a courtesy to the agency, we are submitting five copies of this notification.

This cover letter and the notification are available for public dissemination. All other material submitted with this notification as attachments is deemed proprietary and designated confidential.

Thank you for your attention to this matter. Please do not hesitate to contact me if you have any questions.

Sincerely,


Paul D. Rubin
Counsel to Humet

PDR:jjj
Attachments

¹ The notification also provides for an alternative twelve week intended use.

Notification of the Marketing of a New Dietary Ingredient

Humifulvate

Pursuant to section 413 of the Federal Food, Drug, and Cosmetic Act, Humet Plc. (“Humet”), located at H-1121 Budapest, Konkoly Thege u. 29-33, Hungary, hereby notifies the Food and Drug Administration that it will market in the United States the new dietary ingredient, humifulvate. Humifulvate is a mixture of humic, fulvic, and phenolic acids in a humate/polyphenolic complex.

The humifulvate referenced in this notification is the exact same dietary ingredient referenced in the new dietary ingredient notification submitted by Corvina Natural Products, Inc. (“Corvina”) on November 28, 2000, to which FDA had no objection. Corvina’s notification is incorporated into this notification by reference and is attached. Humet is the manufacturer of the humifulvate referenced in this and the November 28, 2000 notification, and Corvina has been the United States distributor of the Humet humifulvate dietary supplement products.

The Corvina notification contained an intended use of the humifulvate dietary supplement product of up to two months. This notification differs from the Corvina notification only in that the intended use of humifulvate in this notification is for up to six months. Alternatively, if FDA objects to the six months indication, Humet plans to market the humifulvate-containing supplement with an indicated use of up to twelve weeks and intends that this notification also cover that intended use. The data and information contained in this notification are the same as those contained in the Corvina notification, other than (1) this notification cites the continued safe use of the humifulvate dietary supplement product since the submission of the Corvina notification, and (2) this notification includes data from new safety studies to support further the safe use of humifulvate and the intended use for up to six months.

I. Description of Humifulvate

Humifulvate is a chemically distinct and identifiable mixture of humic, fulvic, and phenolic acids in a humate/polyphenolic complex. A torpha torf preparate byproduct of the incomplete natural decomposition (humification) of organic plant materials, humifulvate is derived from Hungarian peat found primarily along the northern shores of Lake Balaton in Hungary. Humifulvate is processed into a concentrate for inclusion in dietary supplements in liquid and solid forms intended for oral consumption.

The natural source of humifulvate is a unique peat bog estimated to be between 3,000 and 10,000 years old; the chemical and biological properties of this bog have been studied for over 40 years.[1] This extensive scientific research has established that this peat deposit is slightly alkaline (pH –8), has an ash content of 28% to 43%, and contains significant

quantities of two predominate humate compounds, humic acid and fulvic acid, along with minor amounts of phenolic acid. The peat deposit also contains calcium huminate, a degradation product of lignans, shell remnants, calcareous materials, sand, and other minerals.

Humic and fulvic acids are multi-substituted polyaromatic heterocyclic macromolecules that incorporate protocatechic acid, vanillic acid, vanillin, resorcinol, ferulic acid, benzoic acid, and other cyclic polyphenols resulting from the degradation of the structural lignans in plant cell walls. These constituents of humic and fulvic acids are rich in carboxyl, hydroxyl, and carbonyl groups as well as in phenols, quinones, and semiquinones.[2-4] Within each macromolecule, aromatic groups are linked by amino acids, amino sugars, peptides and other aliphatic carbon chains similar to those found within the human body (see Figure 1).[5] Fulvic acids obtained from peat may represent degradation products of humic acids; they contain more oxygen-rich reactive groups than do humic acids, and are of smaller molecular weights than are humic acids.[5] Despite the complexity in its composition, infrared spectroscopic analyses have revealed that humifulvate is a distinct mixture of predominantly humic and fulvic acids; therefore, the humate/polyphenolic complex comprising this new dietary ingredient is referred to by the term humifulvate.

