AIBMR Life Sciences, Inc.

December 17, 2019

Susan Carlson, PhD
Division Director
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
Department of Health and Human Services
5001 Campus Drive
College Park, MD 20740

Dear Dr. Carlson:

In accordance with regulation 21 CFR Part 170 Subpart E (Generally Recognized as Safe (GRAS) Notice), on behalf of HealthTech BioActives, S.L.U. (the notifier), the undersigned, Kayla Preece, submits, for FDA review, the enclosed notice that neohesperidin dihydrochalcone is GRAS for use in foods.

Should you have any questions or concerns regarding this notice, please contact me at 253-286-2888 or kayla@aibmr.com.

Sincerely,

Kayla Preece (agent of the notifier)
Scientific and Regulatory Consultant
AIBMR Life Sciences, Inc. ("AIBMR")

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#902

Notice to US Food and Drug Administration of the Conclusion that the Intended Use of Neohesperidin dihydrochalcone is Generally Recognized as Safe

Submitted by the Notifier:

HealthTech BioActives, S.L.U.
Ctra. Beniel a Zeneta, 143-145
El Raiguero-La Villa
30130 Beniel (Murcia)
Spain

Prepared by the Agent of the Notifier:

AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
Seattle WA 98112

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Figures and Tables

Part 1: Signed Statements and Certification

1.1 Submission of GRAS Notice

HealthTech BioActives, S.L.U. (the notifier) is submitting a new GRAS notice in accordance with 21 CFR Part 170, Subpart E, regarding the conclusion that neohesperidin dihydrochalcone (NHDC) is Generally Recognized as Safe (GRAS) for its intended use, consistent with section 201(s) of the Federal Food, Drug and Cosmetic Act.

1.2 Name and Address of the Notifier and Agent of the Notifier

Notifier

Francisco Borrego Ríos
HealthTech BioActives, S.L.U.
Ctra. Beniel a Zeneta, 143-145
El Raiguero-La Villa
30130 Beniel (Murcia)
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Agent of the Notifier

Kayla Preece, ND
Scientific and Regulatory Consultant
AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
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Tel: (253) 286-2888
kayla@aibmr.com

1.3 Name of the Substance

Neohesperidin dihydrochalcone

1.4 Intended Conditions of Use

NHDC is intended to be used as an ingredient in various food categories (as listed in Part 3) at maximum levels of 10–1000 ppm, depending upon the specific food

category. NHDC is not intended for use in foods where standards of identity would preclude such use, infant formula, or any products that would require additional regulatory review by USDA.

1.5 Statutory Basis for GRAS Conclusion

The conclusion of GRAS status of NHDC for its intended conditions of use, stated in Part 1.4 of this notice, has been made based on scientific procedures.

1.6 Not Subject to Premarket Approval

We have concluded that NHDC is GRAS for its intended conditions of use, stated in Part 1.4 of this notice, and, therefore, such use of NHDC is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act.

1.7 Data and Information Availability Statement

The data and information that serve as the basis for this GRAS conclusion will be available for review and copying during customary business hours at the office of Ctra. Beniel a Zeneta 143-145, El Raiguero-La Villa 30130 Beniel (Murcia) – Spain or will be sent to FDA upon request.

1.8 Exemption from Disclosure under the Freedom of Information Act

None of the data and information in Parts 2 through 7 of this GRAS notice are considered exempt from disclosure under the Freedom of Information Act (FOIA) as trade secret or commercial or financial information that is privileged or confidential.

1.9 Certification of Completion

We hereby certify that, to the best of our knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of NHDC.

12/17/2019

Francisco Borrego Ríos
Director
HealthTech BioActives, S.L.U. – Beniel (Murcia)

Date

Part 2: Identity, Manufacture, Specifications, and Physical or Technical Effect

2.1 Identification

Neohesperidin (or neohesperidine) dihydrochalcone, sometimes abbreviated to neohesperidin DC or simply NHDC, is an off-white, crystalline powder identified by CAS 20702-77-6.[1] Its molecular formula is $C_{28}H_{36}O_{15}$ with a molecular weight of 612.58 DA. It is a 3, 2', 4',6'-tetrahydroxy-4-methoxydihydrochalcone affixed to a neohesperidosyl at 4' via a glycosidic bond. Its structure is pictured in Figure 1. Its solubility in water is 0.4–0.5 g/L at 25°C and 650 g/L at 80°C. It is also soluble in other solvents at 20°C including ethanol at 12 g/L and acetone at 0.7 g/L. Its European Food Safety Authority (EFSA) E number, an identifying number given to all EFSA approved food additives, is 959.

NHDC is not found in nature and was developed in the early 1960s by chemists at the United States Department of Agriculture's Agricultural Research Service.[2] Its parent compound, neohesperidin, is found in bitter orange (*Citrus aurantium*) at levels of 100–200 ppm in its juice and 97,000 ppm in the peel of its unripe fruit, and is a natural flavanone, a subclass of flavonoids.[3, 4] Flavonoids are phenolic plant metabolites with a phenylbenzopyran chemical structure.[5] Flavanones, such as hesperidin, have non-planar chemical structures and a chiral center around their C2 atoms where an alternate ring of their chemical structure can be affixed in different configurations.[6] Evidence is mounting that NHDC has antioxidant properties similar to that of flavonoids of similar structure.[7-12]

NHDC is highly stable under normal dry conditions.[8] Under acidic aqueous conditions, hydrolyzed breakage of its glycosidic bond can take place in predictable amounts, creating well-defined impurities in the solution further discussed in subpart 2.3.2.

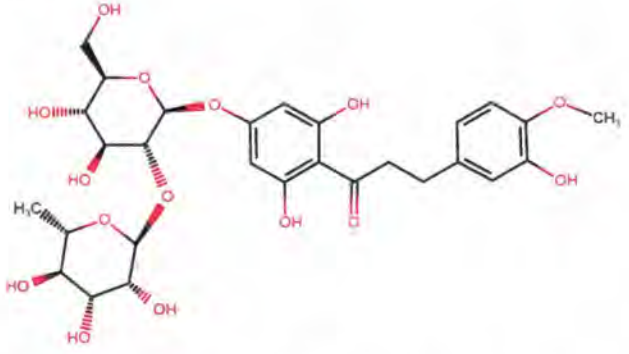

Figure 1. Neohesperidin dihydrochalcone[1]

2.1.1 Sweetness

NHDC has been utilized in food products since 1989 and is hundreds of times sweeter than sucrose.[9-11] The sweetness, which contains a slight licorice flavor, has a delayed onset but a protracted duration. [12] As it is generally considered best to use blends of intense sweeteners to mimic the intensity, flavor, and sweetness of sucrose, NHDC is usually combined with other sweeteners to create the desired effect.[9]

2.2 Manufacturing

2.2.1 Manufacturing Overview

The manufacturing of NHDC is a two-step process of hydrogenation and crystallization. Throughout the process, volumes, temperature, pH, pressure, and times are monitored and adjusted as necessary to meet manufacturing limits. The identity of all materials used in the process are confirmed with the suppliers' analytical data sheets, which are checked for compliance.

The process begins with purified crystals of neohesperidin ($C_{28}H_{34}O_{15}$, CAS 13241-33-3, see Figure 2) that have been determined by high performance liquid chromatography (HPLC).[13] Dried, immature fruits of *C. aurantium* are used by HealthTech BioActives to make neohesperidin crystals in a multi-step extraction process and are used as the starting material for the creation of NHDC as well as many other products, hence its manufacturing process is not otherwise covered here.

Neohesperidin is analyzed for purity by ensuring that >90% is neohesperidin, <2% is moisture, and the presence of naringin is less than 3% and hesperidin is less than 2%. The purified crystals are dissolved in a 4% (w/w) potassium hydroxide solution. Palladium-on-charcoal (Pd/C) catalyst is then added to the solution under pressure of hydrogen gas in order to facilitate hydrogenation. When the reaction is complete, the mixture is neutralized with sulfuric acid and heated to 90 °C. It is then put through a filter to remove the catalyst.

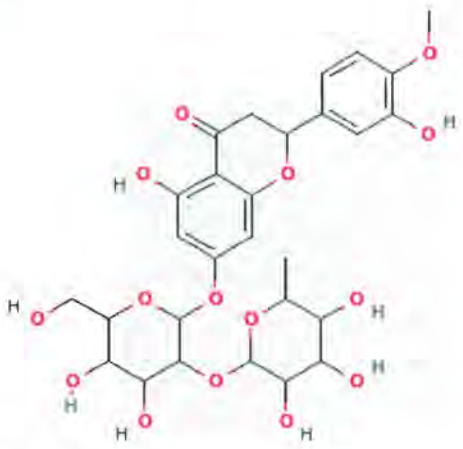

Figure 2: Neohesperidin[13]

The solution is cooled and NHDC is crystallized from the solution. The crystals are filtered out of the solution and rinsed with water. The filtered crystals are once again dissolved in water and filtered through a 0.6 μm filter to remove small particles and any microorganisms. The solution is again cooled for the purified solution to recrystallize. The resulting NHDC crystals are vacuum-dried, milled and packed. The flowchart of the manufacturing process is shown in Figure 3.

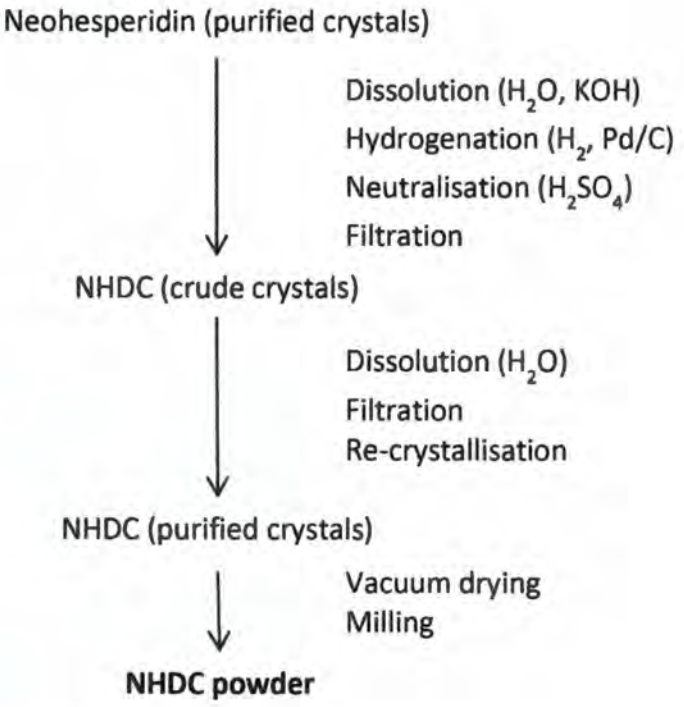

Figure 3. Manufacturing Flowchart

2.2.2 Good Manufacturing Practice

NHDC from HealthTech BioActives is produced in an FDA-registered facility according to ISO 9001, ISO 14000, ISO 22000 and FSSC22000 requirements under strict adherence to current GMP standards set to comply with the U.S. Code of Federal Regulations, 21 CFR part 110.

2.2.3 Raw Materials

Raw materials used in the production of HealthTech BioActives' NHDC are of appropriate food grade.[8] No material of human or animal origin is used. NHDC from HealthTech BioActive is non-GMO and not irradiated.

2.3 Specifications

NHDC is described in the European Pharmacopeia (Ph. Eur.) as Monograph 1547 and has a monograph in the United States Pharmacopeia (USP) published on December 1, 2019 that was developed with the help of HealthTech BioActives. The

product currently has a USP reference standard (catalogue number 1458086).[8] The specifications for the food-grade NHDC product, along with the specification methods, are listed in Table 1 below. They are in compliance with European Union's Commission Regulation 231/2012 of 9 March 2012 which details the criteria of purity of food additives in foodstuffs.[14]

Table 1. NHDC Specifications

Tested Parameters	Specification	Method
Identification		
Spectroscopy identification test, Infrared Spectroscopy	Conforms to standard	USP 197A
HPLC	The retention time of the major peak of the Sample Solution corresponds to that of the Standard Solution, as obtained in the Assay.	USP 621
Assay (%)	96.0–102.0	USP 621
Water Determination (%)	NMT 12.0	USP 921, method 1
Residue on Ignition (%)	NMT 0.2	USP 281
Physical Characteristics		
Appearance	Off-white, crystalline powder having a characteristic, intense sweet taste	Visual
Solubility	Freely soluble in hot water and propylene glycol, soluble in glycerol, very slightly soluble in cold water	USP General Notices 5.30
Impurities		
Neodiosmin (%)	NMT 2.0	USP 621
Naringin dihydrochalcone (%)	NMT 2.0	USP 621
Any other impurity (%)	NMT 0.5	USP 621
Total impurities (excluding neodiosmin) (%)	NMT 2.5	USP 621
Microbiological Tests		
Total Aerobic Microbial (CFU/g)	NMT 1000	USP 61, USP 62
Total Yeast & Mold (CFU/g)	NMT 100	USP 61, USP 62
Escherichia coli	Absent in 1 g	USP 61, USP 62
Salmonella spp.	Absent in 25 g	USP 61, USP 62

Abbreviations: CFU: colony forming units, HPLC: high performance liquid chromatography, NMT: no more than

2.3.1 Batch Analysis

Production conformity and consistency of HealthTech BioActives' NHDC are tested in production lots. Batch analyses of five non-consecutive lots, representing 12 months of production, are shown below and are reasonably consistent and meet the product specifications for marker compounds, physical/chemical composition, NHDC content, manufacturing impurities, and microbial analyses (see Table 2).

