DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: February 27, 2001

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	humifulvate
Firm:	Corvina Natural Products, Inc.
Date Received by FDA:	December 6, 2000
90-Day Date:	March 6, 2001

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 **after March 6, 2001**. Thank you for your assistance.

Felicia B. Satchell

Felicia B. Satchell

See RPT 61

95S-0316

RPT 91

Corvina Natural Products, Inc.

JMIFULVATE™ CHEALATED MINERAL SUPPLEMENTS,
HERBALS & VITAMINS

Andrew G. Pichler, M.D.
Exclusive U.S. Distributor for:
Humet Corporation; Budapest Hungary
6633 Coyle Avenue #2, Carmichael, CA 95608
(916) 961-2266 FAX (916) 967-7939

February 27,2001

FDA
Rhonda Kane
Cunsumer Safety Officer

Dear Ms. Kane;

The following parts of our submission should be designated confidential, in that it's revelation to potential competitors would harm Corvina's interests as they contain proprietary data in the notification section sub-parts 3ii, begining page 4 and ending on page 6, in it's entirety.Toxicological Tests and References there of, which include references: 1,5,11,13 17-21,23-28,32,34,37-45,47-52,55-58,60-63,65 and 67.

Thank you very much for your help.

Please do not hesitate to call if you have any questions.

Thank you,

ANdrew G. Pichler,M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

APR 16 2001

VIA E-MAIL AND FAX

Andrew G. Pichler, M.D., F.A.C.S.
President
Corvina Natural Products, Inc.
6633 Coyle Avenue
Carmichael, California 95608

Dear Dr. Pichler:

This correspondence responds to two letters. The first is a letter to the Food and Drug Administration (FDA) from Mr. János Civin, Humet Plc., dated February 22, 2001, that requests a letter stating whether FDA has any objection to the marketing of humifulvate as a dietary supplement in the United States (U.S.). Mr. Civin explained in the letter that his company is the manufacturer of the dietary ingredient called humifulvate for which you, as his agent, submitted to FDA a premarket notification, pursuant to 21 U.S.C. § 350b(a)(2). The second is a letter dated March 16, 2001 from Jonathan W. Emord of Emord & Associates, P.C., who we understand is representing your company. Mr. Emord's letter responds to concerns FDA has about recent statements attributed to the manufacturer of humifulvate that its product is intended to be used in the treatment of the human immunodeficiency virus (HIV) and heart disease.

As you are aware, on December 30, 1999, you submitted a premarket notification for the new dietary ingredient humifulvate. FDA responded to this submission in a letter dated February 25, 2000, stating our conclusion that the information in your notification did not provide an adequate basis to conclude that humifulvate will reasonably be expected to be safe, when used under the conditions recommended or suggested in the labeling of your product. On November 28, 2000, you resubmitted your notification and supplemented it with additional information. To date, FDA has not responded to your resubmission.

In accordance with 21 U.S.C. § 350b(a)(2), a manufacturer or distributor that desires to market a dietary supplement containing a new dietary ingredient must submit a premarket notification to FDA. This notification must be sent to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce. The notification must explain the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. In other words, for 75 days after the filing date (i.e., the date that FDA received the premarket notification), a manufacturer cannot market the dietary supplement that contains the new dietary ingredient.

Under certain circumstances, FDA may contact the submitter of a premarket notification. Examples of these circumstances are when: 1) the notification does not contain all of the information required under 21 C.F.R. § 190.6; 2) the information in the notification is inadequate to provide assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury; or 3) we have questions or concerns about the information contained in the notification.

Failure of FDA to respond to a notification, such as your resubmission on humifulvate, does not constitute an agency finding that the new dietary ingredient or the dietary supplement that contains it is safe or is not adulterated under 21 U.S.C. § 342. No response by the agency 75 days after the filing day simply means that according to law, the manufacturer or distributor can market a dietary supplement containing the new dietary ingredient. However, FDA is not precluded from taking action in the future against a dietary supplement containing humifulvate if it is found to be adulterated or misbranded. It is the manufacturer's or distributor's responsibility to ensure that any dietary ingredient contained in a dietary supplement is safe and properly labeled. Importantly, new dietary ingredients for use in dietary supplements that FDA has reviewed through the premarket notification process are not "approved" or "authorized" by the agency. For more information concerning FDA's premarket notification program for new dietary ingredients, we encourage you to visit the following Web site: http://www.cfsan.fda.gov/~dms/ds-ingrd.html.