Humifulvate is a negatively-charged metal complexing ligand. There are a number of active sites where metal ions may bind to aromatic and aliphatic carboxyl and phenolic hydroxyl groups within the humifulvate complex, allowing humifulvate to act as an ion exchanger, releasing metal ions of low atomic mass and chelating heavier metals.[6-9] These properties are abolished by either methylation or acetylation of the reactive sites.[1,10]

A full biochemical description of humifulvate can be found in references 5, 11 and 12. Interpretation of the infrared spectroscopical analysis of humifulvate and a description of the types, amounts and ratios of the component parts of humifulvate is provided in reference 13. A schematic rendering of the biochemical structure of humifulvate is included in reference 5.

II. Dietary Supplements Containing Humifulvate

Humet will market dietary supplements containing humifulvate in combination with defined amounts of several minerals and trace elements. The intended use of the new dietary ingredient is as a component of a dietary supplement (humifulvate concentrate; HFC). A single daily dose (10 ml and/or 330 mg) of the dietary supplement (HFC) will contain, in liquid and/or solid form:

New dietary ingredient:

Humifulvate 75 mg (47.86%)

Other minerals:

total added minerals (as ions) 81.7 mg (52.14%)

potassium (K ₂ HPO ₄)	36.7 mg
magnesium (MgSO ₄ x 7 H ₂ O).....	15 mg
iron (FeSO ₄ x 7 H ₂ O).....	14 mg
zinc (ZnSO ₄ x 7 H ₂ O).....	10 mg
manganese (MnSO ₄ x H ₂ O)	3 mg
copper (CuSO ₄ x 5 H ₂ O).....	2 mg
vanadium (NaVO ₃).....	500 mcg
cobalt (CoSO ₄ x 7 H ₂ O).....	200 mcg
molybdenum ((NH ₄) ₆ Mo ₇ O ₂₄)	175 mcg
selenium (Na ₂ SeO ₃)	125 mcg

The supplement label will state that the product is intended for use for up to six months. Use of the dietary supplements as recommended for up to six months, would result in cumulative consumption of up to 13,500 mg of humifulyate in six months.

In addition, use of the supplements as recommended results in typical cumulative exposure of up to 7078 mg of elemental potassium, 2,893 mg of elemental magnesium, 2,700 mg of elemental iron, 1,929 mg of elemental zinc, 579 mg of elemental manganese, 386 mg of elemental copper, 96 mg of elemental vanadium, 39 mg of elemental cobalt, 34 mg of elemental molybdenum, and 24 mg of elemental selenium.

Research results suggest that humifulyate in combination with minerals and trace elements (humifulyate concentrate, HFC) enhances mineral and trace element status in the body, supporting the maintenance of mineral and trace element balances without bypassing normal homeostatic mechanisms for preventing mineral toxicity. Following dissociation of the minerals and trace elements delivered by HFC, the residual humifulyate complex may chelate heavy metals along the intestinal tract, thereby reducing heavy metal burdens. Thus, the intended use of HFC is to (1) support normal mineral and trace element homeostasis; (2) support normal physiologic utilization of minerals and trace elements; and (3) support the health reduction of heavy metal burdens.

A. HFC supports normal mineral and trace element homeostasis.

Studies have demonstrated that HFC supports normal mineral and trace element homeostasis. In one study, two weeks of oral administration of HFC (313.4 mg/day, providing 150 mg of humifulyate daily) was associated with increased blood copper concentrations and improved iron metabolism in 51 healthy adult volunteers.[14] In another uncontrolled study, oral consumption of HFC (156.7 mg/day) for 6 weeks resulted in significant increases in initially low serum iron concentrations.[15] Similarly, serum iron concentrations improved in 14 healthy adults consuming HFC for 3 weeks (156.7 mg/day); in all subjects with initially depressed serum iron or ferritin concentrations, those concentrations approached the respective normal physiologic ranges within the 3 weeks of treatment.[16] In addition, those subjects with supranormal prestudy serum iron concentrations exhibited decreases in serum iron concentrations during the study. In 19

pediatric patients with iron deficiency anemia, serum iron concentrations began to increase within 2 weeks of oral treatment with HFC (31.4 mg HFC/10kg body weight/day) and were significantly increased after 3 weeks of therapy.[17]

In an investigation of the bioavailability of the trace minerals provided by HFC, adult rats that had been fed a diet deficient in trace minerals for 2 weeks were supplemented with either HFC, at a daily dose equivalent to the recommended human daily dose, or an inorganic mixture of salts, identical in composition and daily dosage to the trace minerals in HFC.[18] Following 2 weeks of replacement feeding, whole-body retentions of oral doses of radiolabeled cobalt, iron, zinc, selenium and copper were the same regardless of the form of trace minerals. In addition, the intestinal absorption of dietary iron was significantly increased by HFC.