Table 2. NHDC Batch Analyses

Tested Parameters	Specification	Date of Manufacture/Lot No.				
		04/07/2019 019H012	27/03/2019 019C071	24/01/2019 019A050	11/10/2018 018K010	18/07/2018 018H049
Identification						
Spectroscopy identification tests, Infrared Spectroscopy	Conforms to standard	C	C	C	C	C
HPLC	The retention time of the major peak of the Sample Solution corresponds to that of the Standard Solution, as obtained in the Assay.	C	C	C	C	C
Marker Compounds						
Assay (%)	96.0–102.0	98.7	97.9	97.7	97.8	97.7
Water determination (%)	NMT 12.0	11.1	10.2	10.4	11.2	10.6
Residue on Ignition (%)	NMT 0.2	0.10	0.06	0.04	0.05	0.06
Physical Characteristics						
Appearance	Off-white, crystalline powder having a characteristic, intense sweet taste	C	C	C	C	C
Solubility	Freely soluble in hot water and propylene glycol, very slightly soluble in cold water	C	C	C	C	C
Impurities						
Neodiosmin (%)	NMT 2.0	0.8	1.0	1.2	1.0	0.8
Naringin dihydrochalcone (%)	NMT 2.0	1.2	1.1	1.1	1.1	1.3
Any other impurity (%)	NMT 0.5	0.2	0.4	0.3	0.3	0.4

Total impurities (excluding neodiosmin) (%)	NMT 2.5	1.5	1.8	1.7	1.6	2.1
Microbiological Tests						
Total Aerobic Microbial (CFU/g)	NMT 1000	C	C	C	C	C
Total Yeast & Mold (CFU/g)	NMT 100	C	C	C	C	C
E. coli	Absent per 1 g	C	C	C	C	C
Salmonella spp.	Absent in 25 g	C	C	C	C	C

Abbreviations: C: Complies, CFU: colony forming units, HPLC: high performance liquid chromatography, NMT: no more than

2.3.2 Impurities

NHDC is produced at levels of purity of no less than 96%. However, the manufacturing process naturally creates some very low levels of other chemically related flavonoid impurities including phloroacetophenone neohesperidoside (Impurity A), neodiosmin (Impurity B), neohesperidin (Impurity C), naringin dihydrochalcone (Impurity D), hesperidin dihydrochalcone (Impurity E), hesperetin dihydrochalcone 7' glucoside (Impurity F), hesperetin dihydrochalcone (Impurity G), and an unnamed compound (Impurity H).

Every batch is tested for these impurities. An analysis of 67 batches of NHDC is summarized in Table 3. The maximum value of each of these impurities are listed, as well as the worst-case total value. The results reveal that the quantity of the combined impurities is well below the limits specified in the European Pharmacopeia and the product specifications. Toxicity studies for impurities were investigated and were added to the respective description below when found.

2.3.2.1 Phloroacetophenone Neohesperidoside (Impurity A)

Phloroacetophenone neohesperidoside is a degradation product of NHDC when exposed to an alkaline environment or elevated temperature during the manufacturing process. An acute toxicity study examining phloroacetophenone in mice, rats, and hamsters found the LD_{50} to be between approximately 330–500 mg/kg body weight (bw) when injected intraperitoneally and no deaths occurred after oral gavage with the highest dose tested of 6 g/kg bw.[15] The same researchers examined subacute toxicity in a 30-day study, finding elevated liver enzymes consistently at the highest doses of 150 and 300 mg/kg bw/day given by oral gavage. With the average 90th percentile lifetime daily intake of NHDC estimated as 0.29 mg/kg bw/day for ages 2+ (see Part 3), the maximum amount of phloroacetophenone consumed per the product specifications would be 0.0087 mg/kg bw/day which is well below the NOAEL seen in the 30-day study, which was determined to be 37.5 mg/kg bw/day. The Ph. Eur. and the USP set the limit to no

more than 0.5% of the final NHDC product and in 67 batches tested, the impurity was no more than 0.03% in HealthTech BioActives' NHDC product.

2.3.2.2 Neodiosmin (Impurity B)

Neodiosmin (CAS number 38665-01-9) is a naturally occurring flavone in bitter orange and is extracted from citrus fruit as an incidental compound along with neohesperidin.[16] Due to its chemical structure, it is not altered during the hydrogenation process and remains intact throughout manufacturing. The Ph. Eur. and the USP set the limit to no more than 2.0% of the final NHDC product and in 67 batches tested, the impurity was no more than 0.55% in HealthTech BioActives' NHDC product.

2.3.2.3 Neohesperidin (Impurity C)

Neohesperidin (CAS number 13241-33-3) is naturally found in bitter orange and is the predominant starting material of the hydrogenation step. As the chemical reactions of the manufacturing process are not 100% efficient, neohesperidin that is not hydrogenated in the manufacturing process remains in the final product. The Ph. Eur. and the USP set the limit to no more than 0.5% of the final NHDC product and in 67 batches tested, the impurity was no more than 0.10% in HealthTech BioActives' NHDC product.

2.3.2.4 Naringin Dihydrochalcone (Impurity D)

Naringin dihydrochalcone (CAS number 18916-17-1) is produced when naringin, a naturally occurring flavanone in bitter orange, is hydrogenated. Naringin is found in small amounts with the starting material, neohesperidin, and, as it goes through the process of hydrogenation, it becomes affixed to dihydrochalcone. As its solubility is similar to NHDC, it is present in the final product. The Scientific Committee on GRAS Substances (SCOGS) determined naringin in its purified form did not present a risk with consumption as a food ingredient when used at levels used currently or may be reasonably expected in the future.[17] The Ph. Eur. and the USP set the limit to no more than 2.0% of the final NHDC product and in 67 batches tested, the impurity was no more than 1.56% in HealthTech BioActives' NHDC product.

2.3.2.5 Hesperidin Dihydrochalcone (Impurity E)

Hesperidin (CAS number 520-26-3) is the main flavanone in sweet orange (*Citrus sinensis*) and is present in small amounts in bitter orange. Therefore, it too is present in the starting material. The hydrogenation step affixes hesperidin to dihydrochalcone. It is more soluble than NHDC and the majority of the molecule is eliminated in the production process, with only a low level of the molecule remaining in the final product. SCOGS determined hesperidin in its purified form did not present a risk with consumption as a food ingredient when used at levels used currently or may be reasonably expected in the future.[17] The Ph. Eur. and the USP set the limit to no more than 0.5% of the final NHDC product and in 67 batches tested, the impurity was no more than 0.07% in HealthTech BioActives' NHDC product.

2.3.2.6 Hesperetin Dihydrochalcone 7' Glucoside (Impurity F) and Hesperetin Dihydrochalcone (Impurity G)

Hesperetin dihydrochalcone 7' glucoside and hesperetin dihydrochalcone are products from the hydrolytic cleavage of the glycosidic bonds of NHDC. As there are few of these impurities in the final product, hydrolysis occurring in the manufacturing process is considered minimal. The Ph. Eur. and the USP set the limit to no more than 0.5% of the final NHDC product for each of these impurities, and in 67 batches tested, there was no more than 0.31% of impurity F and 0.10% of impurity G in HealthTech BioActives' NHDC product.

2.3.2.7 Unknown (Impurity H)

This impurity, detected at low levels in all batches, has been tentatively identified as a dihydrochalcone or as a flavonoid on the basis of its retention time and ultraviolet (UV) absorption. The Ph. Eur. or the USP have no defined limit as it is an unknown molecule and in 67 batches tested, the impurity was no more than 0.4% in HealthTech BioActives' NHDC product.

Table 3: Impurities Detected in 67 Independent Batches of NHDC

Impurity	Limit Specified in the Ph. Eur./USP (times the area of the principle peak in the chromatogram obtained with reference solution)	Maximum Level Detected in any of the 67 batches of NHDC (%)
Phloroacetophenone neohesperidoside (Impurity A)	NMT 0.5	0.03
Neodiosmin (Impurity B)	NMT 2	0.55
Neohesperidin (Impurity C)	NMT 0.5	0.10

Naringin dihydrochalcone (Impurity D)	NMT 2	1.56
Hesperidin dihydrochalcone (Impurity E)	NMT 0.5	0.07
Hesperetin dihydrochalcone 7'glucoside (Impurity F)	NMT 0.5	0.31
Hesperetin dihydrochalcone (Impurity G)	NMT 0.5	0.10
Unknown (Impurity H)	-	0.40
Total of all impurities apart from Impurity B	NMT 2.5	2.28*

Abbreviations: NMT: no more than, Ph. Eur.: European Pharmacopeia, USP: United States Pharmacopeia

*worst-case total from a single batch (Batch 016C016)

2.3.3 Residual Solvent Analysis

Water is the only solvent used in the manufacture of NHDC; therefore, residual solvent analysis is not necessary and is not performed.

2.3.4 Residual Contaminant Analysis

Contaminants of polycyclic aromatic hydrocarbons, aflatoxins, melamine, and related compounds are tested once a year. There has been no detection of any of these contaminants above the lower limits of quantification.

2.3.5 Residual Pesticide Analysis

Dried, immature fruits of *C. aurantium* used for the production of neohesperidin are typically gathered well before pesticide treatment of the trees occurs. Nonetheless, various pesticides and related compounds are tested for once a year. In accordance with standard operating procedures, HealthTech BioActives certifies that production batches of NHDC are periodically submitted for 3rd party testing of pesticide residues and that tested batches comply with Regulation (EC) No. 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC Text with EEA relevance.

2.3.6 Heavy Metal Analysis

Contamination of NHDC by heavy metals is not expected due to harvest and processing criteria. However, heavy metals have been tested in the product since 1994 using the European Pharmacopeia 2.4.8 method D. This is a colorimetric qualitative method of measuring heavy metals. Therefore, specific values cannot be

given for the measurements. In recent years, the heavy metals method has been replaced by the ICP-MS method for lead, arsenic, cadmium, and mercury determination. In the past, product was tested either once a year or every 100 batches. As HealthTech BioActives has never received a positive test result in over 20 years, they scheduled individual heavy metal frequency testing to occur once a year, beginning January 2018. Batch analyses performed on 4 batches can be found in Table 4. All samples were below the limit of quantitation.

Table 4. NHDC Heavy Metal Analysis

Batch number ***(Manufacturing Dates)***	**Arsenic (ppm)**	**Lead (ppm)**	**Cadmium (ppm)**	**Mercury (ppm)**
016J047 *(September 2016)*	< 0.10	< 0.10	< 0.10	< 0.050
017B075 *(March 2017)*	< 0.10	< 0.10	< 0.10	< 0.050
018D068 *(May 2018)*	< 0.03	< 0.04	< 0.10	< 0.050
019C045 *(March 2019)*	< 0.03	< 0.04	< 0.10	< 0.050

Abbreviations: ppm: parts per million

2.3.7 Shelf-Life Stability

Five-year shelf-life stability studies from the time of manufacture have been performed on NHDC, consisting of 60-month long-term stability testing and 12-hour accelerated photostability testing. NHDC lot numbers 03E034, 03E040, 03E041, 04C007, and 05F080 (manufactured in May 2013, March 2014, and June 2015, as denoted in the table below) are reported here. For long-term and accelerated stability tests, product was stored in double polyethylene bags in 5 kg metric drums and remained at 30 ± 2°C with 75% ± 5% relative humidity. At all time points, outcome measures for the real-time stability study included the same physical and chemical tests and test methodologies used for commercial batch analysis, except infrared absorption, solubility and residue on ignition testing. The accelerated stability study utilized photostability testing, performed in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1B guideline. A xenon lamp (OSRAM, XBO 150 W/CR OFR) was used as the light source and quinine chemical actinometry was used to monitor exposure. The sample was irradiated for 12 hours and was determined to be stable after exposure. Loss on drying and assay percentage parameters were tested for during the accelerated study.

All measures were stable and within specification throughout the tests with no significant changes occurring in the parameters assayed. Results from sample analysis at initial and final time points are summarized below for the real-time (Table 5) and accelerated (Table 6) stability tests.