In comparison, all drugs must be approved by FDA before they can be marketed in the U.S. A drug is defined under 21 U.S.C. § 321(g)(1)(B) as an article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or animals. Therefore, any representation that a product is intended for one or more of these purposes suggests that it is a drug and would be subject to regulation under the drug provisions of the Federal Food, Drug and Cosmetic Act.

Mr. Emord stated in his letter that he has discussed with you and Mr. Civin FDA's concerns about disease claims (e.g., for the treatment of HIV and heart disease) made for humifulvate in the U.S. He also reassured us that neither the manufacturer nor you as the distributor

would be making any disease claims in the future about humifulvate marketed in the U.S. If your decision changes and you want to market humifulvate as a drug, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, HFD-310, 7520 Standish Place, Rockville, Maryland 20855.

If you have any questions concerning this matter, please contact me at (202) 205-4168.

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements

Copy to:
Mr. Jonathan W. Emord
Emord & Associates, P.C.
Burke Professional Center
Burke, Virginia 22015

EMORD & ASSOCIATES, P.C.
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5282 LYNGATE COURT
BURKE, VIRGINIA 22015

1050 SEVENTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20036

PHONE: (202) 466-6937 • FAX: (202) 466-6938
WEB SITE: www.emord.com
E-MAIL: emordall@erols.com

March 16, 2001

VIA TELECOPIER 202-205-5295
AND VIA REGULAR MAIL
Ms. Rhonda R. Kane, M.S., R.D.
Consumer Safety Officer
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

Dear Ms. Kane:

My colleague Claudia A. Lewis-Eng and I spoke with you last week concerning Humet Trade, Research and Development Company's introduction of a new dietary ingredient, Humifulvate, to the American market. I am the food and drug lawyer representing the company's American operations. Those operations are under the direction of Dr. Andrew G. Pichler, President of Corvina Natural Products, Inc., Carmichael, California. This letter reports on actions taken by Humet and its American representative to guard against any unauthorized health claims concerning Humifulvate.

In our conversation you explained that FDA had received reports that Humet, based in Budapest, Hungary, had disseminated information on the Humifulvate product suggesting that it was useful in the treatment of disease. I have explained FDA's health claims regulations to, and have shared your concerns with, Humet's Chief Executive Officer in Hungary and with Dr. Pichler.

I am informed by Humet's Chief Executive Officer, Mr. János Civin, that the company has every intention of complying fully with the laws governing dietary supplements, takes your caution very seriously, has tried to identify the source of the health claims you believe came from Humet without success, but has nevertheless informed all management at the Budapest facility who work with Humifulvate that under it is a violation of the laws of the United States to claim any association between Humifulvate and a disease or disease condition. Moreover, Mr. Civin has ordered management to avoid making any such representations about the Humifulvate product destined for the American market.

Humet's American representative, Dr. Pichler, will oversee the introduction of Humifulvate to the American market. He is aware of the FDA's health claims

regulations and confirms that he has not allowed, and will not allow, any health claims not approved by FDA to appear in labeling for Humifulvate. Consistent with Humet's position, he reiterates that neither Corvina Natural Products nor its domestic licensees has any intention of allowing Humifulvate to bear any unapproved health claim.

Should you have any additional concerns not addressed by Humet management and Humet's American representative, please feel free to contact me directly.

Sincerely,

Jonathan W. Emord

HUMET ®

Trade, Research and Development Co.
H-1121 Budapest, Konkoly Thege str. 29-33.

