

ATTACHMENT 4

HUMET[®]-R syrup 300 ml

**HUMET
Trading, Research and Development Co.
BUDAPEST**

COMPOSITION

1. Name of the Product:

HUMET®-R syrup, 300 ml
Product for macro- and microelement supplementation

2. Composition of the proprietary medicinal product.

Qualitative and quantitative composition of the product with INN of the active ingredient(s) and excipients:

Name of the -active ingredients-	Quantity of added element mg/300 ml	Quantity of added salt mg/300 ml	Reference standards	Function
1. Humic acid (dried content of extract)		2250	manufacturer stand. specification	Chelate forming agent
2. di-Potassium hydrogen phosphate ($K_4P_2O_7$) (K_2HPO_4)	K	177 673	374 1500	Ph.Eur. PH Stabilizing agent
3. Magnesium sulfate ($MgSO_4 \times 7H_2O$)	Mg	450	4563	Ph.Eur. Active ingredient
4. Ferrous sulfate heptahydrate ($FeSO_4 \times 7H_2O$)	Fe	420	2091	USP/Ph. Eur. Active ingredient
5. Zinc sulfate heptahydrate ($Zn SO_4 \times 7 H_2O$)	Zn	300	1319	Ph.Eur. Active ingredient
6. Manganese sulfate monohydrate	Mn	90	277	USP Active ingredient

7. Cupric sulfate pentahydrate ($ZnSO_4 \cdot x 7H_2O$)	Cu	60	236	USP	Active ingredient
8. Sodium meta-vanadate $NaVO_3$	V	15	36	Fluka Chemie AG purum	Active ingredient
9. Cobalt sulfate $CoSO_4 \cdot x 7H_2O$	Co	6	29	Molar Chemicals Hungarian Standard	Active ingredient
10. Ammonium heptamolybdate (NH_4) ₆ Mo ₇ O ₂₄ · 4H ₂ O	Mo	5,25	10	USP	Active ingredient
11. Sodium selenite Na_2SeO_3	Se	3,75	8	Sigma for analytical use	Active ingredient

Inactive ingredients

Orange syrup			150 ml	Szobi Szörp Rt. Hungary	Flavoring material, increase of viscosity
Purified water			up to 300 ml		

Control tests on the finished product

Product specifications and routine tests

Product specifications and tests for release

1. Properties

1.1. Characteristics: A brown suspension with a typical sour fruity odor and taste. The suspension can be mixed with water in any proportion, its color remains dark, brownish even after a tenfold dilution.

2. Pharmaceutical tests

2.1. Filling volume

Filling volume: 300 ml \pm 3%

Test: according to Ph.Hg. VII.1. p.425. K/g. 3.2.1., or Ph.Eur.

For the volume control calibrated jars or cylinders with ml graduation are used.
Acceptable limits: 300 ml \pm 3%, i.e. from 291 to 309 ml.

2.2. Mechanical impurities

The suspension should not contain any macroscopically detectable extraneous particles. Test: according to Ph.Hg. VII.1. p. 425. K/g. 3.2.2. or Ph. Eur.

"Approx. 10 ml of the thoroughly shaken and homogeneous suspension is to be tested in a test tube, at appropriate illumination, against a black and white background, in transmitting light. For the detection of extraneous particles, in case of necessity, a manual eyeglass with fourfold magnification may be used as well."

2.3. Particular size

None of the linear dimensions of the suspended grains in the suspension should

"A 0.10 g sample of the thoroughly shaken suspension is to be smeared on a slide in a thin, even layer, with another slide. In four different sections of the layer we measure the largest linear dimension of 25 neighboring particles of the dispersed substance under a microscope."

During the test we detect the occurrence in percentage of different sized particles.

2.4. Homogeneity

The particles sedimented during storage should be shaken to make the solution homogeneous.

Test: according to Ph.Hg. VII.I.p. 425. K/g. 3.2.4. or Ph. Eur.

From the suspension, after shaking it vigorously 8-10 times, we pour 10 ml sample into a test tube. The content of the test tube is to be shaken up repeatedly, three times. The suspension liquid should seem homogenous for 60 seconds, when being tested macroscopically.