The benefits of HFC supplementation on mineral and trace element homeostasis appear to be transmittable to newborn progeny. In one experiment, piglets born to iron deficient sows that had been supplemented with HFC (1,500 mg daily, providing 717.9 mg of humifulvate) during gestation exhibited significantly higher plasma hemoglobin concentrations than did piglets born to iron deficient sows that had received standard parenteral iron supplementation or no treatment.[19] Similarly, the pups of Sprague-Dawley rats that had been fed iron deficient diets plus HFC (10 mg/kg daily, providing 4.8 mg/kg of humifulvate) exhibited plasma hemoglobin concentrations, hematocrits, and transferrin saturation similar to those of pups born to iron deficient dams that had received supplemental iron.[20] Newborn pups of rats fed a trace mineral deficient diet supplemented throughout gestation with HFC at a daily dose equivalent to the recommended human daily dose had significantly greater whole-body contents of cobalt and zinc than did newborn pups of rats fed the same trace mineral deficient diet supplemented with equivalent amounts of inorganic trace mineral salts.[18]

B. HFC supports normal physiologic utilization of minerals and trace elements.

Studies also demonstrate that HFC supports normal physiologic utilization of minerals and trace elements. Improvements in appetite and general well-being in pediatric patients with iron deficiency anemia were attributed to treatment with HFC for 3 weeks (31.4 mg HFC/10kg body weight/day).[17] Daily oral administration of HFC (4.5 mg/kg body weight, providing 2.2 mg/kg of humifulvate) to nine children with chronic eczema resulted in marked improvement in the degree of eczema in eight of the children in 3 weeks.[17] Cyclic discontinuation and reinstatement of supplementation were associated with exacerbation and amelioration, respectively, of disease severity.

Among a set of case reports [21-24] describing the effectiveness of HFC (156.7 mg/day, providing 75 mg humifulvate daily, for varying lengths of time) as an adjuvant during cytostatic therapy in patients with confirmed tumors, one group of patients was reported to exhibit enhanced erythropoiesis during supplementation [24] and all groups of patients reported improvements in appetite, weight gain, general resistance to stress and capacity to

work, while nausea, fatigue and need for analgesics were reduced. In a group of 29 adults experiencing hair loss attributed to trace element deficiencies who were treated with HFC (156.7 to 313.4 mg/day, providing 75 to 150 mg humifulvate daily, for 4 to 6 weeks), subjects who exhibited increases in serum iron concentrations also exhibited improvements in hair growth and regeneration.[25] Among a select group of 25 elite adult athletes who added HFC to their training regimens for 3 weeks (313.4 mg/day), most of the subjects reported perceptions of increased resistance to stress of training and enhanced ability to focus during training bouts.[26]

Rats fed HFC 10 mg/kg, providing 4.8 mg/kg of humifulvate) daily for 14 days prior to ischemic insult experienced greater coronary blood flow, aortic blood flow and left ventricular and diastolic pressure following insult than did placebo-fed rats, suggesting that HFC may be cardioprotective.[27] Female adult rats given HFC (960 mg/kg, providing 459.5 mg/kg of humifulvate) prior to whole body irradiation exhibited significantly faster recovery of platelet counts following irradiation.[28]

C. HFC supports the healthy reduction of heavy metal burdens.

Finally, studies show that HFC supports the healthy reduction of heavy metal burdens. HFC contains negatively charged functional groups that contribute to the elimination of heavy metals stored in cells by organic bonding that resembles the transport of metalloproteins. Oral HFC had been demonstrated to increase urinary excretion of cadmium [15] and to decrease blood concentrations of cadmium [14, 15, 29] and lead [14, 29-32] in adults treated with 156.7 to 313.4 mg/day providing 75 to 150 mg/day of humifulvate for 3 to 12 weeks.¹ Oral HFC also has been reported to inhibit the intestinal absorption of cadmium and lead from food as well as their uptake from environmental sources.[14]