Food and Drug Administration
Department of Health and Human Services

Attention to Rhonda R. Kane M.S., R.D.
Consumer Safety Officer

22nd February 2001

Fax: + 1 202 205 4168

Dear Ms Kane,

Our company, Humet Plc. (H-1121 Budapest, Konkoly Thege street 29-33, Hungary, Europe) is the manufacturer of a dietary ingredient called humifulvate. To the best of our knowledge, a material with such composition was not in the diet of US citizens before 15th October 1994., that's why our representative in the US, Corvina Natural Products Inc. submitted a notification -to FDA, first on the 31st December 1999., and you responded on the 25th February 2000. Our modified version was filed by FDA on the 28th November 2000 and 6th December 2000.
This letter is sent under the authorization of our reprentative in the US (dr. Andrew G. Pichler Corvina Natural Products Inc., 6633 Coyle Avenue, Carmichael, California 95608).
As to your letter of 24th January 2001, the 75 days period, which is at FDA-s disposal was over on the 20th February (docket number 95S-0316). According to the laws, if FDA is not asking for any completion, or does not reject our application, the introduction of the product to the US market is not prohibited. Our representative has not received any answer until today, and therefore we came to the conclusion that the distribution of humifulvate in the US from the 20th February is not against the law of the United States.

Dear Ms Kane,

The request I approach you seems to be rather unusual. I kindly ask you to confirm, that whether FDA had any objection against distributing humifulvate in the States. before 20th February 2001
The reason behind my request is that Humet Plc is a company registered in Hungary , and on the Budapest stock exchange. Being the president

of this company my obligation is to publicize every information ***immediately*** according to the Hungarian Law, which can significantly influence the value of the shares. I would like you to know, that in the last three days the investors and the press put an enormous pressure on Humet Plc. to issue a press release about FDA's standpoint .
It would be a great help for me to have a written document from FDA, which imposes no obligations on FDA, but can inform the Hungarian public correctly. With such a statement I could fulfil my obligation required by the Hungarian Law.

I know that my request is unusual for FDA, but I ask you - taking into consideration our obligations required by the Hungarian law - to send your answer as soon as possible to dr. Andrew Pichler, to the President of Corvina Natural Products by fax or email.

The email address and fax number of dr. Andrew Pichler are the following:
Mootzyone@aol.com
Fax: 916-967-79-39

Sincerely yours,

János CIVIN
CEO

Friday February 23, 7:18 am Eastern Time

Humet wins U.S. trade permission

(UPDATE: Adds share price in paragraph 5)

BUDAPEST, Feb 23 (Reuters) - Hungary's Humet Rt said on Friday it had got permission from the U.S. Food and Drug Administration (FDA) to sell its Humet-R syrup, which is used to ease fatigue and boost mental and physical performance.

The Hungarian dietary supplement maker said its flagship product is also used in treating those infected with the HIV virus and helps protect against heart disease.

"I will travel to the U.S. on Sunday to meet the heads of two partners, Country Life and Life Plus International," Humet Chairman Janos Civin told Reuters. "These firms would sell Humet products in the U.S."

The Budapest Stock Exchange suspended trading in Humet until the announcement and when dealings resumed the share surged. By 1155 GMT the share was 19.5 percent higher at 184 forints.

Humet expects FDA approval to boost its prestige and expand the market for its Humet-R syrup. Presently the market is mainly Hungary, the United Kingdom, Portugal, Taiwan and Poland.

But Civin said the company needs a 400 million forint ($1.36 million) investment if it is to raise Humet-R production to one million doses per month.

He said a 460 million forint capital increase planned for May may be brought forward in order to begin investments as soon as possible.

Humet's net sales rose 28.4 percent to 157 million forints last year accoring to Hungarian-accounted data. After-tax profit increased by 5.7 percent to 38 million forints.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

JAN 24 2001

Andrew G. Pichler, M.D., F.A.C.S.
President
Corvina Natural Products, Inc.
6633 Coyle Avenue
Carmichael, California 95608

Dear Dr. Pichler:

This is to inform you that the notification and addendum, respectively dated November 28, 2000 and December 6, 2000, you submitted pursuant to 21 U.S.C. 350b(a)(2) were filed by the Food and Drug Administration (FDA) on December 6, 2000. Your notification concerns the substance called humifulvate derived from Hungarian peat that you assert is a new dietary ingredient. This new dietary ingredient notification is a resubmission of your notification concerning humifulvate, dated December 30, 1999, and follows our letter dated February 25, 2000, in response to that notification.

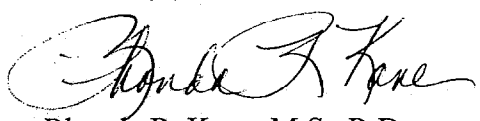
In accordance with 21 C.F.R § 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., after February 19, 2001), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains humifulvate.