2.5. pH:

Requirement: pH 3.0-3.5

Test: with litmus paper or with Radelkis pH/ION ANALYSER (OP- 274)

3. Assays

3.1. Identification tests

3.1.1. Carbohydrate

After heating 2-3 ml of the sample carefully in a metal spoon or a porcelain skillet, caramel will be formed with a burnt sugar odor, which after further heating will be carbonized.

3.1.2. Identification of humic acid - metal chelate content

We dilute approx. 10 ml of homogenized sample with approx. 30 ml of distilled water, then mix it with 10 ml 2N HCl solution and boil the solution. After filtering and rinsing the appearing precipitate is the humic acid metal chelate,

3.2. Purity

3.2.1. Microbiological purity

According to Ph.Hg.VII. I. p. 307. F.2. class III.

Max.: 1000 microorganisms/ml of which max.: 100 fungi/ml

Not allowed: Enterobacteriaceae
Pseudomonas aeruginosa
Staphylococcus aureus

3.2.2. Lead content (method 3.3.1.)

Max. 1.5 mg/300 ml

3.2.3. Arsen content (method 3.3.1.)

Max 1.5 mg /300 ml

3.2.4. Aluminium content (method 3.3.1.)

Max. 20 mg/300 ml

3.3. Metal composition assay

3.3.1. Quantitative determination of active ingredient(s) and metal contamination

Determination of metal content is carried out by inductively coupled plasma-optical emission spectroscopy (ICP – OES) method.

Prescription and limits of the acceptance:

Elements	Nominal content mg/300 ml	Minimum mg/300 ml	Maximum mg/300 ml
K	1100	1100	1500
Mg	450	427	517
Fe	420	357	441
Zn	300	255	315
Mn	90	76.5	94.5
	60	51	63

Mo	5.25	4.5	5.5
Se	3.75	3.2	4.2
Pb			1.5
As			1.5
Al			20

3.3.2. The ICP-OES measurement

3.3.2.1. The devices to be applied

STAR-System open microwave destruction device (CEM - USA)

Electric pipette (BIOHIT) – precision: 100-5000 $\mu\text{l} \pm 1\%$

ICP-OES: Perkin Elmer Optima 3200 DV

3.3.2.2. Reagents

HNO_3 65% CARLO ERBA RPE ISO.

H_2O_2 30% REANAL analytical reagent

Purified water: double distilled water

Standard solutions for ICP 100 mg/l ± 2 mg/l (MERCK):

K, Mg, Fe, Zn, Mn, Cu, V, Co, Mo, Se, Ca, Pb, Al, As,

3.3.2.3. Preparation of the sample

After complete homogenization of HUMET[®]-R syrup we fill 0.5 cm³ sample solution (3 parallel samples) into a heating glass of STAR instrument and the preparation program is started.

After the destruction of the organic substances the remaining solution is washed three times into 25 ml measuring flask and diluted with distilled water up to the mark.

This solution is called stock solution.

The preparation program is the following:

The equipment automatically portions the materials step by step to the substance and regulates the temperature of the mixture.

Starting volume of the reagents: cc. HNO_3 10 ml

	Heating time	Temperature	Reaction time	Reagent	Volume	Dosage
1	3:00	110° C	10:00	-	-	-
2	00:01	110° C	10:00	H_2O_2	10 ml	1 ml

3.3.2.4. The measurement

The stock solution is evaporated into an ICP-OES device and the intensity of the emitted light is measured.

Before the beginning of the measurement the device should be calibrated. The calibration of the device should be repeated after every tenth sample. The deviation of the results of the control tests of the standard solutions should not exceed $\pm 3.5\%$. If any of the results exceeds this value the device should be calibrated again and the tests should be repeated.

Composition of the standard solution:

Standard I. solution

Element	Concentration (mg/l)
Co	0,35
V	1,00
Mo	0,35
Mn	6,00
Cu	3,50
Fe	80,0
Mg	30,0
Zn	20,0
Al	10,0
As	1,0

Standard II. solution

Element	Concentration (mg/l)
K	100
Se	1,50
Ca	10,0
Pb	1,00

Preparation of humic acids for infrared spectroscopic examination

The samples for infrared spectroscopic analysis carried out in the Isotop Institut were prepared by the analytical laboratories of Horizon Multiplan Ltd. Budapest, Konkoly Thge u. 29-33.