When radiolabeled strontium bound to humifulvate was fed to adult rats, the intestinal absorption and subsequent incorporation into bone of radiolabeled strontium was lower than when similar rats were fed free radioactive strontium salt.[33] In adult pigs fed 31.3 to 313.4 mg HFC daily (providing 15 to 150 mg/day of humifulvate), urinary excretion of mercury was significantly increased.[34] Isolated humic acid has inhibited the absorption of cadmium by rat intestine [35] and has reduced the accumulation of cadmium in the kidneys of rats.[36] Following 2 weeks of a trace mineral deficient diet, adult rats given oral HFC (at a daily dose equivalent to the recommended human daily dose) for 2 weeks exhibited significantly more rapid excretion of an oral cadmium burden, compared to similar rats given replacement trace minerals as inorganic salts.[18]

¹ While this study was not intended to evaluate the safety of HFC, it reflects the safe use for up to 12 weeks of consumption because no significant adverse effects were reported in study subjects taking HFC for up to 12 weeks. Similarly, the other studies in Section II generally support the safety of humifulvate.

III. Evidence of Safety

A. History of Use

HFC has been marketed in Europe under the brand name Humet®-R syrup since 1993. Since the submission of Corvina's notification on November 28, 2000, sales and human consumption of HFC in syrup form have continued in several countries without report of adverse events. The humifulvate found in HFC has been reviewed and approved by the Hungarian National Institute of Pharmacy. Humet®-R syrup is registered in Hungary as a medicinal preparation (not a drug) (OGYI-430-1993). Humet®-R syrup also is registered for sale in Great Britain, [37] Taiwan, Portugal, Russia, Lithuania, the Netherlands, Austria, and Romania.

Typical cumulative exposure to humifulvate during historical use can be estimated. Use of HFC as recommended in Europe and currently in the U.S. (156.7 mg/day of the supplement, containing 75 mg/day of humifulvate, for up to two months) results in the cumulative consumption of up to 9,402 mg HFC, of which 4,500 mg is humifulvate. In addition, use of the HFC as recommended in Europe and currently in the U.S. results in typical cumulative exposure of up to 2,202 mg of elemental potassium, 900 mg of elemental magnesium, 840 mg of elemental iron, 600 mg of elemental zinc, 180 mg of elemental manganese, 120 mg of elemental copper, 30 mg of elemental vanadium, 12 mg of elemental cobalt, 10.5 mg of elemental molybdenum, and 7.5 mg of elemental selenium.

B. Safety Studies

1. New Studies Not in the Corvina Notification

Since the submission of Corvina's notification, three new safety studies on HFC have been conducted and completed. These studies provide further support for the safety of humifulvate and support an intended use of HFC for up to six months.

The first study is a six month (180-day) repeated dose oral toxicity study of dotated potassium humate powder in beagle dogs. The study examined whether dotated potassium humate powder produced any toxicity when administered to beagles daily at various dose levels for 180 days. The study provided information on target organ toxicity and the "no observable adverse effect level" ("NOAEL").

The doses chosen on the basis of the results of a preliminary study were 0, 15, 50, and 150 mg/kg/day for 180 days (corresponding to daily doses of HFC of 0, 7.123, 23.74, and 71.23 mg/kg/day). Each of the four treatment groups consisted of four males and four females. The groups receiving placebo or 150 mg/kg/day also each included 2 male and 2 female "recovery animals." The test item was applied daily (on a 7 days/week basis) by oral application, in gelatin capsule. Blood samples were taken from all animals receiving placebo or 150 mg/kg/day after 1, 3, and 6 months. All animals were sacrificed after 6 months for detailed post-mortem examination.

The main observations are outlined in the “Tabulated Summary, 180-day Toxicologic Study” at Attachment A. There were no differences among the animals receiving 0 or 15 mg/kg/day (up to 3.5 times the recommended human intake) for 180 days. Vomiting and watery feces were rarely associated with consumption of 50 mg/kg/day (12 times the recommended human intake) for 180 days. Mild myocardial and hepatic lesions appeared in a few of the dogs receiving 150 mg/kg/day (35 times the recommended human intake) for 180 days.