Please note that acceptance of this notification for filing is a procedural matter and, thus, 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. As another procedural matter, your notification will be kept confidential for 90 days after the filing date. After March 6, 2001, the notification will be placed on public display at FDA's Docket

Management Branch in docket number 95S-0316. However, any information that is trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public.

Please contact us at (202) 205-4168, if you have any questions concerning this matter.

Sincerely yours,



Rhonda R. Kane, M.S., R.D.
Consumer Safety Officer
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

CORVINA NATURAL PRODUCTS, INC.
6633 Coyle Avenue
Carmichael, CA 95608

DATE: November 28, 2000

Confidential and Proprietary Information Submitted to:

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
US Food and Drug Administration
200 C Street SW
Washington DC 20204

Re: Notification of New Dietary Ingredient: Humifulvate

Pursuant to the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 USC 350 b(a)(2), and FDA regulations, 21 CFR 190.6, Corvina Natural Products, Inc. (Corvina), hereby submits this notification and information concerning a new dietary ingredient that Corvina intends to market for use as or in a dietary supplement. Corvina previously submitted a similar notification on December 24, 1999. This notification contains additional scientific materials to those submitted with the earlier submission. Pursuant to the provisions of DSHEA, Corvina will not introduce the ingredient or deliver the ingredient for introduction into interstate commerce until at least 75 days after the date that FDA receives this notification.

1. Name and Address of Manufacturer and Distributor of the Dietary Ingredient

The name and complete address of the manufacturer of the new dietary ingredient/supplement is as follows:

Humet Research and Development Company
(formerly known as HORIZON-MULTI-PLAN, LTD)
H-1121 Budapest
Konkoly Thege u. 29-33
Hungary
(telephone: 011361-160-1828)

The name and complete address of the distributor of the new dietary ingredient/supplement is as follows:

Corvina Natural Products, Inc.
6633 Coyle Avenue #2
Carmichael, CA 95608
(telephone: 916-961-2266)

Manufacturer of other minerals in the supplement:

SIGMA-ALDRICH, Ltd.
Budapest
Hungary

2. Name of the Dietary Ingredient

The name of the new dietary ingredient is Humifulvate.

3. Description of the Dietary Ingredient

The description of the new dietary ingredient is as follows:

Humifulvate is a chemically distinct and identifiable mixture of humic, fulvic and phenolic acids in a humate/polyphenolic complex. A tolpha torf preparate (TTP) byproduct of the incomplete natural decomposition (humification) of organic plant material, 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 7-8), 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, 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 spectrosopic 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]

Humifulvate concentrate (HFC) consists of humifulvate in combination with minerals and trace elements. Research results suggest that HFC enhances mineral and trace element status, 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 humifulvate complex may chelate heavy metals along the intestinal tract, thereby reducing heavy metal burdens.

A full biochemical description of humifulvate can be found in references 5,11 and 12. Interpretation of the infrared spectrological 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.

3i. Level of Dietary Ingredient in Dietary Supplements

The new dietary ingredient, humifulvate, is intended to be supplied in a dietary supplement 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) of the dietary supplement (HFC) will contain, in liquid or solid form:

New dietary ingredient:

Humifulvate ..... 75 mg (47.86%)

3ii. The Conditions of Use Recommended in Labeling of or Ordinary Course of Use of Dietary Supplement containing the New Dietary Ingredient (Structure/Function Claims)

1. Humifulvate concentrate (HFC) supports normal mineral and trace element homeostasis.

   Two weeks of oral administration of HFC (313.4 mg/day, providing 150 mg of humifulvate 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 (1500 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 new born pups of rats fed the same trace mineral deficient diet supplemented with equivalent amounts of inorganic trace mineral salts.[18]

2. Humifulvate concentrate (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 reinstitution 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 the 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 end 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]

3. Humifulvate concentrate (HFC) supports the healthy reduction of heavy metal burdens.

   Humifulvate concentrate (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 has 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. 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 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]

4. History of Use and Evidence of Safety

4i. History of Use of Dietary Ingredient

Humifulvate concentrate (HFC) has been marketed in Europe under the brand name of Humet®-R syrup since 1993. It is marketed as a dietary supplement for increasing overall vitality and promoting overall health. 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 non-prescription preparation (GYI-430/1993). Humet®-R syrup also is registered for sale in Great Britain,[37] Taiwan, Portugal, Russia, Lithuania, and the Netherlands.