Separation of humic acids were done according to process describes the standard operating procedure of quality control of HUMET-R preparation.

Method

300 ml of HUMET-R syrup (one bottle) was diluted with 300 ml purified water and centrifuged with 6000 cycles/minute for 10 minutes.

The supernatant was separated and the remaining suspension reconstructed stirring up with 300 ml water. This process repeated two times.

The humic acid containing precipitate separated from sugar by the above described process is solved in 50 ml of 1% potassium hydroxid solution and stirred for 15 minutes. The solved humic acids were centrifuged for 10 minutes with 6000 cycles/minute.

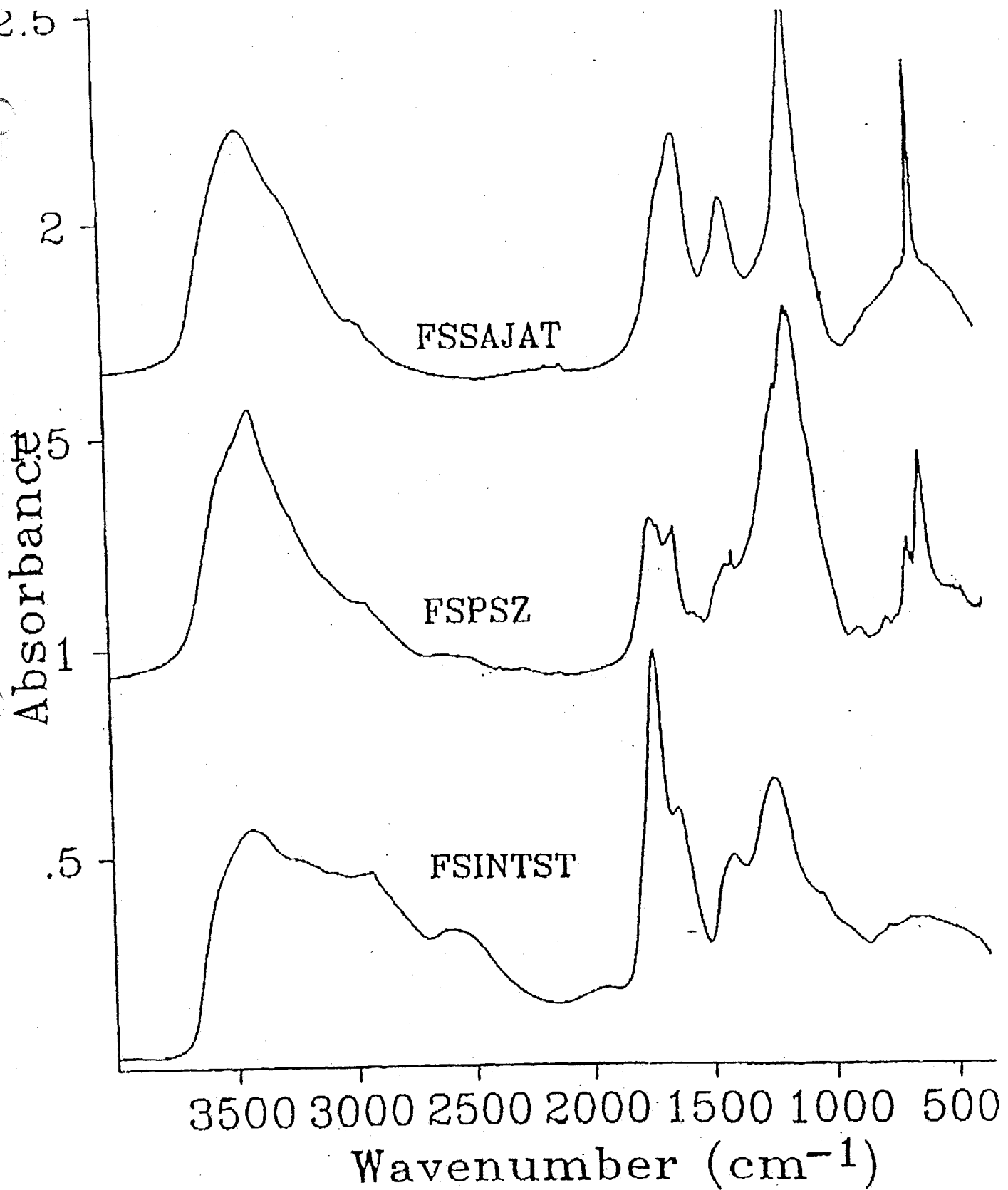
The alkaline supernatant was separated and adjusted the pH to 2. The precipitate containing the grey and brown humic acids centrifuged with 6000 cycles/minute.