The dogs consuming supplemental dotated potassium humate powder exhibited significant increases in circulating molybdenum, selenium, and vanadium concentrations, suggesting increased efficiency of absorption of these necessary trace elements. There was no evidence of toxic accumulation of minerals or of accelerated excretory losses of required nutrients.

A 180-day NOAEL for dotated potassium humate powder of 15 mg/kg/day was observed. This amount of dotated potassium humate powder is equivalent to 7.12 mg/kg/day of HFC for 180 days, or a total cumulative intake of 1281.6 mg/kg of HFC. In a 70 kg human, this NOAEL is equivalent to a cumulative HFC intake of 89,746 mg HFC. This amount is about 9 times greater than the present typical human exposure over two months, and is about three times greater than the total cumulative exposure in individuals electing to continue supplementation for six months. Furthermore, it is not known where, between daily intakes of 15 and 50 mg/kg/day, the “true” NOAEL lies. Consequently, it is likely that the NOAEL is two to three times greater than that estimated in the study.

The second new study is a short-term safety and tolerance study for a formulation of humic acid and trace minerals (HUMET®). In a single-blinded, placebo-controlled randomized outpatient safety-tolerance study, 20 healthy male subjects consumed capsules containing either HFC with trace minerals in solid form (HUMET®) or placebo (once daily after the main meal) as follows:

Week 1: 1 HUMET® capsule (containing 156.7 mg HFC; 75 mg humifulvate®) + 2 placebo capsules

Week 2: 2 HUMET® capsules (containing 313.4 HFC; 150 mg humifulvate®) + 1 placebo capsule

Week 3: 3 HUMET® capsules (containing 470.1 mg HFC; 225 mg humifulvate®)

No drop-outs occurred during the study and subject compliance was good. Each volunteer consumed a total of 6583.4 mg of HFC in 3 weeks, equivalent to 70.02% of the recommended consumption over two months. Supplementation with HFC had no effect on routine laboratory parameters, circulating trace metal concentrations, serum endothelin levels, qualitative assessment of myeloperoxidase activity or overall physical status.

Adverse events were minor and rare and included gastrointestinal disorders and increased appetite. Increased cognitive performance and increased physical performance were also

observed. One subject exhibited a single transient increase in liver enzyme activities when blood was erroneously collected immediately following a bout of strenuous exercise training. Details are outlined in [Attachment B](#). The investigators concluded that three weeks of human consumption of humifulvate in daily doses equivalent to an average of twice the recommended daily intake is safe and well-tolerated.

The third new study investigated the mutagenic effect of dotated potassium humate powder with a micronucleus test. The main objective of the study was to determine whether dotated potassium humate powder (containing humifulvate) increases the rate of chromosomal damage or of damage to the mitotic apparatus in intact mammalian animals. Mutagenic potential is estimated from the observed rates of production of micronuclei in polychromatic erythrocytes of animals treated with humifulvate or placebo. In this case, the potential mutagenic activity of humifulvate was examined in bone marrow of NMRI mice.

Six sets of ten mice per set (five males and five females) were used. Two sets received dotated potassium humate powder (containing humifulvate; 2000 mg/kg, corresponding to a human intake of 66,479 mg of HFC) once daily via gastric intubation. Two sets received distilled water (“negative controls”) and two sets received cyclophosphamide (60 mg/kg; “positive controls”). For each of the three treatments, a set of ten mice (five males and five females) were sacrificed after 24 and 48 hours.

The single administration of 2000 mg/kg of the test item did not induce a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes (MPCEs) in male and female mice at either 24 or 48 hours after treatment (compared to placebo). No other biologically important effect was produced in the animals receiving the test item. Cyclophosphamide caused a significant increase in the number of MPCEs after 48 hours, validating the test.

The investigators concluded that, under the conditions of this mouse micronucleus test, the test item dotated potassium humate powder in a single dose of 2000 mg/kg (corresponding to 424 times the typical human dose) was not mutagenic in NMRI mice. Details are outlined at [Attachment C](#).