Typical cumulative exposure to the new dietary ingredient during historical use can be estimated. Use of the dietary supplement, HFC, as recommended (156.7 mg/day of the supplement, containing 75 mg/day of the new dietary ingredient, humifulvate, for up to 2 months), results in the cumulative consumption of up to 9402 mg of humifulvate concentrate, of which 4500 mg will be the new dietary ingredient, humifulvate. In addition, use of the dietary supplement as recommended results in typical cumulative exposure of up to 2202 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.

4ii. Evidence of Safety of Dietary Ingredient

Toxicological and mutagenicity studies evaluating the safety of the dietary supplement (humifulvate concentrate; HFC) containing the new dietary ingredient (humifulvate) provide data attesting to the safety of humifulvate. All toxicological studies, mutagenicity studies and studies on laboratory animals have utilized the dietary supplement, HFC. Independent laboratory analyses utilizing infrared spectroscopy and

fingerprinting have confirmed the consistent composition of the standardized HFC used in these studies.

Documentation of the safety of the amounts of each mineral and trace element in HFC can be found in reference 12.

a. Toxicology Studies

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 4786 mg/kg of humifulvate and about 80 times the typical cumulative human exposure to humifulvate when HFC is used as recommended). Acute studies in rats and mice have revealed no toxicity in daily doses exceeding 1000 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). The acute oral LD_{50} 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 recommended).[38] An independent testing laboratory (Pharmaceutical Control and Developing Laboratory Co., Ltd., Budapest, Hungary) determined HFC to be "practically non-toxic."[39]

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 (containing about 300 times the recommended daily dose of humifulvate, if a dose of 150 mg of HFC is ingested by a 75-kg human).

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) 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 LD_{50} (10,000 mg/kg) daily for 24 days; body weights, hematological variables, 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 organs 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) 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 humifulvate if HFC is 50% humic acid.

Reports summarizing the effects of prolonged oral intake of HFC in rats are provided in references 44 and 45.

The available scientific evidence indicates that humifulvate 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.

b. 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, Szabadsagpuszta, 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, humifulvate.

c. Studies of Safety in Humans

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 36 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.

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).[53] Similarly, there was no difference in the occurrence of adverse reactions or events 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).[55] In 2 open-label uncontrolled studies, another 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; 156.7mg/day; equivalent to 37.5% of the typical cumulative human exposure to humifulvate)[54] or 12 weeks of HFC treatment (60 adults; 156.7 mg/day; equivalent to 150% of the typical cumulative human exposure to humifulvate).[56]

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) 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) 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 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 with two reports of unspecified "mild side effects."[57,58]

A cohort of 60 children with a variety of illnesses, including iron deficiency anemia, alopecia, and eczema have 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).[61] One patient reported an allergic skin reaction and one patient reported diarrhea and other unspecified "abdominal complaints."

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." 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) 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 or subject complaints.[60] Three patients with cancerous tumors received oral HFC (unspecified dosages) continuously for 5 years without adverse effect.[22,23]

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 exposures of up to 9 times the typical cumulative human exposure to humifulvate.

d. 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 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,[69] standards for exposure to heavy metals that are used by many manufacturers of dietary supplements to ensure the safety of their products.

Although cadmium has only an oral inhalation limit, data from one study has 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 from food in most areas that are not polluted with environmental cadmium range between 10 mcg and 40 mcg,[71] 5 to 25 times the amount contained in a single dose of HFC. The FAO/WHO Expert Committee on Food Additives and Food Contaminants recommended a tolerable weekly cadmium intake of 400 mcg to 500 mcg for an adult, or a daily average of 64 mcg to 79 mcg (about 35 to 40 times the amount of cadmium contained in a single dose of HFC).

e. Absence of Polycyclic Aromatic Hydrocarbons in HFC

The National Institute of Food and Nutrition Science (OETI) in Budapest, Hungary, reported that it was unable to detect any polycyclic aromatic hydrocarbons in samples of HFC, including benzo-(a)-pyrene, benzo-(b)-fluoroanthene, indenopyrene, benzo-(k)-fluoroanthene, fluoroanthene, or benzo-(ghi)-perylene.