Table 5. Real-Time Stability Study

Tested Parameter	Specifi-cation	Long-Term Stability Test (30 ± 2° C, 75 ± 5% RH)									
		Time (months)									
		Batch: 03E034 May 2013		Batch: 03E040 May 2013		Batch: 03E041 May 2013		Batch: 04C007 March 2014		Batch: 05F080 June 2015	
		0	60	0	60	0	60	0	48	0	24
Marker Compounds											
Assay (%)	96.0–101.0	97.6	97.4	97.9	97.8	97.7	97.4	97.0	98.0	98.0	97.6
Water Determination (%)	NMT 12.0	10.3	11.2	9.9	11.1	10.6	11.1	10.9	11.0	9.9	10.9
Physical Characteristics											
Appearance	Conforms	C	C	C	C	C	C	C	C	C	C
Impurities											
Neodiosmin (%)	NMT 2	1.2	1.3	1.0	1.1	1.4	1.5	0.8	0.7	0.6	0.6
Naringin DC (%)	NMT 2	1.2	1.2	1.2	1.2	1.1	1.2	1.7	1.7	1.1	1.2
Any other impurity (%)	NMT 0.5	0.3	0.4	0.3	0.4	0.3	0.4	0.2	0.4	0.3	0.3
Total Impurities (excluding neodiosmin) (%)	NMT 2.5	2.5	2.0	1.7	1.9	1.6	1.9	1.9	2.3	1.4	1.9
Microbiological Purity											
Total Plate Counts (CFU/g)	< 1000	C	C	C	C	C	C	C	C	C	C
Total Molds & Yeasts (CFU/g)	< 100	C	C	C	C	C	C	C	C	C	C
Salmonella	Absence 25g	C	C	C	C	C	C	C	C	C	C
Escherichia coli	Absence 1g	C	C	C	C	C	C	C	C	C	C

RH = Relative Humidity, C=Complies, CFU=Colony Forming Units, NMT=No More Than

Table 6. Accelerated Stability Study (Irradiation Time = 12 hours)

Parameter	Specification	Before Irradiation	After Irradiation
Batch 1			
Assay (%)	NLT 96	98.2	98.9
Loss on drying (%)	NMT 11	10.6	10.9
Batch 2			
Assay (%)	NLT 96	97.8	97.0
Loss on drying (%)	NMT 11	10.9	10.8

NHDC = neohesperidin dihydrochalcone; NLT = no less than; NMT = no more than.

2.4 Physical or Technical Effect

NHDC is not intended to produce any physical or other technical effects that are relevant to the safety of the ingredient.

Part 3: Dietary Exposure

3.1 Intended Use

For the purpose of this GRAS notice, HealthTech BioActives' NHDC, manufactured in accordance with current GMP, is intended to be used as an ingredient in the food categories and at the addition levels shown in Table 7 below. The ingredient is not intended for use in foods where standards of identity would preclude such use, infant formula, or any products that would require additional regulatory review by USDA.

Table 7. Intended use of NHDC

NHANES Food Category	NHANES Category Code	Typical Serving Size (RACC) (g or mL)	Maximum Concentration (ppm)	Maximum Amount per Typical Serving (mg)
Sweet Crackers	541	30	50	1.5
Biscuits	521	55	50	2.75
Cornbread, corn muffins, tortillas	522	55	50	2.75
Other muffins, popovers	523	110	50	5.5
Other quick breads	524	55	50	2.75
Fruit juices (with and without citrus)	612, 641	240	10	2.4
Nectars	642	240	10	2.4
Carbonated soft drinks	924	360	10	3.6
Fruit drinks	925	240	10	2.4
Nonfruit beverages	926	240	10	2.4
Nutrition drinks and powders (reconstituted powders assumed here)	951, 952	240	50	12
Energy drinks	9531	360	50	18
Sports drinks	9532	360	50	18
Cakes	531	80	50	4
Cookies	532	30	50	1.5
Pies	533	125	50	6.25
Cobblers, eclairs, turnovers, pastries	534	125	50	6.25
Danish, doughnuts	535	55	50	2.75
Coffee cake	536	55	50	2.75
Sugar replacements or substitutes	912	1*	1000	1
Jellies, jams, preserves	914	21*	20	0.42
Ices and popsicles	916	52*	20	1.04
Candies	917	2–30	50	0.1–1.5
Cottage cheeses	142	110	20	2.2
Yogurt	114	170	20	3.4
Flavored milk and milk drinks	115	240	10	2.4
Frozen milk desserts	131	90	20	1.8

Puddings, custards, other milk desserts	132	90	20	1.8
Soups with legumes as major ingredient	416	245	10	2.45
Soups with grain as major ingredient	584	245	10	2.45
Dark-green vegetable soups	723	245	10	2.45
Deep-yellow vegetable soups	735	245	10	2.45
Tomato soups	746	245	10	2.45
Vegetable soups	756	245	10	2.45
Puerto Rican stews/soups with starchy vegetables (viandas)	775	245	10	2.45

RACC=reference amount commonly consumed
* Not a RACC category or serving weight not available via RACC, so data (rough average) taken from USDA Food Composition Database

3.2 Exposure Estimates

Exposure to NHDC from the intended use categories was estimated for the U.S. population using food consumption data from the What We Eat in America (WWEIA) dietary component of the National Health and Nutrition Examination Surveys (NHANES). The most recent data available at the time of this writing (2015–2016) were analyzed using Creme Food Safety software 3.6 (www.cremeglobal.com). These data were obtained from 7027 individuals who underwent two non-consecutive 24-hour dietary recall interviews (the first was collected in-person, the second by phone 3–10 days later). WWEIA food codes that were considered most similar to the intended use categories were utilized in the assessment and were assigned the relevant intended use concentrations. Note that nutrition powder (food code 952) was not utilized in the exposure assessment (even though it is an intended use) as concentrations in powder may vary widely based on serving size indicated to be used in a final reconstituted nutrition beverage to allow for a consistent amount in the final beverage. Exposure estimates for nutrition drinks (food code 951) are considered reasonable surrogates for exposure to nutrition powders as well.

Creme software is a probabilistic modeling tool that uses high-performance computing to predict intake (including total aggregate exposure) of food groups and/or individual food ingredients. Creme Food Safety performs calculations using large-scale food consumption data sets. It bases the calculated estimates on each individual's body weight from the survey, as opposed to averaged body weights. Calculations also incorporated the NHANES assigned sample weights for each individual in the survey, which measure the number of people in the population represented by that specific subject and help to ensure that the results statistically represent the entire U.S. population. Sample weights for NHANES participants incorporate adjustments for unequal selection probabilities and certain types of non-response, as well as an adjustment to independent estimates of population sizes for specific age, sex, and race/ethnicity categories. The data are shown for "food

consumers" (which includes only data from individuals who reported consuming one or more food/beverage categories intended to contain the ingredient over the two-day survey period, as opposed to the whole population). Results are given as both absolute exposure (mg/day), as well as exposure relative to body weight (mg/kg bw/day).

The relative standard error (RSE; calculated by dividing the standard error of the estimate by the estimate itself and multiplying by 100) is a statistical criterion that can be used to determine the reliability of estimates as pertains to the population (the larger the RSE the less reliable the estimate).[18] RSE values greater than 25–30% are often considered reasonable cut-offs by which to consider a value unreliable.[18, 19] For the purpose of this safety assessment, an RSE value of greater than 25% was used to indicate that the estimated value was unreliable with regard to representing the population. RSE values are shown in the tables below for the 90th percentile values only, as the 90th percentile values are the most pertinent for the exposure estimates.

The NHDC exposure estimates derived from the Creme assessment based on the intended use categories and concentrations are shown below in Tables 8 and 9.

Table 8. Total (aggregate) absolute exposure to NHDC by proposed use food consumers using NHANES 2015–16 data

Population Group	Age in yrs	N (% of total)	Absolute NHDC consumption Daily Average by Food Consumers (mg/day)				RSE Value 90th (%)	Lifetime 90th % (mg/day)
			Mean	Mean std err	90th%	90th% std err		
Children	2–12	1474 (99.6)	7.8	0.2	13.8	0.4	2.9	12.3
Adolescents	13–19	829 (97.5)	10.0	0.6	20.0	1.3	6.5	17.8
Adults	20+	4036 (95.5)	10.0	0.3	20.2	0.7	3.5	18.0
Total Population	2+	6339 (96.3)	9.6	0.2	19.3	0.5	2.6	17.2

Creme run #431

Table 9. Total (aggregate) exposure to NHDC by proposed use food consumers relative to body weight using NHANES 2015–16

Population Group	Age in yrs	N (% of total)	NHDC consumption relative to body weight Daily Average by Food Consumers (mg/kg bw/day)				RSE Value 90th (%)	Lifetime 90th % (mg/kg bw/day)
			Mean	Mean std err	90th%	90th% std err		
Children	2–12	1474 (99.6)	0.30	0.01	0.57	0.02	3.5	0.50

Adolescents	13–19	829 (97.5)	0.15	0.01	0.32	0.02	6.3	0.28
Adults	20+	4036 (95.5)	0.12	0.00	0.26	0.01	3.8	0.22
Total Population	2+	6339 (96.3)	0.15	0.00	0.33	0.01	3.0	0.29

Creme run #431

According to the estimates in the tables above, the majority (approximately 96.3%) of the U.S. total population ages 2 and above are identified as potential consumers of NHDC from one or more of the proposed food uses. The 90th percentile estimated lifetime exposure to NHDC for the total population is 17.2 mg/day (0.29 mg/kg bw/day), while the 90th percentile estimated daily average exposure is 19.3 mg/day (0.33 mg/kg bw/day). The highest potential consumer population at the lifetime 90th percentile on a relative to body weight basis is children (ages 2–12), at an estimated 0.5 mg/kg bw/day, while the highest potential consumer population at the lifetime 90th percentile based on absolute consumption is adults (ages 20+) at an estimated 18 mg/day.

It should be noted that these estimates are considered conservative, as they assume that 100% of the intended use food products in the market will contain the maximum intended use levels of NHDC. While food labels will list NHDC as an ingredient and may even highlight it in marketing, it is assumed that many consumers will not always realize that it is present in a food product. In other words, it may be an "invisible" ingredient to many consumers, which decreases the chance that only food products that contain it will be chosen by consumers. Additionally, there will be cost and market share limitations of adding the ingredient to foods and beverages in general, making it even less likely that an individual would consume them in all of the intended use food groups consumed daily.

Since HealthTech BioActives' NHDC has been sold for decades in Europe, HealthTech BioActives has exposure estimates for various populations with regard to NHDC consumption in Europe. The Food Additives Intake Model (FAIM) 2.0 tool, which was developed by the EFSA Additive and Nutritive Sources (ANS) Panel, was utilized for estimations. The maximum permitted levels were considered for the exposure estimate, and the mean for all age groups was 0.16–2.13 mg/kg bw/day while the 95th percentile was 0.40–3.08 mg/kg bw/day. To get a rough comparison between estimated consumption in the U.S. versus Europe, in order to compare estimates of the 90th percentile estimate (as noted in the Creme analysis above) to the 95th percentile estimate (as noted in the FAIM analysis), doubling the 90th percentile in order to obtain the 95th percentile is considered reasonable.[20] Doubling the 90th percentile daily average from the Creme analysis (0.33 mg/kg bw/day) would result in an estimated 95th percentile of 0.66 mg/kg bw/day. This is

within the 95th percentile range in the FAIM analysis, suggesting that estimated consumption in the U.S. and Europe may be somewhat similar.

Part 4: Self-limiting Levels of Use

Addition levels are limited by the palatability of the ingredient. As the ingredient is up to 950–1800 times sweeter than sucrose, the intensity of sweetness can be unpalatable at elevated levels.[11, 21] Additionally, the product has a distinct licorice-like aftertaste that can be perceived by many as unpleasant at concentrations of 160 ppm, which is well above the intended use of NHDC other than for use as a sweetener (which is expected to be diluted prior to consumption).[9]

Part 5: Experience Based on Common Use in Food Prior to 1958

The GRAS conclusion for NHDC is based on scientific procedures, and thus, experience based on common use in food prior to 1958 is not considered pivotal information. NHDC was developed in the early 1960s by chemists at the United States Department of Agriculture's Agricultural Research Service and was therefore not discovered prior to 1958.[2]

Part 6: Narrative

6.1 Absorption, distribution, metabolism, and excretion (ADME)

NHDC is structurally similar to other flavonoids. Therefore, ADME data from other flavonoids, such as eriocitrin, hesperetin and naringenin, were used to supplement the minimal ADME data found for NHDC.

Absorption of NHDC and structurally similar flavanone glycosides is theorized to be low due to their bulky, hydrophilic glycosidic moiety, as has been shown in a Caco-2 model testing various flavonoids.[22] In the small intestines, flavonoid glycosides can be hydrolyzed by lactase phlorizin hydrolase.[23] However, they are largely undigested until they reach the large intestines where microbiome-mediated hydrolysis and fermentation takes place.[23]

NHDC was shown to be deglycosylated to hesperetin dihydrochalcone by cooperative action of various intestinal microbes in a human fecal fermentation experiment.[21] This reaction is followed by the metabolism of the substance into 3-(3-hydroxy-4-methoxyphenyl) propionic acid and 3-(3,4-dihydroxyphenyl) propionic acid by the intestinal microbes.[21] A similar metabolism profile has been noted for eriocitrin, a similarly structured citrus flavonoid.[24] In an unpublished study by Booth et al. that was reviewed by World Health Organization/Food and Agriculture Organization (WHO/FAO) and used as evidence in their 2012 Joint WHO/FAO Expert Committee on Food Additives (JECFA) report, the fermentation of NHDC with rabbit feces for 30 minutes under anaerobic conditions produced m-hydroxyphenylpropionic acid and dihydroisoferulic acid.[25] These metabolites are not new or uncommon to humans or other mammals.[26] The metabolites that are absorbed through the lumen epithelium of the large intestines are exposed to the phase I and phase II detoxification pathways of the liver and are processed accordingly. Additionally, any NHDC that is absorbed has been found to bind to human serum albumin, which plays a significant role in the transport and disposition of flavonoids throughout the body.[27]

Overall, it is approximated that about 200 different proteins are involved in flavonoid ADME.[23] It is predicted that age, sex, microbiome-individuality, and genotype can explain varying degrees of utility of flavonoids. Additionally, it is predicted that flavonoids and the intestinal microbiome have a bidirectional relationship, where consumed flavonoids have an influence on microbial community and the microbial community have an influence on the metabolism and absorption of the flavonoids.[28]

Sprague-Dawley rats were used to determine pharmacokinetics of NHDC by single dose administration of NHDC either orally (20 mg/kg) or intravenously (IV) (2 mg/kg).[29] Peak concentration after oral administration was noted at 980.3 μg/L at

approximately 10 minutes and, after IV administration, was noted at 2125.9 μg/L at approximately 5 minutes. Its half-life was determined to be between 30 minutes and 1 hour, suggesting that NHDC is rapidly absorbed and eliminated. In the same study, levels in tissues were examined after IV administration and revealed small amounts of NHDC in the heart (1.8 μg/g), kidneys (1.4 μg/g), liver (1.4 μg/g), spleen (0.8 μg/g), stomach (0.8 μg/g) and brain (0.7 μg/g) at 5 minutes post-administration. All levels were below 0.4 μg/g by 1 hour post-administration. Tissue accumulation after oral administration was not tested.