The supernatant containing the fulvic acids were separated and the precipitate is dried on less than 70 °C for 5-6 hours.

The preparation is the grey and brown humic acids together measured by gravimetry

The applied wavelengths and the detection limits of the ICP device (5 sec measurement time)

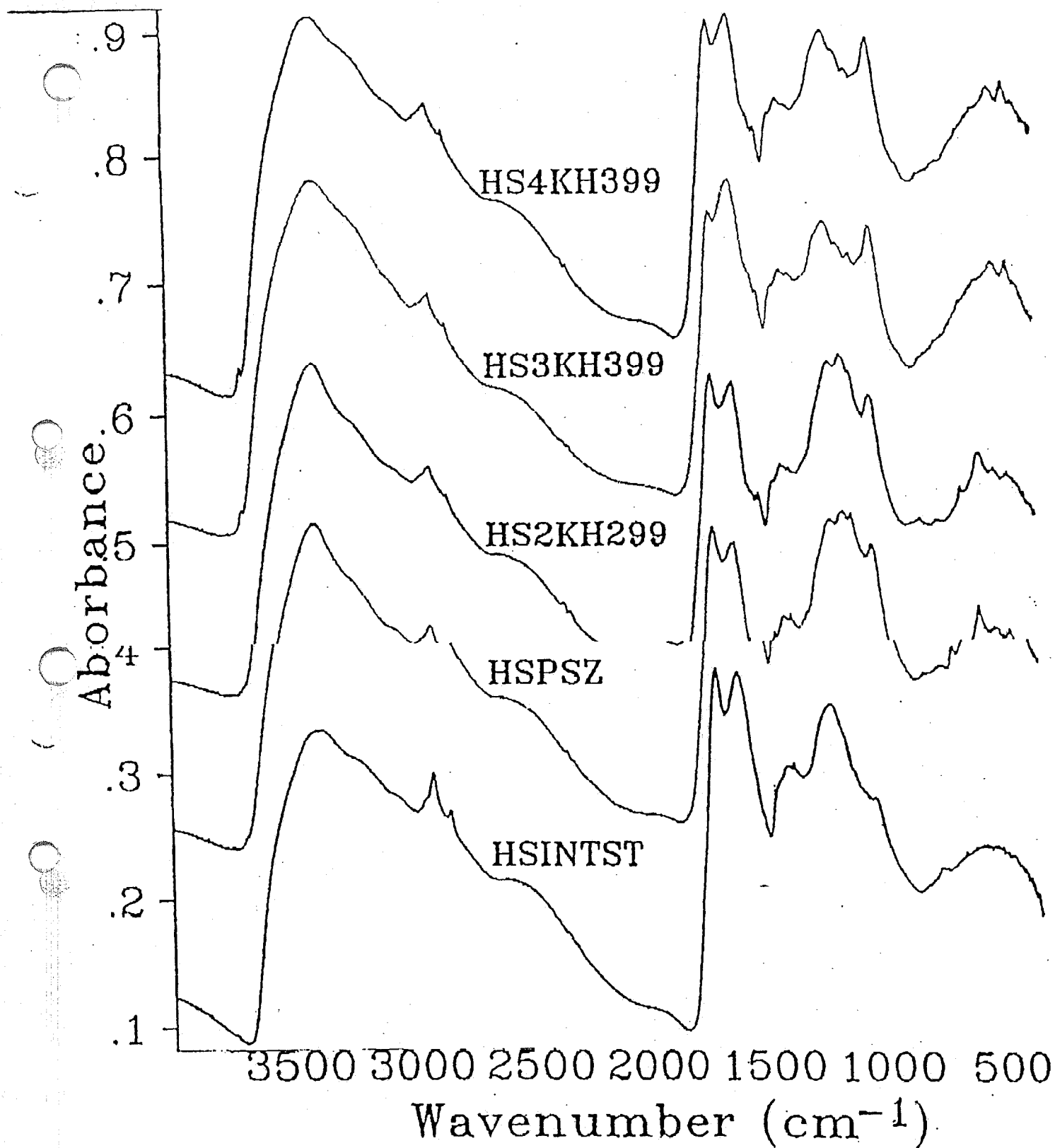
Elements	Wavelength	Detection Limits ($\mu\text{g/l}$)
Co	228,616	2
	230,786	4
V	290,880	4
	292,402	8
Mo	202,031	6
	204,597	10
Mn	257,610	1
	259,372	2
Cu	324,752	2
	327,393	2
Fe	234,349	4
	259,939	8
Mg	279,077	10
	279,553	10
Zn	202,548	4
	206,200	4
K	766,490	5
Se	196,026	15
Ca	317,933	2
Pb	220,353	2
Al	237,313	10
As	197,197	3