f. Lack of Involvement of HFC in Endemic Chinese Diseases

Two peripheral vascular diseases, Blackfoot's Disease and Keshan-Beck Disease, endemic to regions in China have been associated with the ingestion of humic acids and fulvic acids, obtained from local aquatic sources, in conjunction with relatively large amounts of arsenic.[72,73] The clinical signs of these two diseases may well be manifestations of chronic arsenic poisoning *per se*.[72] The sources and components of HFC have never been implicated in any case of arsenism or peripheral vascular disease; the arsenic content of HFC is well below that associated with clinical disease.

5. Commercial and Confidential Designated Materials

The cover letter containing the notification is available for dissemination to the public. This expanded notification and all other materials submitted with the notification, including all attachments, are deemed proprietary and are therefore designated confidential.

6. **Conclusion and Certification**

The enclosed information and scientific studies referenced herein establish that the dietary ingredient, Humifulvate, when used under the conditions recommended, is safe.

Respectfully Submitted,

Andrew G. Pichler, M.D.
President
Corvina Natural Products, Inc.

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[41] {Attachment 7.1}
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Corvina Natural Products, Inc.

HUMIFULVATE™ CHEALATED MINERAL SUPPLEMENTS,
HERBALS & VITAMINS

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Received via fax
Dec. 6, 2000

Dec 6, 2000

Ms. Rhonda Kane
Food and Drug Administartion
Div. of Standards & Labeling Regulations
Room 2804
200 C Street, SW
Washington, D.C. 20204

Dear Ms. Kane;

Attached is the English translation of the particular article that you have indicated.

Thank you for your help and if you have any further questions please call.

Yours truly,

Andrew Pichler, M.D., F.A.C.S.
Corvina Natural Products. Inc.

PANNON University of Agriculture
Faculty of Animal Breeding, Kaposvár, Hungary
Department of Chemistry, Biochemistry

STUDY REPORT

Effect of feeding with doted and undoted humic acid preparation on the mineral status in the rat

Kaposvár
1997.

1. Sponsor

HORIZON-MULTIPLAN Research and Development Company
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3. Contract file number

- at the Sponsor: 33-1-03
- at the Contractor: HM-97.

4. Date and place of delivery

- place: see the address in point 2 above
- duration: from March 16 to May 15, 1997
  (Feeding period: from March 25 to April 24)

5. Research work in connection with the project topic

5.1 Introduction

The active ingredient of the syrup preparation developed by the Sponsor and known as HUMET®-R consists of humic acids derived from peat as well as essential macro- and microelements (K, Mg, plus Fe, Zn, Mn, Cu, V, Co, Mo and Se). The conglomerate of these elements, known as 'doted humic acid' has been found ideal as a mineral supplement based on clinical trials and other human and animal observations and experiments conducted made to date [1-3]. Its effects have been manifested in the elimination of deficiencies of the essential elements contained therein, the reinforcement of immune reactions when needed, the increase of mental and physical capacities as well as the weight gain and improved reproduction indices in farm animals. More and more experimental data suggest that the said preparation provides certain measure of protection against heavy metals ingested per os [4-7].

Although the physiological benefits of HUMET®-R can be regarded as well-documented in many respects, research work focusing on these issues have recently intensified. This is mainly because of the very complex effect of the preparation due to its numerous components, and consequently a thorough knowledge of the exact mechanisms of action – essential for developing further products as well – may be gained only after the clarification of various details. The topic described below relates to one of these details, for it covers the effects of doted and undoted humic acid on the mineral status of the body, more precisely on the availability of bivalent cation-forming elements. The study design has been developed jointly by the representatives of the Sponsor and the Contractor in compliance with the current professional requirements.