Rats administered a single dose of ^{14}C-labeled NHDC at 1, 10, and 100 mg/kg by gavage resulted in 80% recovery of the ^{14}C within 24 hours, primarily in the urine and some in the feces.[2] Trace amounts were seen in the gastrointestinal tract after 24 hours. In the same unpublished article by Booth et al., summarized by JECFA, NHDC was given to rats at 0.5% in the diet and metabolites were examined in the urine.[25] It was not specified when the urine was collected. NHDC was the major compound identified. Similarly, after oral administration of 500 mg of naringin in a healthy human volunteer, naringin was found in the urine unaltered.[30] In another healthy human volunteer pharmacokinetic study, 500 mg of naringin and 500 mg of hesperidin were orally administered in 240 mL of water in a single dose to a single volunteer.[31] Urine was collected, and the metabolized molecules of naringenin and hesperetin were detected within 3 hours and were found in the urine for 38 hours. Total urine recovery of naringenin and hesperetin was 4.9 and 3.0%.

To examine metabolism of two other flavonoids in human subjects, Kanaze et al. had six healthy volunteers fast overnight. They were then administered 136 mg of combined hesperetin and naringenin. Thirteen blood samples were collected over the next 12 hours. Urine was collected at 5 intervals over 24 hours. Results revealed that both compounds were rapidly absorbed, detected within 20 minutes of consumption, and peaked between 3.4 and 4 hours after consumption. Elimination half-life was 2–3 hours. Urinary elimination was the only elimination pathway monitored and accounted for only 3–6% of the amount consumed, indicating the molecules are metabolized in the body and are quickly processed or, alternatively, that compounds were eliminated through the stool.[32]

Due to the rapid excretion of NHDC, it is unlikely that the compound is to remain in any tissue for long periods. EFSA came to the same conclusion for its recommendation related to use in animals, stating: "Given the likely rapid metabolism and excretion of NHDC, it would not be expected to accumulate in edible tissues of mammals and poultry given this substance in feed."[26]

6.2 Toxicology Studies

6.2.1 Bacterial Reverse Mutation Test

In order to evaluate the mutagenic potential of NHDC, bacterial reverse mutation tests have been conducted and all reveal negative results, suggesting that NHDC is non-mutagenic.

Two strains of *Salmonella typhimurium* (TA98, TA100) were tested in two studies. In one study, NHDC was tested at concentrations of 40 or 120 mg/plate.[33] In another study, NHDC and some of its metabolites, including hesperetin, and hesperetin dihydrochalcone, were tested at 829, 1640, or 8197 nmol/plate with and without S9 cells.[34] Both showed no mutagenicity.

S. typhimurium strains TA1535, TA100, TA1537, TA1538, and TA98 were tested at an unspecified concentration and showed no mutagenic changes under incorporation and preincubation conditions.[35, 36] Strains TA100, TA1535, TA97, and TA98 were tested up to 10 mg/plate of NHDC under preincubation conditions and showed no differences compared to controls.[37]

6.2.2 *In vitro* Mammalian Chromosomal Aberration Test

In order to evaluate the clastogenic potential of NHDC, an *in vitro* chromosomal aberration assay was performed. In 2018, HealthTech BioActives sponsored an unpublished investigation by Grindey on the clastogenicity of NHDC at levels between 0–2000 μg/mL with S9 activation for 3 hours and without S9 activation for 3 and 27 hours. The study was done according to GLP and OECD 487 guidelines. No cytotoxicity was seen after either of the 3-hour treatments. Concentrations above 750 μg/mL were above the relative increase in cell count threshold and revealed cytotoxicity. Therefore, in the main assessment, cultures were exposed to NHDC for 3 hours at dosages of 200, 650, or 2000 μg/mL in the presence and absence of S9. They were then exposed for 27 hours at 65, 400, 650, or 750 μg/mL in the absence of S9. A negative control of 1% dimethyl sulfoxide was utilized and positive controls were used for both presence (cyclophosphamide) and absence of S9 (vinblastine and mitomycin C, respectively). There was no aneugenicity or clastogenicity noted in any of the tested samples.

6.2.3 *In vivo* Mammalian Micronucleus Test

In order to evaluate the genotoxic potential of NHDC, *in vivo* mammalian micronucleus assays were performed.

Two doses of NHDC were administered by gavage at a 24–hour interval to male Swiss-Webster mice at test concentrations of 0 (vehicle-control), 200, 500, 1000, and 5000 mg/kg bw in a study by MacGregor et al. (1983).[38] The negative

control/vehicle was 2% acacia in water and the positive control was triethylenemelamine. Each group consisted of six animals, and all treatments were administered at a uniform volume of 10 mL/kg bw.

All animals were observed immediately following dosing and at regular intervals until sacrifice for mortality, signs of toxicity, or adverse reactions to treatment.[38] Bone marrow smears were prepared in duplicate, suspended in fetal bovine serum, on standard microscope slides from samples obtained from the femurs of each animal from each dose group immediately following sacrifice, 6 hours after the second treatment. Four thousand polychromatic erythrocytes per animal were scored for frequency of micronuclei with one slide from each animal being scored blind. A statistically significant increase in micronucleated erythrocytes was seen at 500 mg/kg bw/day due to a single animal having extremely elevated levels compared to others in the group. A repeat of this dosing did not reproduce the changes and it was concluded that the finding was not test item related.

In 1981, Sahu et al. investigated *in vivo* genotoxicity of NHDC in Swiss male rats administered 2 doses intraperitoneally, 24 hours apart.[39] Doses of 200, 400, and 800 mg/kg bw/day, vehicle control, and untreated control were examined. There was no positive control for this study. Bone marrow smears were prepared in duplicate, suspended in human AB serum, on standard microscope slides from samples obtained from the femurs of each animal from each dose group immediately following sacrifice, 6 hours after the second treatment. However, animals given 800 mg/kg bw/day died 2 hours after injection. This was also true for animals given the same dose of quercetin and kaempferol, and the authors provided no further discussion regarding the deaths. There were elevated micronucleated erythrocytes at 200 and 400 mg/kg bw/day. Due to these findings, the authors suggested NHDC is clastogenic. However, OECD 474 states that "intraperitoneal injection is generally not recommended since it is not an intended route for human exposure and should only be used with specific scientific justification."[40] Thus it is impossible to determine how these results relate to human ingestion of NHDC, especially in light of the lack of micronucleus findings by the more relevant MacGregor et al. study in mice up to 5000 mg/kg bw/day when given by gavage.

6.2.4 Genotoxicity Summary

Genotoxicity studies are summarized in Table 10.

Table 10. Summary of Genotoxicity Studies

Reference	Test	Test species	Dose	Results
Batzinger, 1977[33]	Bacterial Reverse Mutation	*Salmonella typhimurium* TA98 and TA100	40 or 120 mg/plate +/- S9	Negative
Brown and Dietrich, 1979[35]	Bacterial Reverse Mutation	*S. typhimurium* TA1535, TA100, TA1537, TA1538, TA98	Not reported	Negative
Brown, 1977[36]	Bacterial Reverse Mutation	*S. typhimurium*	Not reported	Negative
MacGregor and Jurd, 1978[34]	Bacterial Reverse Mutation	*S. typhimurium* TA98 and TA100	829, 1640, or 8197 nmol/plate +/- S9	Negative
Zeiger, 1987[37]	Bacterial Reverse Mutation	*S. typhimurium* TA100, TA1535, TA97, and TA98	0.1, 0.333, 1.0, 3.333, or 10 mg/plate +/- S9	Negative
Batzinger, 1977[33]	Host mediated assay	*S. typhimurium* TA98 and TA100 Mice	2500 mg/kg bw	Negative
MacGregor, 1983[38]	Mammalian erythrocyte micronucleus test	Mice	200, 500, 1000 or 5000 mg/kg/bw (gavage)	Negative
Sahu, 1981[39]	Mammalian erythrocyte micronucleus test	Mice	200, 400, or 800 mg/kg/bw (IP)	Positive
Grindey, 2018 (unpublished)	*In vitro* chromosomal aberration assay	TK6 Human cells	Up to 2000 µg/mL	Negative

6.2.5 Ninety-day Repeated-Dose Oral Toxicity Study

A 13-week study was conducted by Lina et al. (1990) to evaluate the potential health hazards, including identification of toxic effects and target organs, of repeated oral exposure to NHDC.[41] Though other sub-chronic studies have been performed, Lina et al. is the only study performed in compliance with GLP and OECD guidelines with a sufficient number of test animals.

Four groups of 20 Wistar rats of each sex were administered NHDC through their diet at concentrations of 0, 0.2, 1.0, and 5.0%.[41] The authors stated that this percentage of the diet corresponded to 150, 757, and 4011 mg/kg bw/day for males and 166, 848, and 4334 mg/kg bw/day for females. Animals were weighed weekly and observed for signs of toxicity. An ophthalmoscopic exam was done prior to the study and at week 13 on the control and high-dose groups. Body weight and food intake was recorded weekly and water consumption was measured at weeks 7 and 12. Blood samples were collected from 10 of each group on day 84/85 and assessed for hematologic changes as well as on day 91/92 for biochemical assessment. Blood and urine were also collected from all animals on day 87 after a 16 hour fast for glucose and urinalysis analysis.

Gross necropsy was performed on all animals and organs were weighed.[41] The following organs were observed microscopically in the control and the high group: adrenals, brain, cecum (with and without content), gonads, heart, kidneys, liver, spleen, thymus, thyroid (with parathyroids), aorta, lymph nodes (axillary and mesenteric), colon, duodenum, epididymides, eyes, ileum, jejunum, lungs, mammary glands, esophagus, pancreas, pituitary, prostate, rectum, sternum, stomach, salivary glands, trachea, urinary bladder, and uterus.

There were no test item-related deaths.[41] There was one death of a female in the intermediate-dose group due to renal failure. This was an isolated event and was considered unrelated to the test item. Diarrhea was reported at week 3 for the high-dose group. This was transient and considered to be non-adverse. No ophthalmologic changes were noted. There were no significant hematologic differences in the control versus test item groups. A decrease in total protein was noted in the high-dose male group but was not seen in the female group and was not considered toxicologically relevant. Alkaline phosphatase (ALP) and bilirubin were increased in the high-dose female group. Historical reference ranges were not given. There was a non-statistically significant increase in bilirubin with the male group and no difference was seen in the male ALP levels. As there was no consistency between the two sexes, no changes in other liver function markers, no signs of hemolysis, and no changes in micro or macro features of the liver, it is unlikely that the elevated ALP and bilirubin in the high-dose female group is toxicologically relevant. Urine pH was statistically significantly decreased in both the male and female high-dose groups. However, there were no clinical, macroscopic or microscopic correlates. There was a statistically significant increase in the weight of full and empty cecum in the high male and female dose groups. No histopathologic changes were noted in the tissue walls. The authors discussed that ceceal enlargement has been noted in studies with poorly digested carbohydrates or certain non-nutrient substances (e.g. food colorings, saccharin, polyethylene glycol) and is considered of little or no toxicologic relevance.[42]

The high-dose male group had a mean body weight of 9% lower than that of the control group.[41] This group had poor weight gain in the first two weeks of treatment, weighing 22–27% less than the control group due to significantly decreased intake of food consumption. Weight gain was 13–29% lower for this group at weeks 6 and 10. The decrease in weight in the high-dose male group was not considered toxicologically relevant and was attributed to decreased food intake early in the study. There was a 19% decrease in weight gain in the high-dose female group after the first week of treatment. However, by the end of the study all female groups showed no statistically significant differences in weight compared to controls. The weight of the testes and brain were proportionally increased compared to the body of the male high-dose group. However, this can be accounted for by their overall smaller size. Based on these results, the no observed effect level (NOAEL) was determined to be the intermediate dose tested of 757 mg/kg bw/day, although the findings in the high-dose group were still considered of minimal toxicological concern. The author states the NOAEL as "about 750" mg/kg bw/day. Note that other organizations describing this study have referred to the NOAEL as 750–760 mg/kg bw/day.