2. Toxicology Studies

Toxicology studies support an intended use of up to six months. Studies in which the dosage well exceeded the human exposure expected based on the intended use did not yield significant adverse events. In fact, an independent testing laboratory (Pharmaceutical Control and Developing Laboratory Co., Ltd., Budapest, Hungary) determined HFC to be “practically non-toxic.”[39]

For example, no signs of toxicity, gross organ pathology or death have been reported in single dose toxicity tests in male and female adult rats given up to 10,000 mg of standardized HFC per kg body weight (equivalent to up to 4,786 mg/kg of humifulvate and about 80 times the typical cumulative human exposure to humifulvate when HFC is used as currently

recommended for up to two months). Acute studies in rats and mice have revealed no toxicity in daily doses exceeding 1,000 mg HFC per kg body weight (equivalent to 478.6 mg/kg of humifulvate and about 500 times the typical daily human exposure to humifulvate as currently indicated). The acute oral LD₅₀ for HFC was determined by the National Institute of Food and Nutrition Science (OETI) in Budapest, Hungary, to be greater than 10,000 mg of HFC per kg body weight (about 80 times the typical cumulative human exposure to humifulvate when HFC is used as currently indicated for up to two months).[38]

During a "limit test," adult male and female rats given 600 mg/kg of HFC (providing 287.3 mg/kg of humifulvate) within 24 hours exhibited no signs of weight loss or macroscopic organ pathology.[39] Isolated cases of pulmonary hemorrhage and emphysema, thymic hemorrhage, splenic hyperemia and uterine changes occurred with similar frequency in both treated and matched control rats; it was reported that these findings were consistent with indications of agonal death. No other symptoms of toxicity or lethality were observed during 14 days of post-treatment observation. From these data it was determined that the maximal tolerable dose (MTD) of HFC is greater than 600 mg/kg within a 24-hour period (for a 75-kg human, about 300 times the recommended daily dose of 150 mg HFC).

Adult rats given a single dose of 960 mg/kg of HFC (providing 459.5 mg/kg of humifulvate, about 8 times the typical cumulative human exposure to humifulvate as currently recommended for up to two months) exhibited no adverse reactions or signs of toxicity following sublethal whole body irradiation.[40] Reports summarizing acute oral toxicity studies in laboratory animals are provided in references 41-43.

In controlled cumulative toxicity testing, adult rats were fed HFC at the LD₅₀ (10,000 mg/kg) daily for 24 days. Body weights, hematological variable, indices of thyroid function and microscopic organ histology were unaffected by the supplement.[46] However, some treated rats exhibited splenic hemosiderosis and both control and treated rats exhibited signs of peribronchial lymphocytic infiltration. In another study, adult rats fed HFC at 5, 15, or 50 mg/kg daily for 28 days (amounting to about 1.25, 3.75 and 12.5 times the typical cumulative human exposure to humifulvate, respectively) exhibited no effects of HFC on body weights, clinical chemistry, hematological variables, enzyme functions, or organ weights.[47] However, 3 weeks of HFC at 150 or 500 mg/kg daily (providing 71.8 or 239.3 mg/kg of humifulvate daily and amounting to about 28 and 93 times the typical cumulative human exposure to humifulvate, respectively, as currently recommended for up to two months) was associated with decreases in body weights and in liver and kidney weights, which the authors attributed to undocumented reductions in appetite.

Adult rats fed a diet deficient in trace minerals and supplemented with either HFC at a daily dose equivalent to that recommended for humans or an equivalent amount of inorganic trace mineral salts exhibited no differences in average body weights, organ weights (liver, lung, kidney, brain, heart, spleen), changes in these weights, total litter weights, individual birth weights of progeny, daily urine volumes and daily fecal weights.[18] However, adult rats given humic acid at the equivalent of 280 times the recommended human daily dose

retained approximately 20% to 30% less dietary iron, zinc and selenium than did the rats fed HFC.