Comparison of the IR spectrogram of fulvic acid to standard (IHS)

- FSSAJAT = fulvic acid (HUMET Co.Ltd)
- FSINTST = fulvic acid standard (International Humic Society)

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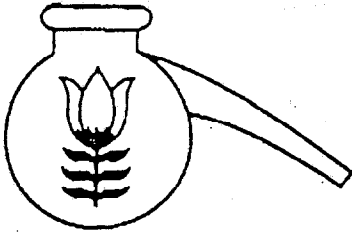


Comparison of the IR spectrogram of humic acid to standard (IHS)

- HS2KH299, HS3KH399, HS4KH399 = humic acid (HUMET Co.Ltd)
- HSINTST = humic acid standard (International Humic Society)

Assignment of IR spectrogram of small molecular weight humic and hmatomelanic acid.

(1) Sáv helye, cm^{-1}	(2) Sávtípus
3700 – 2300	ν OH
3010 2990 2980	$\nu = \text{CH}$
2940 2850	νCH_3 ; νCH_2
1680	$\nu \text{C}=\text{O}$
1435 1410 1380	βOH ; βCH_2 δCH_3
1210 1000	$\nu \text{C}-\text{O}-\text{O}$; $\nu \text{C}-\text{O}$
960 870 800 710 600	γOH ; $\gamma = \text{CH}$



FLORA RESEARCH

November 23, 1999

Amy Addington MS
AIBMR

I received your fax dated November 23, 1999 in which you requested some clarification regarding the IR fingerprint of the Humifulvate product (FR ID# 990720055, Corvina ID# Humet-R HR 93001). Included is a brief summary of the methodology and the conclusions that were drawn from that analysis.

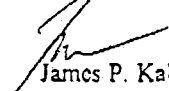
IR Spectroscopy is a useful tool for the quantitative and qualitative analysis of chemical compounds. Recent advances in sampling techniques combined with modern software have expanded the ease and power of this method. We have utilized IR techniques to develop a humic acid fingerprint of the Corvina Sample referenced above. Humic acid is a loosely defined mixture of chemical compounds originating from humus. It is believed that the origin of these humic acids is from the lignin or carbohydrate fraction of decaying plant matter.