6.2.5.1 Additional Sub-chronic Studies

Gumbmann et al. (1978) fed male and female rats 0 or 5.0% NHDC in their diets for 122 days (male) and 170 days (female).[2] Weight gain and organ weights were measured. The main finding was elevated thyroid weights in the treated male group. However, in the same published paper, no abnormal thyroid weights were noted in rats fed 5.0% NHDC for 1 year or in rats fed 10% NHDC for 11 months. Therefore, this finding was not considered test item related. The one-year and 11-month studies are further described in subpart 6.2.6.

The JECFA document summarized sub-chronic studies from the unpublished Booth report.[25] In Booth's study series, a follow-up investigation was conducted on the liver lipidosis observed in the female groups of Booth's multi-generational reproductive study (see summary in subpart 6.2.7 below).[25] In the follow-up study, two groups of 6 females were fed a diet of 0 or 1280 mg/kg feed of NHDC (stated in the report to be equivalent to 0 or 128 mg/kg bw/day) for 90 days. An alternative basal diet was used in this study, as other studies had reported liver lipidosis with the initial basal diet. Results revealed no histopathologic changes to the liver. However, the experimental group had an 11% lower body weight than the control group.

In a follow-up study to further investigate the decrease in weight, two groups of 5 males and 10 females were fed a diet of 0 or 5000 mg/kg feed (stated in the report to be equivalent to 0 or 500 mg/kg bw/day) of NHDC for 90 days.[25] The basal diet was the same as the initial follow up study. At 70 days, a reproductivity phase of the trial was initiated. Males were sacrificed at 90 days and females were sacrificed

at 113 days. Organ weight, histopathology, and hematology assessments were within normal limits.

The decrease in body weight observed in Booth's initial 90-day study was not seen in the follow-up study. The liver lipidosis observed in the initial phase of Booth's reproductive study was not observed in the subsequent study. The NOAEL of the two studies was determined by JECFA to be 500 mg/kg bw/day.

6.2.6 Summary of Sub-chronic Trials

A summary of the sub-chronic trials is in Table 11.

Table 11. Summary of Sub-chronic Clinical Trials

Reference	Dose in % of diet	Duration	# Subjects	Parameters	NOAEL In mg/kg bw/day (% diet associated with dosage)	Comments (results)
Lina, 1990[41]	0, 0.2, 1.0, 5.0%	90 days	Rat (Wistar), 20/sex/group	Mortality, body weight, hematology, blood chemistry, gross necropsy, histopathology, urinalysis, ophthalmologic	750 (1.0 %)	- Increased ceceal weight in high test group -Decrease body weight in the high-dose male group -Decrease blood protein in the high-dose male group -Increase ALP and bilirubin in female high-dose group
Gumbmann, 1978[2]	0, 5.0%	Male-122 days Female-170 days	Rat (Fischer), 5 male and 6 female/ group	Body weight, food intake, gross necropsy, organ weights, histopathology, reproductive performance	Not derived	-Statistically significant increase in thyroid weight in test group males
Booth, 1965 unpublished [25]	0, 0.128%	90 days	Rat (unknown strain), 6 female/group	Gross necropsy, body weight, histopathology	128 (0.128%)	-Decrease body weight in test groups
	0, 0.5%	Male-92 days	Rat (unknown strain), 5	Organ weights, hematology,	500 (0.5%)	-No compound related findings

		Female-113 days	male and 10 female/ group	reproductive parameters		

6.2.7 Chronic studies

Six male and female animals of the F2 generation of the three-generation toxicity study by Gumbmann et al. (further discussed in subpart 6.2.7) were maintained for one year and given 0, 0.5, 2.5, and 5.0% of NHDC in their diet (equivalent to 0, 250, 1250, or 2500 mg/kg bw/day as calculated utilizing Lehman's factor).[2, 43] There were no microscopic differences between the control and test groups. Results showed a slightly statistically significant decrease in body weight in the female intermediate group, but as it was not considered a dose-dependent effect, it was likely non test item-related. The high-dose males had a slight statistically significant decrease in liver weight compared to controls. It was concluded that the results were not test item-dependent as no histopathological findings were noted. There was no NOAEL reported by the authors but JECFA concluded the NOAEL to be the highest dose tested, 2500 mg/kg bw/day, which is considered reasonable.[25]

In the same published study, a two-year study was conducted on male and female dogs with 3 dogs per sex per group.[2] They were given 0, 200, 1000, and 2000 mg/kg bw/day NHDC in their diets. For the high-dose group, this amount was approximately 6.0% of their diet. They were examined at 6-month intervals and urine, clinical biochemistry and hematology were analyzed. ALP was increased throughout the study in the high-dose male dogs but there were no histologic or other plasma indications of liver insult. Plasma thyroxine levels were decreased in high-dose females from 6 months–2 years. A slight dose-related increase in liver weights was noted in the high-dose male group. Relative testes weights were described as lower within the report; however, it is unclear if the change compared to control was statistically significant based on the data presented in the report's tables. Testicular atrophy and degeneration were confirmed histologically and was noted in 1 dog in both the intermediate-dose and high-dose male groups. The other 2 dogs of both groups showed no changes. Mild thyroid hypertrophy and hyperplasia were noted in 2 dogs of each sex in the high-dose groups. JECFA determined the NOAEL to be 1000 mg/kg bw/day due to the thyroid changes noted.[25]

6.2.8 Carcinogenicity Study

In 1978, Gumbmann et al. investigated the carcinogenicity of NHDC in Fischer rats in a 2-year study.[2] Twenty-four individual animals of each sex were fed diets

composed of 0, 0.5, 2.5, or 5.0% NHDC. Within 10 weeks, weight gain of the high-dose group in both sexes was significantly inferior compared to the control and became even more significantly inferior in the high-dose female group by the 60th week. Half of the high-dose groups of both sexes were continued with the regular feed regimen and the remaining half was supplemented with 3% USP Salts XIV fortified with 40 ppm of zinc and 2 ppm of cobalt as well as 3% additional brewers dried yeast. By the 100th week, there was no difference in weights between the control and supplemented high-dose groups. Authors speculated that NHDC in the unsupplemented lab diet created a marginal deficiency in nutrients possibly due to interference with absorption.

There were statistically significant increases in the weights of all organs in the unsupplemented high-dose female group and in the heart in the mid-dose female group compared to controls. The unsupplemented high-dose male group had statistically significant increases in the weights of the liver and kidneys and the supplemented high-dose male group had a statistically significant increase in spleen weight compared to controls. Bearing in mind the confounding influence of unsupplemented diet, the results suggest that the test item does not influence organ weight in a consistent dose dependent manner.

The mortality rates of the study were unclearly described as the mortality rates reported in the text differed from mortality rates reported in the article's table.[2] According to the table, at 100 weeks, the control group of both sexes had 16 of 24 survivors; the 0.5% groups had 12/24 (male) and 19/24 (female) survivors; the 2.5% groups had 20/24 (male) and 19/24 (female) survivors; the 5.0% unsupplemented groups had 8/24 (male) and 7/24 (female) survivors; and the 5.0% supplemented groups both had 11/24 survivors. The text states that mortality was greatest in the control groups of both sexes, excluding males fed 0.5% NDHC, and that the mortality in males of the 2.5% and 5.0% groups was 4/24 and 5/24, respectively. Additionally, timing of deaths throughout the study were not described and necropsies at the time of death were not reported. Therefore, it is impossible to determine causes of death. Due to the information in the table and text differing dramatically and issues surrounding nutrient deficiencies, no conclusions regarding the influence of the test item on mortality can be drawn.

The incidence of tumors and non-neoplastic lesions were uniformly distributed throughout all groups, with two possible exceptions.[2] Focal renal cortical atrophy tended to be higher compared to controls in females in the low-, medium-, and unsupplemented high-dose groups, with elevations not seen in the female control and supplemented high-dose groups. Additionally, thyroid follicular hyperplasia and hypertrophy were seen in all groups except the supplemented high-dose group, which the authors pointed out is consistent with iodine deficiency. As the changes were not dose-dependent when the animals were supplemented, the study suggests that these results are not test item-dependent.

Overall, due to inconsistencies in the report and possible early nutrient deficiencies, the study is inconclusive. The experts of the 2012 JECFA Report of Certain Food Additives came to the same conclusion.[25]

6.2.9 Reproductive and Developmental Toxicity Studies

Waalkens-Berendsen et al. (2004) gave groups of 28 mated female Wistar rats diets with concentrations of 0, 1.25, 2.5 5.0% of NHDC (authors noted this was equivalent to approximately 0, 800–900, 1600–1700, 3100–3400 mg/kg bw/day) from day 0–21 of gestation.[44] On day 21, animals were sacrificed, and gross macroscopic necropsy completed; uterus, ovaries and cecum were weighed and corpora lutea were counted. Fetuses were removed, weighed, sexed, and examined for gross abnormalities. Placentas were weighed and counted. Early and late resorption of dead fetuses and implementation were counted. Half of all the fetuses in the control and high-dose group were examined microscopically for skeletal and visceral abnormalities. No statistically significant differences were noted in maternal, reproductive, or developmental markers. There were minor statistically significant increases in relative food consumption in the intermediate- and high-dose groups on days 14–21 but they were not considered related to the test item as there were no corresponding findings in absolute food consumption. A dose-dependent increase in full and empty cecum weights were noted and, as previously stated, commonly occur reversibly in rodents with ingestion of poorly digestible carbohydrates or other non-nutritive substances. The authors stated that its occurrence in the study suggests that NHDC is not readily digested and absorbed, and it was not considered a toxicologic effect. The NOAEL was considered to be the highest dose tested, equivalent to approximately 3100 mg/kg bw/day.

A 3-generation reproductive study was completed by Gumbmann et al. (1978) on weanling Fischer rats with 6 rats of each sex per group.[2] They received NHDC at concentrations in their diet of 0, 0.5, 2.5, and 5.0% (equivalent to approximately 0, 250, 1250, or 2500 mg/kg bw/day). The F0 generation was fed the respective test-item amounts, was mated, and produced the F1 generation. The same protocol was followed to produce the F2 and F3 generations. After production of the F3 generation, the F2 generation was continued on the diet for a year as mentioned in subpart 6.2.6. When F1 rats were weaned from the F0 generation, the F0 generation produced the F1b generation and the embryos were removed by cesarean on Day 20 to be examined for gross and skeletal changes. No adverse changes were noted, other than a slight statistically significant decrease in pup survivability in the F3 generation at the intermediate and high group, which was not further described or discussed. Similar results were not found in the above 2004 reproductive study by Waalkens-Berendsen et al. Neither the author nor JECFA determined a NOAEL due to absence of quantitative data.[25]

In the unpublished Booth study, NHDC was added to the diet of 5 female and 5 male rats at concentrations of 0, 6.4, 64, 640, and 1280 mg/kg (equivalent to 0, 0.64, 6.4, 64, and 128 mg/kg bw/day using Lehman's factor as stated in the JECFA report) for 148 days.[25, 43] After 90 days on this diet, the study transitioned into its reproductivity phase, where the rats were continued on the same diets for another 58 days. The number of litters, number of pups in each litter, and the weight of pups at 3-week weaning were noted. Blood samples were collected from the control and the two highest groups. Animals were necropsied at 148 days and select organs were weighed and microscopically examined. High-dose males had 12% lower body weight. Liver lipidosis was noted in females at various dose levels. This finding was further investigated by the authors and was discussed in subpart 6.2.5.1 with no further findings. With regard to weaned pups, the control had 21 pups total and there were 11 pups in the 0.64 mg/kg group, 6 pups in the 6.4 mg/kg, 15 pups at 64 mg/kg and 8 pups at 128 mg/kg, revealing possible but not clear dose-dependent changes. JECFA stated that the difference in litter numbers seen in this study could not be confirmed in a follow up study performed by the same authors at a higher dose level; thus, the Committee was of the opinion that effects on pup numbers were not test article-related. Unfortunately, more detailed explanation of the results of the reproductive parameters measured was not shared.

6.2.10 Summary of Chronic, Carcinogenicity, Reproductive and Developmental Toxicity Studies

A summary of the chronic/reproductive studies on NHDC is shown in Table 12 below.

Table 12. Summary of Chronic and Reproductive and Developmental Studies

Reference	Dose Groups	Duration	Subjects	Parameters	NOAEL mg/kg bw/day	Comments (results)
Waalkens-Berendsen, 2004[44]	0, 1.25, 2.5, 5.0% Diet	21 days	Rat (Wistar) 28 mated females	Gross necropsy, food consumption, reproductive organ weight, placenta number and weight, fetus number and weight of all fetuses and skeletal and visceral morphology in half of the control and high-dose fetuses	3100 (5.0%)	- Increased ceceal weight in test groups - Increased food consumption in mid- and high-dose groups on days 14–21 - No statistically significant changes in maternal, reproductive or developmental outcomes

Gumbmann, 1978[2]	0, 0.5, 2.5, 5.0% Diet	1 year	Rat (Fischer) 6/sex/group	Body weight, organ weight, histopathology	2500 (5.0%)	Slightly decreased pup survivability in mid- and high-dose in F_3 generation (not clearly described or discussed)
	0, 10% Diet	11 months	Rat (Sprague Dawley), males, number not given	Body weight, organ weight, histopathology	Not derived	Statistically significant decrease in final body weight and statistically significant increase in relative testes weight compared to control
	0, 0.5, 2.5, 5.0% Diet	2 years	Rat (Fischer), 24/sex/group	Mortality, body weight, hematology, blood chemistry, urinalysis, organ weight, histopathology	Not derived	Outcome unclear due to confounding factors in dietary deficiencies
	0, 200, 1000, 2000 mg/kg bw/day (high-dose was ~6% in diet)	2 years	Dog (Beagle), 3/sex/group	General physical exam, hematology, blood chemistry, urinalysis, gross necropsy, organ weights, histopathology	1000	Statistically significant increase in thyroid weight at high-dose
Booth, 1965 unpublished [25]	0, 0.64, 6.4, 64, 128 mg/kg bw/day Diet	148 days	Rat (unknown strain), 5/sex/group	Body weight, reproductive performance (number of litters, number of pups per litter, pup body weight), hematology, gross necropsy, organ weight, histopathology	128	-Statistically significant decrease body weight in male high-dose group -Liver lipidosis in unspecified female dose group -Decreased number weaned pups at all dose levels compared to controls, not seen at a higher dose level by same authors.