The reason for narrowing the study topic as explained above is that among all the mineral components of HUMET®-R which humic acids form complexes

with the metal ions only, therefore effects on absorption and bio-availability can be detected primarily in regard to these elements [8-12]. It has been reported that humic acids are complex macro molecules, coming probably from lignin, to be found in the organic fraction of the soil and in dead plant remains still in the carbonisation stage (e.g. peat). They are made up of a polycyclic nucleus and the polysaccharides, polypeptides and phenols loosely bound to it. Their bio-activity is mainly based on their capacity to chelate in a reversible bond bivalent and multivalent metal ions with the help of their free functional groups (-COOH, phenolic and alcoholic –OH, $-NH_2$ etc.). The chemical formations produced this way, just like undoted humic acids, have considerable expanding capacity, while they are predominantly hydrophobic in nature, and the metal ions located in the chelate rings are clearly dehydrated. It has been assumed that the beneficial results obtained from the administration of the HUMET®-R preparation are attributable for the most part to these properties [1].

5.2 Materials and methods

The experiment was started with 30 female rats of the *Wistar* 579 phylum, each with a bodyweight of 80-125 g, divided into three groups of equal sizes, but due to deaths occurring for unknown reasons, results could be gained finally for only 8 animals in Group I (control group) and 9-9 animals each in Groups II and III.

The animals were let to acclimatise for four days, then experimental feeding lasted for thirty days. The animals were kept each in a standard cage of 55x28x20 cm in size, furnished with refilling water feeder. Animal keeping circumstances were otherwise fully compliant with the generally accepted recommendations [13]; lighting: diffused light through 15-16 hours a day; temperature 18-22°C; relative humidity: 50-60%; ventilation: air exchange approx. 18 times per hour. Rats were given rat feed of standard composition (Annex I.) and drinking water of excellent quality; both administered ad libitum.

This experiment focused on testing two substances in liquid form as made available to us by the Sponsor, notably a humic acid preparation (HA) and the same supplemented with various essential elements (HAD). As stated by the Sponsor, the humic acid concentration of HAD was just half of that of the HA liquid. When we had occasion we also determined the mineral content of the test materials in the appropriate detail (Annex II.).

In the course of experimental feeding the animals of Groups II and III received 320µl/body weight kg HA and 640µl/body weight kg HAD, respectively. Administration took place always by using the gastric tube technology. In an effort to guarantee the above daily dose/body weight ratio, the body weights of animals were taken by five-day intervals and the volume of the test material administered to individual animals was then adjusted to their gain in weight.

On day 31 following the administering of test materials the animals were anaesthetised with chloroform and then slaughtered, then subjected to so-called whole-body analysis for metals that form divalent cations [14, 15]. To do this, the bodies of rats – after removing the stomach and intestines – were homogenised in a mash in an equipment specially manufactured for this purpose using corrosion-proof material. The mash was then incinerated at 600±50°C. After this the ashes were diluted into a soft nitric acid solution, and concentrations of calcium, magnesium, manganese, copper, zinc and iron were determined using the atomic absorption technique [16, 17]. An PYE UNICAM SP-190 AAS instrument with air/acetylene burner was used for such assays. The following measurement wavelengths were used: Ca: 422.7 nm, Mg: 285.2 nm, Mn: 279.5 nm, Cu: 324.8 nm, Zn: 213.9 nm and Fe: 243.8 nm.

Measurement results were given for the so-called wet weight and processed using multi-factor variance analysis.

5.3 Results and discussion

Apart from the four deaths as mentioned before no abnormalities in the health condition and behaviour of the animals could be observed during the study. The weight gain in the animals was appropriate for the species and the age of the animals (Annex III.). No significant difference in body weights could be observed across the groups when compared on the same days.

The results (Tables 1 and 2) have shown that humic acid alone did not increase the absorption of the macro- and microelements examined; moreover it even caused the reduction of iron uptake (p=5%). Essentially the same applies to calcium and magnesium, though with less convincing statistical certainty (p=20%).

As we had expected, doted humic acid caused higher macro- and microelement concentrations in rat bodies compared to undoted humic acid. However, it must be noted here that the beneficial effects of doted humic acid compared to the control group could be demonstrated with statistical significance (p=5%) only in the case of calcium, magnesium and iron.

Table 1.