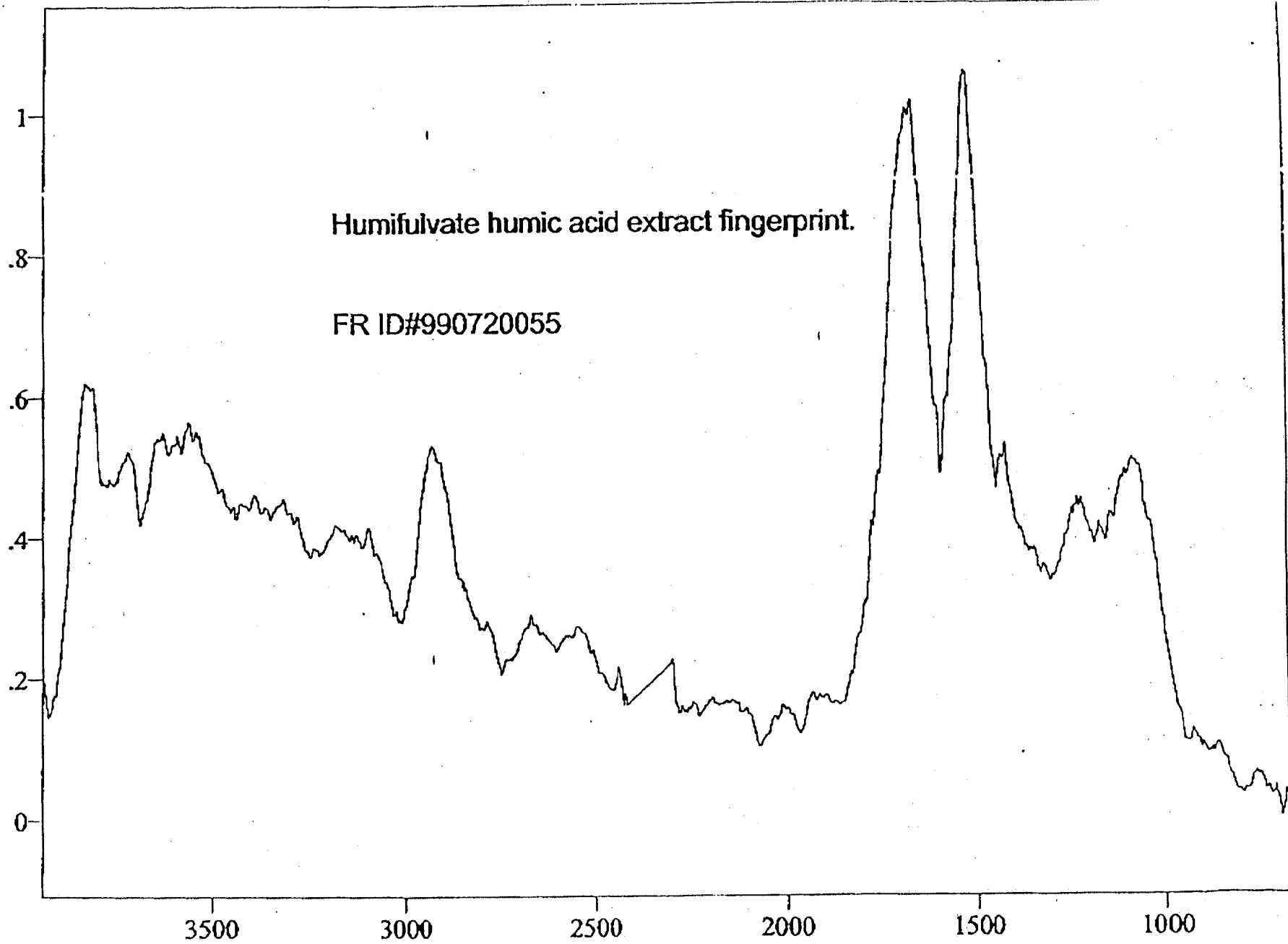
The sample was extracted to isolate the humic acid portion. This fraction was then prepared for IR Spectroscopy using an ATR smear technique. The IR energy is directed into the ATR prism and passes a few microns into the sample. It is then reflected back into the monochromator and detector. The intensity of absorption bands is measured across a wide wavelength (4000-600 wavenumbers). This provides a "fingerprint" of the compound. This fingerprint can be compared to that of various standards to determine the chemical identity of the sample.

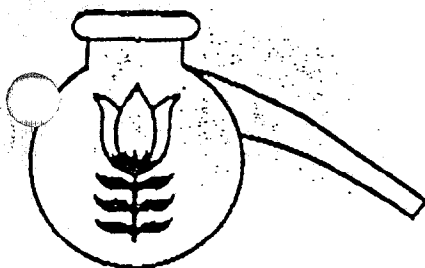
The IR spectra obtained was compared to the IR spectra of the humic acid standard (provided by the client) and was found to closely resemble that spectra. From this analysis, we can conclude that the sample contains a complex mixture of humic acids. This mixture is expected to vary by location and thus some difference in the spectra obtained from different samples is normal. Comparison of the spectra from different batches of the client's product should show some consistency that can be used to help identify this particular mixture of humic acids from others.