6.3 Additional Scientific Studies

6.3.1 Human Studies

After a search of the public domain, NHDC was not found to have been formally investigated in any published clinical trials involving healthy humans.

6.4 Authoritative Safety Opinions

6.4.1 Select Committee on GRAS Substances

SCOGS evaluated the safety data on *C. aurantium* and concluded its natural extractives were generally recognized as safe (21 CFR 182.20), although it is understood that this regulation pertains to low levels used for flavoring.[45] Additionally, SCOGS evaluated common impurities within NHDC such as hesperidin and naringin and concluded they were GRAS when used at levels used currently or may be reasonably expected in the future.[17]

6.4.2 European Food Safety Authority

In 1985, NHDC was first reviewed by the European Commission's Scientific Committee on Food (SCF).[46] At that time it was determined that there was no clear NOAEL for the ingredient and more studies were requested. NHDC was examined again in 1989 as a sweetener and the lowest NOAEL of all the studies was determined to be 500 mg/kg bw/day, and an acceptable daily intake of 5 mg/kg bw/day was established.[47] It is listed as E959 under Commission Directive 2008/60/EC.[14] In 2010, NHDC was endorsed by EFSA's Panel on Food Contact Materials, Enzymes, Flavorings, and Processing Aids (CEF).[48]

6.4.3 World Health Organization

In its 2012 report, the Joint FAO/WHO Expert Committee on Food Additives referenced NHDC in its review of other similarly structured compounds, referring to an adequate NOAEL for NHDC as 760 mg/kg bw/day per the Lina et al. study.[25, 41]

6.4.4 United States

A thorough search for the current regulatory status of NHDC and related compounds relevant to use in human food in the United States was conducted. A summary of the pertinent search results is shown below:

- An FDA GRAS notice (GRN 796) was found in the FDA GRAS Notice Inventory database for hesperidin as a nutritive ingredient for use as an ingredient in flavored milk and imitation milk drinks, dry powdered milk mixtures (not reconstituted), yogurt, coconut beverages, cookies, cereal, cereal/granola/nutrition bars, fruit/fruit flavored and vegetable juices/drinks, table fats and vegetable oils, candies (chocolate and dietetic candy), tea, carbonated soft drinks, fortified water, nutrition drinks, nutrition powders, energy drinks, and sports drinks at the level of 500 mg per serving. GRN 796 received FDA's "no objections" letter on February 20, 2019.

6.5 Allergenicity

NHDC does not contain or have added, and is manufactured in a facility free of, all eight major allergens (milk, egg, fish, Crustacean shellfish, tree nuts, wheat, peanuts, and soybeans) identified, and required to be disclosed in labeling, in the Food Allergen Labeling and Consumer Protection Act (FALCPA). Additionally, NHDC does not contain gluten, oats, celery, mustard, sesame seeds, sulfur dioxide and sulfites or any derivatives or products of the aforementioned.

No reports of allergic reactions to NHDC were found in our investigations.

6.6 Past Sales and Reported Adverse Events

According to HealthTech BioActives, an approximate total of 16,000 kg of the company's NHDC was sold in 2018 alone. Total sales in the last 5 years are found in Table 13. HealthTech BioActives states that no adverse event reports associated with the consumption of this ingredient to date have been received by the company.

Table 13. Past 5 years sales history

	2014	2015	2016	2017	2018
Total Sold Worldwide (kg)	27,088	24,844	25,897	12,455	15,378

6.7 Basis for the GRAS Conclusion

HealthTech BioActives' NHDC has been the subject of a thorough safety assessment as described above. The totality of evidence supporting safety is comprised of data and information that establish the safety of NHDC under the conditions of its intended use and data and information that is corroborative of safety. The general availability and general acceptance, throughout the scientific community of qualified experts, of the data and information that establish the safety

of NHDC under its intended conditions of use establish the general recognition of this data and information. Together, the establishment of safety based on scientific procedures and its general recognition form the basis for HealthTech BioActives' conclusion of GRAS status of NHDC for its intended use.

6.7.1 Data and Information that Establish Safety

The scientific data, information, and methods forming the basis of this conclusion are:

- The establishment of identity and the method of manufacture and specifications, demonstrating the safe production and the high-quality control for this extract;
- The totality of evidence from bacterial reverse mutation tests, and an *in vivo* gavage mammalian micronucleus study in mice suggesting a lack of genotoxic potential of NHDC;
- The 90-day repeated dose oral toxicity study in rats by Lina et al. (1990), establishing the lack of adverse health effects and/or target organs of repeated exposure to NHDC, with a NOAEL of 750 mg/kg bw/day, the highest dose tested.
- Additional repeated dose oral toxicity studies in rodents (1-year) and dogs (2-years) by Gumbmann et al. (1978), with a NOAEL of 5% of the diet (2500 mg/kg bw/day) in rats, and 1000 mg/kg bw/day in dogs, and a reproductive study in rats by Waalkens-Berendsen et al. (2004), suggesting a NOAEL of 3100 mg/kg bw/day, the highest dose tested.
- An established ADI of 5 mg/kg bw/day for NHDC in Europe.

In the GLP, OECD compliant ninety-day study by Lina et al., the NOAEL was 750 mg/kg bw/day in male and female Wistar rats. Based on the intended use of the ingredient as a sweetener at a maximum addition level of 10–1000 parts per million (ppm) depending on the food category, the NOAEL allows for an adequate MOS (NOAEL/Exposure; 750 mg/kg/0.5 mg/kg) of 1500-fold for the 90th lifetime percentile of highest users relative to body weight basis, which is children (ages 2–12), supporting a conclusion that the intended use of NHDC is reasonably certain to be safe. The aggregate NHDC estimated 90th percentile lifetime exposure on a daily basis for the total population is 17.2 mg/day or 0.29 mg/kg bw/day (allowing for a MOS of approximately 2600-fold). In conclusion, NHDC is reasonably certain to be safe under the conditions of its intended use.

6.7.2 Data and Information that is Corroborative of Safety

The safety of NHDC is corroborated by an unpublished, *in vitro* chromosomal aberration assay on NHDC suggesting no genotoxicity concerns, and an unpublished 90-day repeated dose toxicity study by Booth et al., summarized by JECFA, with a NOAEL of 500 mg/kg bw/day (which would still allow for a MOS of over 1700 for the total population based on estimated exposures (500/0.29 mg/kg bw/day)). The 2-year carcinogenicity study by Gumbmann et al. was considered inconclusive due to issues related to nutrient deficiencies in the study; however, animals supplemented with nutrients in the high-dose NHDC groups did not show any differences in tumor or non-neoplastic lesions compared to controls. Additionally corroborative is the 5-year history of sales for human consumption of approximately 105,000 kg (more than approximately 5.8 billion 18 mg servings) of HealthTech BioActives' NHDC over a 5-year period with no serious adverse event reported.

6.7.3 General Recognition

The scientific data, information, and methods herein reported, that provide the basis of this GRAS conclusion by scientific procedures, are published and available in the public domain. Part 7 of this GRAS notice contains the citations for the published studies. These publicly available data and information fulfill the requirement of the GRAS standard for general availability of the scientific data, information, and methods relied on to establish the safety of NHDC for its intended conditions of use. The peer-review of the published studies and lack of Letters to the Editor or other dissenting opinions provide ample evidence of general recognition among qualified experts that there is reasonable certainty that consumption of NHDC for its intended use is not harmful. The general availability and acceptance of these scientific data, information, and methods satisfy the criterion of the GRAS standard that general recognition of safety requires common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use.

6.8 Data and Information that are Inconsistent with the GRAS Conclusion

We have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with our conclusion of GRAS status.

6.9 Information that is Exempt from Disclosure under FOIA

There are no data or information in this report that are considered trade secret or commercial or financial information that is privileged or confidential.

Part 7: Supporting Data and Information

Initial literature searches for the safety assessment described in Part 6 of this GRAS notice were conducted through November 13, 2019.

7.1 Data and Information that are *not* Generally Available

Several referenced studies are not found in the public domain. These include:

- Multiple studies performed by Booth et al. that were referenced in the EFSA's JECFA report (subparts 6.1, 6.2.5.1, and 6.2.9) and
- The chromosomal aberration study performed by Grindey in 2018 and referenced in the HealthTech Bioactives' Toxicology Report (subpart 6.2.2).

As they were unpublished and not in the public domain, these studies cannot be considered pivotal to the determination of GRAS. However, due to the fact that there are other published, GLP and OECD compliant genotoxicity[31-37] and oral sub-chronic and chronic studies[2, 41] whose results are favorable to a GRAS conclusion, these studies provide corroborative evidence to the safety of NHDC at the specified use levels.

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From:	Kayla Preece
To:	Harry, Molly
Cc:	Amy Clewell; John Endres; Jared Brodin
Subject:	GRN 902: Response to FDA Questions
Date:	Tuesday, May 26, 2020 11:04:30 AM
Attachments:	FDAResponseEmail-Final.docx Gumbmann 1978.pdf contaminant and pesticide (018D068).pdf contaminant and pesticide (019C045).pdf contaminant and pesticide I (016K007).pdf contaminant and pesticide II (016K007).pdf contaminant and pesticide III (016K007).pdf

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Hello Ms. Harry-

Attached you will find requested documentation as well as responses to the questions from the FDA. Please let us know if you have any additional questions.

--

Best regards,
Kayla

Kayla Preece, ND

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GRUPO FERRER
Joaquina, Helena
Raiguero, 143-145
30588 ZENETA (MURCIA)

Laboratory reference	19/PN028074		
Customer reference	1010108, 018D068		
Type of sample	NEOHESPERIDINA DC	**Weight**	371g
Status	Grind	**Temperature at reception**	Room
Date of reception	25/02/2019 15:05:23	**Expiration date**	25/05/2019
Packaging	Customer	**Transport**	DHL
Quotation reference	DES180463	**Regional agency**	Phytocontrol Alicante

Ordered analysis

Pesticides	Dithiocarbamates (CS2) Multirésidus GC250 + Multirésidus LC350
Heavy metals	5 Métaux
Mycotoxines	Aflatoxins B1 B2 G1 G2
Polycyclic aromatic hydrocarbons (PaH)	4 PAHs
Other contaminants	Melamine

Sample at reception

Results of analysis

	Result	Unit	LOQ	Limit	End of analysis
Pesticides					
Multiresidues GC 250	ND				05/03/2019
Multiresidues LC 350	ND				04/03/2019
Specific monoresidues					
Dithiocarbamates (CS2)	ND	mg/kg	0,05		27/02/2019
Heavy metals					
Lead*	< 0,04	mg/kg	0,04		05/03/2019
Cadmium*	< 0,01	mg/kg	0,01		05/03/2019
Arsenic*	< 0,03	mg/kg	0,03		05/03/2019
Mercury*	< 0,005	mg/kg	0,005		05/03/2019
Palladium*	0,42 ± 0,08	mg/kg	0,01		05/03/2019
Mycotoxines					
Aflatoxin B1	ND	µg/kg	1		26/02/2019
Aflatoxin B2	ND	µg/kg	1		26/02/2019
Aflatoxin G1	ND	µg/kg	1		26/02/2019
Aflatoxin G2	ND	µg/kg	1		26/02/2019
Aflatoxins (Σ B1,B2, G1,G2)	ND	µg/kg	1		26/02/2019
Polycyclic aromatic hydrocarbons (PaH)					
Benzo(a)pyrene	ND	µg/kg	0,5		27/02/2019
Benzo(a)anthracene	ND	µg/kg	0,5		27/02/2019
Benzo(b)fluoranthene	ND	µg/kg	0,5		27/02/2019
Chrysene	ND	µg/kg	0,5		27/02/2019
Sum of the 4 HAP	ND	µg/kg	0,5		27/02/2019
Other contaminants					
Melamin	ND	mg/kg	0,1		27/02/2019

Detail of the analyzed parameters and the methods used in following page(s)

Legend

ND = Not Detected D = Detected LOQ = Limit of Quantification NA = Not Analysed

(m):assayed without associated analyte(s) with analyzes carried out only within the scope of Regulation No 396/2005 and its amendments or Directives 2006/125 / EC and 2006/141 / EC.