Groups of adult rats fed potassium humate providing either 60 or 240 mg/day of humic acid for 2, 4, 6 or 8 weeks exhibited growth rates, food consumption rates, physical agility, kidney and liver weights, white blood cell counts, red blood cell counts, thrombocyte counts, mean blood cell volumes, mean thrombocyte volumes, plasma hemoglobin concentrations, hematocrits, mean hemoglobin contents per red blood cell and mean red blood cell hemoglobin concentrations that were not different from those of control-fed rats.[48] There were no adverse reactions, signs of toxicity or deaths during 8 weeks of exposure to the equivalent of up to what would be 80% to 3 times the typical cumulative human exposure to humifulyate if HFC is 50% humic acid, as currently recommended for up to two months. The available scientific evidence indicates that humifulyate is not toxic or harmful when ingested by laboratory animals in amounts equivalent to between 0.8 and 500 times the typical cumulative human exposure as currently recommended for up to two months. Reports summarizing the effects of prolonged oral intake of HFC in rats are provided in references 44 and 45.

3. Mutagenicity Studies

HFC has been found to exhibit no mutagenic activity under the Ames test criteria, using the *Salmonella typhimurium* reverse mutation assay, in tests conducted by the Toxicological Research Center, Ltd. Veszprem, Szabadságpuszta, Hungary.[51] Additional studies conducted by the Medical Research Institute, Budapest, Hungary, using human peripheral blood lymphocytes, also have indicated that HFC is not mutagenic and does not increase the number or frequency of chromosome aberrations (clastogenesis) under test conditions.[44, 45, 52] Some data from these tests further suggest that HFC may be mildly anticlastogenic *in vitro* under certain conditions. Taken together, these findings attest to the nonmutagenic nature of HFC and its primary component, humifulyate.

4. Human Studies

The safety of HFC has been demonstrated in 525 individuals; 157 otherwise healthy adults being treated for elevated blood lead or cadmium concentrations;[53-56] 18 adults [57, 58] and 12 children [58] being treated for overt signs of lead poisoning; 114 adults and children with cancers;[59, 60] 60 children with iron deficiency anemia, alopecia, eczema or severe illness;[61] and 164 healthy adult volunteers, including 35 elite athletes in training.[62-66]

The results of most of these studies of the safety of HFC in humans have been reviewed by the appropriate governmental agencies in Great Britain, Taiwan, Portugal, Russia, Lithuania, and the Netherlands prior to those agencies granting approval for the over-the-counter marketing of HFC as an oral dietary supplement in their respective countries. Additional details of these studies are compiled in reference 12. Importantly, several of these studies demonstrate the safety of humifulyate for an indicated use of up to six months. Furthermore, taken as a whole, the studies demonstrate an overall safety of humifulyate in

doses well exceeding the current recommended intake and the intake proposed in this notification, thus demonstrating that humifulvate is safe for the proposed indicated time periods.

In an open-label uncontrolled study, 207 healthy adults with elevated blood lead concentrations were reported to experience one case of gastrointestinal discomfort and one case of skin allergic reaction during either 3 weeks of HFC treatment (147 subjects; 156.7 mg/day; equivalent to 37.5% of the typical cumulative human exposure to humifulvate as currently recommended for up to two months)[54] or 12 weeks of HFC treatment (60 adults; 156.7 mg/day; equivalent to 150% of the typical cumulative human exposure to humifulvate as currently recommended for up to two months).[56] Importantly, in this second study, the safety of humifulvate was demonstrated for 12 weeks, one of the proposed indications in this notification.

A cohort of 60 children with a variety of illnesses, including iron deficiency anemia, alopecia, and eczema has been treated with daily doses of HFC of 50 mg/10 kg body weight for periods of 3 weeks to 6 months (equivalent to 375 mg/day for a 75 kg adult, or up to 7.5 times the typical cumulative human exposure to humifulvate as currently recommended for up to two months).[61] One patient reported an allergic skin reaction and one patient reported diarrhea and other unspecified “abdominal complaints.” Again, the six month time period is one proposed in this notification.

A cohort of 64 adults with cancerous tumors was treated with 156.7 mg/day of HFC for up to 18 months (equivalent to up to 9 times the typical cumulative human exposure to humifulvate as currently recommended for up to two months) with reports of epigastric pain in 6 patients, heartburn in one patient and stomach complaints and nausea in 5 patients.[59] Another cohort of 10 adults with cancerous tumors has been treated with oral HFC at unspecified dosages for an average treatment period of 2.6 years without any reported adverse events of subject complaints.[60] Three patients with cancerous tumors received oral HFC (unspecified dosages) continuously for 5 years without adverse effect.[22, 23] These time periods for consumption well exceed those proposed in this notification.