I have also included some additional information on IR theory from a handbook that will give you a better understanding of the technique. I hope that you find this information of value. Please don't hesitate to call on me if I can be of any further assistance.

Sincerely,


James P. Kababick
Director
Flora Research





FLORA RESEARCH

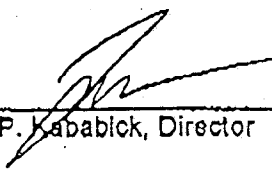
ANALYTICAL REPORT

DATE: November 18, 1999
CLIENT: Corvina Natural Products
ANALYSIS: Qualitative IR Fingerprint of Humic Acid
METHOD: IR Spectroscopy
FLORA'S SAMPLE ID: 990720055
CLIENT'S SAMPLE ID: Humiffulvate
Humet-R HR 93001

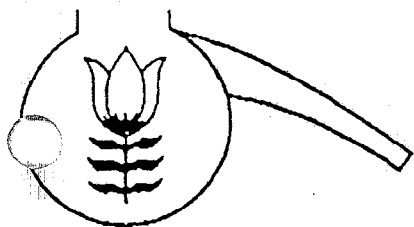
RESULTS:

The sample was composited and extracted to isolate the humic acid fraction. This fraction was subjected to IR Spectroscopy to authenticate the material as a humic acid containing product. The IR spectra (see attached) confirms that the material contains humic acids. The spectra closely matches that of the humic acid standard reference material.

REPORT PREPARED BY:


James P. Kababick, Director

11-18-99
Date



FLORA RESEARCH

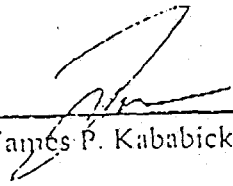
ANALYTICAL REPORT

DATE: August 27, 1999
CLIENT: Corvina Natural Products
ANALYSIS: Quantitative Analysis of 13 Elements
CLIENT'S SAMPLE ID: Humic Acid
FLORA'S SAMPLE ID: 9900504003

RESULTS:

Aluminum:	20.7 ppm
Arsenic:	0.07 ppm
Cadmium:	0.02 ppm
Cobalt:	18.8 ppm
Copper:	182 ppm
Iron:	1280 ppm
Lead:	0.07 ppm
Magnesium:	1500 ppm
Manganese:	294 ppm
Molybendum:	16.5 ppm
Potassium:	4920 ppm
Selenium:	0.70 ppm
Vanadium:	43.2 ppm
Zinc:	906 ppm

REPORT PREPARED BY:


James P. Kababick, Director

8-27-99
Date

Determination of carcinogenic polyaromatic hydrocarbons

NATIONAL INSTITUTE
OF FOOD AND NUTRITION
SCIENCE (OËTI)
1097 Budapest, Gyáli út 3/a.

Budapest, May 30, 1991.
Re: Test of product 'HUMET'
Ref. No.: RH/4/Sné
Your Clark: —
Our Clark: Rita F. Zalsi

Mailing address: Budapest, 100
P.O.B. 52, 1476
Phone: 334-130
Tx: 226001
Cable: OËTI

Case number: 1845/1991.OËTI

With reference to your commission, we state the followings:

We tested "HUMET", your peat-derivative humic-acid-based metal complex product of 200 ml supplied to us by you, for carcinogenic polyaromatic hydrocarbons. By the method applied (sampling in dimethylsulfoxide, aqueous dilution, transfer of polyaromatic hydrocarbons to iso-octane by shaking, purification of pooled extract on silica gel layer, VRK determination on acetylated cellulose layer after scraping and dissolution), no carcinogenic polyaromatic hydrocarbons were detected so their possible amounts are:

< 0.2	µg/L	of benzo-(a)-pyrene
< 0.4	µg/L	of benzo-(b)-fluoro-anthene
< 0.8	µg/L	of indeno-pyrene
< 0.4	µg/L	of benzo-(k)-fluoro-anthene
< 2	µg/L	of fluoro-anthene
< 0.8	µg/L	of benzo-(ghi)-perylene

As to the tested contaminations, the sample is no subject to objection in respect of nutrition toxicology.

Katalin Soós M.D.
Head of Department