Used methods mentioned in following page(s) :

MOC3/05 version 0 : Determination of pesticide residue content by GC-MS-MS : internal method.

MOC3/11 version 0 : Determination of the content in dithiocarbamates on fruits and vegetables by GC-MS/HS : internal method.

MOC3/23 version 2 : Determination of the content of PAH by GC-MS/MS : internal method.

MOC3/85 version 0 : Determination of heavy metals elements (metallic and non-metallic) in all product of animal and vegetable origin including babyfood by ICP-MS: internal method.

MOC3111 version 2 : Determination of mycotoxins in product of plant origin LC-MS-MS: internal method.

MOC3134 version 1 : Determination of melamin content in feed and food, including babyfood, by LC-MS/MS : internal method

MOC3407 version 0 : Determination of pesticide residue content by LC-MS-MS : internal method.

Comments

The analytical results are only valid within the perimeter of application of the used method.

The limit values are based on the regulations and / or guidelines and / or recommendations listed below :

Pesticides

• Human and Animal Nutrition (raw materials): Regulation (EC) No 396/2005 and subsequent amendments on maximum residue levels of pesticides in or on food and feed of plant and animal origin.
• Animal Feed: Directive 2002/32 and subsequent amendments on undesirable substances in animal feed. The maximum levels apply to feedingstuffs with a moisture content of 12%.

Heavy metals

• Food:
Regulation (EC) No 1881/2006 and subsequent amendments setting maximum levels for certain contaminants in foodstuffs.
Copper and Mercury (depending on matrix) : Regulation (EC) No 396/2005 and subsequent amendments on maximum residue levels of pesticides in or on food and feed of

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plant and animal origin.
• For wine: OIV - Maximum acceptable limits of various elements in wine (2015 edition).
• Animal Feed: Directive 2002/32 and subsequent amendments on undesirable substances in animal feed. The maximum levels apply to feedingstuffs with a moisture content of 12%.
• Food additives: Regulation (EU) n°231/2012 and subsequent amendments laying down specifications for food additives listed in Annexes II and III to Regulation (EC) N°1333/2008 of the European Parliament and of the council.

Mycotoxines

• Food : Regulation (EC) No 1881/2006 and subsequent amendments setting maximum levels for certain contaminants in foodstuffs.
Recommendations 2013/165/UE on the presence of T-2 toxin and HT-2 in cereals and cereal products.
• Animal Feed: Directive 2002/32 and subsequent amendments on undesirable substances in animal feed. The maximum levels apply to feedingstuffs with a moisture content of 12%.

Polycyclic aromatic hydrocarbons (PaH)

• Food: Regulation (EC) No 1881/2006 and subsequent amendments setting maximum levels for certain contaminants in foodstuffs.
Units may vary depending on the matrix: µg/kg (raw) or µg/kg MG (fat).

more information :

Melamin : According EC 594/2012, the maximum limit of melamin on food is 2,5 mg/kg unless it can be proven that the level of melamine higher than 2,5 mg/kg is the consequence of authorized use of cyromazine as insecticide. The melamine level shall not exceed the level of cyromazine.

This provision does not apply on baby food. The limit on powdered infant formulae and follow-on formulae is 1mg/kg

Signature

The updating of regulatory information as regard to the European regulation or any other published standard is ensured by our Regulatory Monitoring department.

Report validated by :

Audrey COSTE
Analytical Validation

- This certificate was electrically produced and validated. The name and the function of the persons in charge on it document were produced on a protected procedure and personalised. This certificate is authentic. A paper version signed of this document can be obtained on simple demand.
- The results of analysis concern only objects subjected to the analysis.
- In absence of accurate and of opposite indication, the Limit of Detection is equal to half of the Limit of Quantification (excluding subcontracted parameters).
- The reproduction of this report is authorized only in its complete form except when authorised by the laboratory.
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Pesticides

Multiresidues GC 250

FB3/02.c vers. 24 (01/02/2019)

Unit ÷ : mg/kg	Result	LOQ	method
1,4-Dimethylnaphtalene	ND	0,01	MOC3/05
2,4,6 trichlorophenol (TCP) (m	ND	0,01	MOC3/05
2-Phenylphenol(somme)	ND		
2-Methoxybiphenyl	ND	0,01	MOC3/05
2-Phenylhydroquinone	ND	0,01	MOC3/05
2-Phenylphenol	ND	0,01	MOC3/05
3,4-dichloroaniline	ND	0,01	MOC3/05
4,4-Dichlorobenzophenone	ND	0,01	MOC3/05
Acetochlore	ND	0,01	MOC3/05
Acibenzolar-S-methyl (m)	ND	0,01	MOC3/05
Aclonifen	ND	0,01	MOC3/05
Acrinathrine	ND	0,01	MOC3/05
Alachlore	ND	0,01	MOC3/05
Ametryn	ND	0,01	MOC3/05
Amisulbrom	ND	0,01	MOC3/05
Atrazine	ND	0,01	MOC3/05
Benalaxyl dont Benalaxyl-M	ND	0,01	MOC3/05
Bendiocarb	ND	0,01	MOC3/05
Benfluraline	ND	0,01	MOC3/05
Benoxacor	ND	0,01	MOC3/05
Bifenox	ND	0,01	MOC3/05
Bifenthrine	ND	0,01	MOC3/05
Biphenyl	ND	0,01	MOC3/05
Bitertanol	ND	0,01	MOC3/05
Bromocyclen	ND	0,01	MOC3/05
Bromophos-ethyl	ND	0,01	MOC3/05
Bromophos-methyl	ND	0,01	MOC3/05
Bromopropylate	ND	0,01	MOC3/05
Butachlor	ND	0,01	MOC3/05
Butraline	ND	0,01	MOC3/05
Captafol	ND	0,01	MOC3/05
Captan(somme)	ND		
Captan	ND	0,01	MOC3/05
Tetrahydrophtalimide (THPI	ND	0,01	MOC3/05
Carbaryl	ND	0,01	MOC3/05
Carbofuran(+3-hydroxy) (m)	ND		
Carbofuran	ND	0,01	MOC3/05
Carbofuran-3-Hydroxy	ND	0,01	MOC3/05
Furathiocarbe	ND	0,01	MOC3/05
Carbophenothion	ND	0,01	MOC3/05
Carfentrazone-ethyl	ND	0,01	MOC3/05
Chlorbenside	ND	0,01	MOC3/05
Chlordane(cis+trans)	ND	0,01	MOC3/05
Chlorfenapyr	ND	0,01	MOC3/05
Chlorfenson	ND	0,01	MOC3/05
Chlorfenvinphos	ND	0,01	MOC3/05
Chlorobenzilate	ND	0,01	MOC3/05
Chlorothalonil	ND	0,01	MOC3/05
Chlorpropham	ND	0,01	MOC3/05
Chlorpyrifos	ND	0,01	MOC3/05
Chlorpyrifos-methyl	ND	0,01	MOC3/05
Chlorthal dimethyl	ND	0,01	MOC3/05
Chlorthiophos	ND	0,01	MOC3/05
Chlozolinate	ND	0,01	MOC3/05
Clomazone	ND	0,01	MOC3/05
Coumaphos	ND	0,01	MOC3/05
Cyfluthrine (β+γ)	ND	0,01	MOC3/05
Cyhalofop-butyl	ND	0,01	MOC3/05
Cyhalothrine(∑ des isomères)	ND	0,01	MOC3/05
Cymiazole	ND	0,01	MOC3/05
Cypermethrine(α+β+θ+ζ)	ND	0,01	MOC3/05
Cyproconazole	ND	0,01	MOC3/05
Cyprodinil	ND	0,01	MOC3/05
DDT(Σ des isomères)	ND		
o,p'-DDT	ND	0,01	MOC3/05
p,p'-DDT	ND	0,01	MOC3/05
p,p'-DDE	ND	0,01	MOC3/05
p,p'-TDE(DDD)	ND	0,01	MOC3/05
Deltamethrine	ND	0,01	MOC3/05
Demeton-S-methyl	ND	0,01	MOC3/05
Dialifos	ND	0,01	MOC3/05
Dichlobenil	ND	0,01	MOC3/05
Dichlofenthion	ND	0,01	MOC3/05
Dichlofluanide	ND	0,01	MOC3/05
Dichlorvos	ND	0,01	MOC3/05
Diclofop-methyl (m)	ND	0,01	MOC3/05
Dicofol(Σ des isomères)	ND		
Dicofol o,p'	ND	0,01	MOC3/05
Dicofol p,p'	ND	0,01	MOC3/05
Dicrotophos	ND	0,01	MOC3/05
Dieldrin(+Aldrin)	ND		
Aldrin	ND	0,01	MOC3/05
Dieldrin	ND	0,01	MOC3/05
Diethofencarb	ND	0,01	MOC3/05
Difenoconazole	ND	0,01	MOC3/05
Diflufenican	ND	0,01	MOC3/05
Dimetachlor	ND	0,01	MOC3/05
Dinitramine	ND	0,01	MOC3/05
Diphenylamine	ND	0,01	MOC3/05
Disulfoton (m)	ND	0,01	MOC3/05
Ditalimfos	ND	0,01	MOC3/05
Edifenphos	ND	0,01	MOC3/05
Endosulfan (α+β+sulfate)	ND		
Endosulfan α	ND	0,01	MOC3/05
Endosulfan β	ND	0,01	MOC3/05
Endosulfan sulfate	ND	0,01	MOC3/05
Endrin	ND	0,01	MOC3/05
Endrin-ketone	ND	0,01	MOC3/05
EPN	ND	0,01	MOC3/05
Ethalfluraline	ND	0,01	MOC3/05
Ethiofencarb	ND	0,01	MOC3/05
Ethion	ND	0,01	MOC3/05
Ethofumesate (m)	ND	0,01	MOC3/05
Ethoprophos	ND	0,01	MOC3/05
Ethoxyquine	ND	0,01	MOC3/05
Etofenprox	ND	0,01	MOC3/05
Etridiazole	ND	0,01	MOC3/05
Etrimfos	ND	0,01	MOC3/05
Famoxadone	ND	0,01	MOC3/05
Famphur	ND	0,01	MOC3/05
Fenamiphos (m)	ND	0,01	MOC3/05
Fenarimol	ND	0,01	MOC3/05
Fenazaquin	ND	0,01	MOC3/05
Fenchlorphos (m)	ND	0,01	MOC3/05
Fenhexamide	ND	0,01	MOC3/05
Fenitrothion	ND	0,01	MOC3/05
Fenobucarbe	ND	0,01	MOC3/05
Fenpropathrine	ND	0,01	MOC3/05
Fenpropimorphe	ND	0,01	MOC3/05
Fenvalerate (Σ des isomères)	ND	0,01	MOC3/05
Fipronil(+sulfone)	ND		
Fipronil	ND	0,005	MOC3/05
Fipronil-sulfone	ND	0,005	MOC3/05
Fipronil-desulfinyl	ND	0,01	MOC3/05
Fluazifop-p-butyl (m)	ND	0,01	MOC3/05
Fluchloralin	ND	0,01	MOC3/05
Flucythrinate	ND	0,01	MOC3/05
Fludioxonil	ND	0,01	MOC3/05
Flufenacet (m)	ND	0,01	MOC3/05
Fluopicolide	ND	0,01	MOC3/05
Flurochloridone	ND	0,01	MOC3/05
Fluroxypyr-methylheptyl ester (m)	ND	0,01	MOC3/05
Flusilazole	ND	0,01	MOC3/05
Flutolanil	ND	0,01	MOC3/05
Flutriafol	ND	0,01	MOC3/05
Fluvalinate (Tau)	ND	0,01	MOC3/05
Folpet(somme)	ND		
Folpet	ND	0,01	MOC3/05
Phtalimide	ND	0,01	MOC3/05
Fonofos	ND	0,01	MOC3/05
Formothion	ND	0,01	MOC3/05
Furalaxyl	ND	0,01	MOC3/05
Haloxyfop-2-ethoxyethyl (m)	ND	0,01	MOC3/05
Haloxyfop-methyl(R+S) (m)	ND	0,01	MOC3/05
HCB	ND	0,01	MOC3/05
HCH alpha	ND	0,01	MOC3/05
HCH beta	ND	0,01	MOC3/05
HCH gamma	ND	0,01	MOC3/05
Heptachlore(+epoxyde)	ND		
Heptachlore	ND	0,01	MOC3/05
Heptachlore epoxyde cis-	ND	0,01	MOC3/05
Heptachlore epoxyde trans-	ND	0,01	MOC3/05
Heptenophos	ND	0,01	MOC3/05
Hexazinone	ND	0,01	MOC3/05
Iodofenphos	ND	0,01	MOC3/05
Iprodione	ND	0,01	MOC3/05
Isobenzan	ND	0,01	MOC3/05
Isodrine	ND	0,01	MOC3/05
Isofenphos-ethyl	ND	0,01	MOC3/05
Isofenphos-methyl	ND	0,01	MOC3/05
Isoxadifen-ethyl	ND	0,01	MOC3/05
Leptophos	ND	0,01	MOC3/05
Malathion(+Malaoxon)	ND		
Malathion	ND	0,01	MOC3/05
Malaoxon	ND	0,01	MOC3/05
Mepanipyrim	ND	0,01	MOC3/05
Mepronil	ND	0,01	MOC3/05
Metalaxyl dont Metalaxyl-M	ND	0,01	MOC3/05
Metazachlor	ND	0,01	MOC3/05
Methacrifos	ND	0,01	MOC3/05
Methidathion	ND	0,01	MOC3/05
Methoxychlore	ND	0,01	MOC3/05