No adverse events, subject complaints or laboratory evidence of adverse effects were noted in an open-label study of a single cohort of 30 otherwise healthy adults with elevated blood cadmium concentrations who were given HFC (156.7 mg/day, providing 75 mg of humifulvate) daily for 6 weeks (equivalent to 75% of the typical cumulative human exposure as currently recommended for up to two months).[53] Similarly, there was no difference in the occurrence of adverse reactions among 20 healthy adult subjects with elevated blood lead concentrations given HFC (313.4 mg/day, providing 150 mg of humifulvate) or 15 similar subjects given placebo for 6 weeks in an open-label controlled trial (HFC consumption equivalent to 150% of the typical cumulative human exposure to humifulvate as currently recommended for up to two months).[55]

Another 128 healthy adults who were given HFC (156.7 mg/day or 313.4 mg/day) daily for 2 to 6 weeks (with cumulative ingestion of HFC of up to 150% of the typical cumulative

human exposure to humifulvate as currently recommended for up to two months) in 3 open label uncontrolled studies reported only 2 instances of “abdominal pressure and nausea” and one case of “softer feces.”[62, 63, 65] In 2 open-label uncontrolled experiments on a total of 36 elite adult athletes, HFC at 313.4 mg/day for 3 to 4 weeks (equivalent to 75% to 100% of typical cumulative human exposure as currently recommended for up to two months) resulted in no reported adverse reactions or subject complaints.[64, 66]

Taken together, these studies indicate that daily consumption of HFC by healthy adults in amounts that result in total cumulative intakes approximating up to 150% of the typical cumulative human exposure to humifulvate as currently recommended for up to two months, are of no health concern.

Two groups of adults (18 total) and one group of 12 children being treated for acute or chronic lead poisoning have received the equivalents of 15% to 20% of the typical cumulative human exposure to humifulvate as currently recommended for up to two months with two reports of unspecified “mild side effects.”[57, 58] A cohort of 40 adults and children with malignant lymphoma were treated with oral HFC (adults: 156.7 mg/day; children: 78.4 mg/day) for unspecified lengths of time.[67] One patient reported nausea and a “general feeling of weakness.”

These studies on clinical patients with lead poisoning, childhood ailments, malignant lymphoma and solid tumors indicate that oral HFC and its primary component, humifulvate, are without significant adverse effect in such individuals in total exposure of up to 9 times the typical cumulative human exposure to humifulvate as currently indicated for up to two months.

5. Heavy Metal Content of HFC

An independent laboratory analysis performed by Flora Research Laboratory (San Juan Capistrano, CA) in November, 1999, reported that HFC contains 20.7 ppm aluminum, 0.07 ppm arsenic, 0.02 ppm cadmium and 0.07 ppm lead. Based on these data, it can be estimated that a single daily dose of HFC would result in the ingestion of 180 mcg of aluminum, 0.6 mcg of arsenic, 1.8 mcg of cadmium and 0.6 mcg of lead.

Many sources of food can contain up to 10 ppm of aluminum and it has been estimated that at least 2 to 3 mg of aluminum are consumed by many people daily.[68] On this basis it can be concluded that the aluminum in a single dose of HFC would provide about 5% to 10% of an individual’s typical daily exposure to oral aluminum. The amounts of lead and arsenic contained in a single dose of HFC are well within the limits set by “Proposition 65” in the state of California standards for exposure to heavy metals that are used by many manufacturers of dietary supplements to ensure the safety of their products.[69]

Although cadmium has only an oral inhalation limit, data from one study had led to the conclusion that average daily cadmium intake should be kept below 111 mcg,[70] over 60 times the amount contained in a single dose of HFC. Average daily intakes of cadmium

Respectfully Submitted,

A handwritten signature in black ink, appearing to be 'János Civin', written over a horizontal line.

János Civin
on Behalf of
Humet Plc.

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