Results of whole-body analyses in the rat (g/kg wet weight)

- macroelements -

Group	Test material	Ca		Mg	
		$\underline{x}$	SD	$\underline{x}$	SD
I. (n=8)	-	$29.22^{a\square}$	3.05	$1.02^{a\square}$	0.06
II. (n=9)	HAx	$26.48^{a\square}$	3.01	$0.97^{a\square}$	0.05
III. (n=9)	HADxx	32.98^{b}	4.03	1.10^{b}	0.06

[x] undoted humic acid preparation: 320/µl/bodyweight kg/day

[xx] preparation containing doted humic acid: 640/µl/bodyweight kg/day

Legend of indices:

- identical small Latin letters in the same column: no significant difference at probability level p=5%;
- different Greek letters in the same column: significant difference at probability level p=20%.

Table 2.

Results of whole-body analyses in the rat (g/kg wet weight)

- microelements -

Group	Test material	Mn		Cu		Zn		Fe	
		x	SD	x	SD	x	SD	x	SD
I. (n=8)	-	$2.22^{a□□}$	0.21	4.54^{abAB}	0.94	80.56^{abAB}	2.50	133.3^{a}	6.75
II. (n=9)	HAx	$2.11^{a□}$	0.28	3.94^{aA}	0.58	79.03^{aA}	3.83	121.1^{b}	10.8
III. (n=9)	HADxx	$2.29^{a□}$	0.20	4.99^{bB}	0.37	82.74^{bB}	5.33	148.0^{c}	13.2

Footnotes:

same as for Table 1, plus: the various Latin capitals (Zn) refer to the fact that the difference exists at the level of p=10%.

5.4 Conclusions

Given a sufficient macro- and microelement supply, undoted humic acid caused some deterioration in the iron, calcium and magnesium status of the body, while the beneficial effects of doted humic acid were manifested in regard to these same elements. In respect of manganese, copper and zinc, the effects of neither the doted, nor the undoted humic acid could be shown with statistical significance.

Having compared these results with the favourable results obtained with regard to the HUMET®-R preparation earlier, it is suggested that the macro- and microelement supplementation capacity of the doted humic acid depends largely on the original availability of these elements to the body. In this situation the macro- and microelement content of the rat feed was satisfactory, and that is why supplementation in general was not reflected in the whole-body analysis results with a sufficiently convincing level of significance. It is advisable, therefore, to perform the tests on rats that receive during, or received in the weeks preceding, the experimental rat feed that is indeed poor in macro- and microelements. Furthermore, it seems reasonable to use in such experiments also animal groups that receive supplementation without humic acids, i.e. in the usual inorganic forms ($ZnSO_4$, $MnSO_4$ etc.).

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Kaposvár, June 10, 1997.

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Annex I.

Composition of rat feed

Component	g/kg	mg/kg
Dry substance	919	-
Crude protein	237	-

Crude fat	53	-
Crude fibre	105	-
Crude ash	90	-
Nitrogen-free material	434	-
Sodium (Na)	0.31	-
Potassium (K)	10.20	-
Calcium (Ca)	4.60	-
Magnesium (Mg)	2.64	-
Phosphor (P)	4.28	-
Manganese (Mn)	-	43
Copper (Cu)	-	8.5
Zinc (Zn)	-	36
Iron (Fe)	-	200

Annex II.

Mineral content of test materials
(mg/kg liquid)

Element	Humic acid (HA)	Doted Humic acid (HAD)
Calcium	2065	532
Magnesium	248	2490
Manganese	9.5	517
Copper	0.8	338
Zinc	1.9	1769
Iron	257	2127

- Doted humic acid (and probably undoted humic acid, too) contains other minerals as well, but for this project it seemed unnecessary to determine these elements.
- Assays were made from dilute nitric acid ash solution using the AAS measurement technology.
- Dry substance: - HA: 6.1%; HAD: 5.4%.

Annex III.

Development of rat body weights during the experiment (g)

day	Group I. (n=8)		Group II. (n=9)		Group III. (n=9)	
	x̲	SD	x̲	SD	x̲	SD
1.	95.75	14.4	96.9	10.9	98.4	11.5
6.	109.3	15.1	106.3	11.5	104.4	10.8
11.	117.8	13.9	115.5	12.0	123.5	12.2
16.	124.5	13.0	126.2	15.6	129.1	14.0
21.	137.5	14.2	138.6	16.3	134.0	15.7
26.	147.2	14.7	148.4	17.3	140.8	16.1
31.	153.9	18.8	153.1	20.1	147.8	14.2

Content

Notification of New Dietary Ingredient (Humifulvate)

Attachments

Notification