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Metolachlore dont S-Metolachlore	ND	0,01	MOC3/05
Mirex	ND	0,01	MOC3/05
Myclobutanil	ND	0,01	MOC3/05
Nitrofene	ND	0,01	MOC3/05
Nitrothal isopropyle	ND	0,01	MOC3/05
Oxadiazon	ND	0,01	MOC3/05
Oxadixyl	ND	0,01	MOC3/05
Oxyfluorfene	ND	0,01	MOC3/05
Parathion-ethyl	ND	0,01	MOC3/05
Parathion-methyl (m)	ND	0,01	MOC3/05
PCB 028	ND	0,01	MOC3/05
PCB 052	ND	0,01	MOC3/05
PCB 101	ND	0,01	MOC3/05
PCB 118	ND	0,01	MOC3/05
PCB 138	ND	0,01	MOC3/05
PCB 153	ND	0,01	MOC3/05
PCB 180	ND	0,01	MOC3/05
Penconazole	ND	0,01	MOC3/05
Pendimethaline	ND	0,01	MOC3/05
Pentachloroanisole	ND	0,01	MOC3/05
Permethrine(cis + trans)	ND	0,01	MOC3/05
Perthane	ND	0,01	MOC3/05
Phenothrine	ND	0,01	MOC3/05
Phenthoate	ND	0,01	MOC3/05
Phosalone	ND	0,01	MOC3/05
Piperonyl butoxide	ND	0,01	MOC3/05
Pirimicarb	ND	0,01	MOC3/05
Pirimiphos-ethyl	ND	0,01	MOC3/05
Pirimiphos-methyl	ND	0,01	MOC3/05
Plifenate	ND	0,01	MOC3/05
Pretilachlore	ND	0,01	MOC3/05
Procymidone	ND	0,01	MOC3/05
Profenophos	ND	0,01	MOC3/05
Prometryn	ND	0,01	MOC3/05
Propachlore (m)	ND	0,01	MOC3/05
Propazine	ND	0,01	MOC3/05
Propetamphos	ND	0,01	MOC3/05
Prophame	ND	0,01	MOC3/05
Propiconazole	ND	0,01	MOC3/05
Propyzamide	ND	0,01	MOC3/05
Proquinazid	ND	0,01	MOC3/05
Prosulfocarbe	ND	0,01	MOC3/05
Prothiophos	ND	0,01	MOC3/05
Prothoate	ND	0,01	MOC3/05
Pyrazophos	ND	0,01	MOC3/05
Pyridaben	ND	0,01	MOC3/05
Pyridalyl	ND	0,01	MOC3/05
Pyridaphenthion	ND	0,01	MOC3/05
Pyrifenox	ND	0,01	MOC3/05
Pyrimethanil	ND	0,01	MOC3/05
Pyriproxyfen	ND	0,01	MOC3/05
Quinalphos	ND	0,01	MOC3/05
Quinomethionate	ND	0,01	MOC3/05
Quinoxyfen	ND	0,01	MOC3/05
Quintozene(+PCA)	ND		
Quintozene	ND	0,01	MOC3/05
Pentachloroaniline (PCA)	ND	0,01	MOC3/05
Quizalofop-ethyl	ND	0,01	MOC3/05
S 421	ND	0,01	MOC3/05
Sebuthylazine	ND	0,01	MOC3/05
Secbumeton	ND	0,01	MOC3/05
Sulfotep	ND	0,01	MOC3/05
Sulprofos	ND	0,01	MOC3/05
Tebuconazole	ND	0,01	MOC3/05
Tebufenpyrad	ND	0,01	MOC3/05
Tebupirimphos	ND	0,01	MOC3/05
Tecnazene	ND	0,01	MOC3/05
Tefluthrine	ND	0,01	MOC3/05
Terbacil	ND	0,01	MOC3/05
Terbufos	ND	0,01	MOC3/05
Terbuthylazine	ND	0,01	MOC3/05
Terbutryne	ND	0,01	MOC3/05
Tetrachlorvinphos	ND	0,01	MOC3/05
Tetradifon	ND	0,01	MOC3/05
Tetramethrine	ND	0,01	MOC3/05
Tetrasul	ND	0,01	MOC3/05
Tolclofos-methyl	ND	0,01	MOC3/05
Tolylfluanid (m)	ND	0,01	MOC3/05
Tralomethrine	ND	0,01	MOC3/05
Transfluthrine	ND	0,01	MOC3/05
Triadimefon	ND	0,01	MOC3/05
Triadimenol	ND	0,01	MOC3/05
Triallate	ND	0,01	MOC3/05
Triamiphos	ND	0,01	MOC3/05
Triazophos	ND	0,01	MOC3/05
Trichloronat	ND	0,01	MOC3/05
Trifluraline	ND	0,01	MOC3/05
Valifenalate	ND	0,01	MOC3/05
Vinclozoline	ND	0,01	MOC3/05
Zoxamide	ND	0,01	MOC3/05

Multiresidues LC 350

FB3/02.A vers. 2 (07/01/2019)

	Result	LOQ	method
Unit ◊ : mg/kg			
Cinmethylin	ND	0,01	MOC3407
Prallethrin	ND	0,01	MOC3407
2,4 D(acide libre) (m)	ND	0,01	MOC3407
6-Benzyladenine	ND	0,01	MOC3407
Abamectine(somme)	ND		
Avermectine B1a	ND	0,01	MOC3407
Avermectine B1b	ND	0,01	MOC3407
8,9-Z-AvermectinB1a	ND	0,01	MOC3407
Acephate	ND	0,01	MOC3407
Acequinocyl	ND	0,01	MOC3407
Acetamipride	ND	0,01	MOC3407
Aldicarb(somme)	ND		
Aldicarb	ND	0,01	MOC3407
Aldicarb sulfone	ND	0,01	MOC3407
Aldicarb sulfoxide	ND	0,01	MOC3407
Ametoctradine	ND	0,01	MOC3407
Amidosulfuron	ND	0,01	MOC3407
Amitraze(somme)	ND		
Amitraze	ND	0,01	MOC3407
2,4-Dimethylaniline	ND	0,01	MOC3407
N-(2,4-Dimethylphenyl)formamide	ND	0,01	MOC3407
N-2,4-Dimethylphenyl-Np-methylformamidine HCl	ND	0,01	MOC3407
Amitrole	ND	0,01	MOC3407
Asulam	ND	0,01	MOC3407
Atrazine desisopropyl	ND	0,01	MOC3407
Atrazine-desethyl(+deisopropy	ND	0,01	MOC3407
Azaconazole	ND	0,01	MOC3407
Azadirachtin(somme)	ND		
Azadirachtin A	ND	0,01	MOC3407
Azadirachtin B	ND	0,01	MOC3407
Azamethiphos	ND	0,01	MOC3407
Azimsulfuron	ND	0,01	MOC3407
Azinphos-ethyl	ND	0,01	MOC3407
Azinphos-methyl	ND	0,01	MOC3407
Azoxystrobine	ND	0,01	MOC3407
Beflubutamide	ND	0,01	MOC3407
Carbofuran(somme LC) (m)	ND		
Benfuracarbe	ND	0,01	MOC3407
Carbosulfan	ND	0,01	MOC3407
Bensulfuron-methyl	ND	0,01	MOC3407
Bentazone(somme) (m)	ND		
Bentazone	ND	0,01	MOC3407
Bentazone 8 hydroxy	ND	0,01	MOC3407
Bentazone 6 hydroxy	ND	0,01	MOC3407
Benthiavalicarb-isopropyl (m)	ND	0,01	MOC3407
Benzovindiflupyr	ND	0,01	MOC3407
Bifenazate(+diazene)	ND		
Bifenazate	ND	0,01	MOC3407
Bifenazate-diazene	ND	0,01	MOC3407
Bispyribac-sodium	ND	0,01	MOC3407
Bixafen	ND	0,01	MOC3407
Boscalide	ND	0,01	MOC3407
Bromacil	ND	0,01	MOC3407
Bromoxynil	ND	0,01	MOC3407
Bromuconazole	ND	0,01	MOC3407
Bupirimate	ND	0,01	MOC3407
Buprofezin	ND	0,01	MOC3407
Butoxycarboxim	ND	0,01	MOC3407
Butoxycarboxim-sulfoxide	ND	0,01	MOC3407
Buturon	ND	0,01	MOC3407
Cadusafos	ND	0,01	MOC3407
Carbendazime(+Benomyl)	ND	0,01	MOC3407
Carbétamide (∑ de la carbétamide et de son isomère)	ND	0,01	MOC3407
Carboxine	ND	0,01	MOC3407
Chlorantraniliprole	ND	0,01	MOC3407
Chlorfluazuron	ND	0,01	MOC3407
Chloridazon(somme)	ND		
Chloridazon	ND	0,01	MOC3407
Chloridazon-desphenyl	ND	0,01	MOC3407
Chloridazon-methyl-despheny	ND	0,01	MOC3407
Chlorotoluron	ND	0,01	MOC3407
Chloroxuron	ND	0,01	MOC3407
Chlorsulfuron	ND	0,01	MOC3407
Chromafenozide	ND	0,01	MOC3407
Cinidon-ethyl	ND	0,01	MOC3407
Cinosulfuron	ND	0,01	MOC3407
Clethodim(somme) (m)	ND		
Clethodim	ND	0,01	MOC3407
Clethodim sulfoxide	ND	0,01	MOC3407
Sethoxydim	ND	0,01	MOC3407
Clodinafop-propargyl	ND	0,01	MOC3407
Clofentezine	ND	0,01	MOC3407

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Clothianidine	ND 0,01 MOC3407
Cyanazine	ND 0,01 MOC3407
Cyantraniliprole	ND 0,01 MOC3407
Cyazofamide	ND 0,01 MOC3407
Cycloxydime (m)	ND 0,01 MOC3407
Cycluron	ND 0,01 MOC3407
Cyflufenamid	ND 0,01 MOC3407
Cymoxanil	ND 0,01 MOC3407
Cyprosulfamide	ND 0,01 MOC3407
Cyromazine	ND 0,01 MOC3407
Daminozide (m)	ND 0,01 MOC3407
Dazomet (m)	ND 0,01 MOC3407
Demeton-S	ND 0,01 MOC3407
Oxydemeton-methyl(somme)	ND
Demeton-S-methyl sulfone	ND 0,01 MOC3407
Oxydemeton-methyl	ND 0,01 MOC3407
Desmediphame	ND 0,01 MOC3407
Desmetryn	ND 0,01 MOC3407
Diafenthiuron	ND 0,01 MOC3407
Diallate	ND 0,01 MOC3407
Diazinon	ND 0,01 MOC3407
Dichlorprop(acide libre) (m)	ND 0,01 MOC3407
Diclobutrazol	ND 0,01 MOC3407
Dicloran	ND 0,01 MOC3407
Difenacoum	ND 0,01 MOC3407
Difenamide	ND 0,01 MOC3407
Difethialone	ND 0,01 MOC3407
Diflubenzuron	ND 0,01 MOC3407
Dimethenamid-P(Σ des isomeres)	ND 0,01 MOC3407
Dimethoate	ND 0,01 MOC3407
Dimethomorphe(Σ des isomeres)	ND 0,01 MOC3407
Dimoxystrobine	ND 0,01 MOC3407
Diniconazole(Σ des isomères)	ND 0,01 MOC3407
Dinocap(Σ des isomères) (m)	ND 0,01 MOC3407
Dinoseb (m)	ND 0,01 MOC3407
Dinotefuran	ND 0,01 MOC3407
Dinoterb	ND 0,01 MOC3407
Disulfoton-sulfoxe(+sulfoxide) (m)	ND
Disulfoton-sulfone	ND 0,01 MOC3407
Disulfoton-sulfoxide	ND 0,01 MOC3407
Dithianon	ND 0,01 MOC3407
Diuron	ND 0,01 MOC3407
DMST (m)	ND 0,01 MOC3407
DNOC	ND 0,01 MOC3407
Dodemorphe	ND 0,01 MOC3407
Dodine	ND 0,01 MOC3407
Emamectine-benzoate B1a	ND 0,01 MOC3407
Emamectine-benzoate B1b	ND 0,01 MOC3407
Epoxiconazole	ND 0,01 MOC3407
EPTC	ND 0,01 MOC3407
Ethametsulfuron methyl	ND 0,01 MOC3407
Ethidimuron	ND 0,01 MOC3407
Ethiofencarb sulfone	ND 0,01 MOC3407
Ethiofencarb sulfoxide	ND 0,01 MOC3407
Ethiprole	ND 0,01 MOC3407
Ethirimol	ND 0,01 MOC3407
Ethoxysulfuron	ND 0,01 MOC3407
Etoxazole	ND 0,01 MOC3407
Fenamidone	ND 0,01 MOC3407
Fenamiphos-sulfone(+sulfoxide) (m)	ND
Fenamiphos-sulfone	ND 0,01 MOC3407
Fenamiphos-sulfoxide	ND 0,01 MOC3407
Fenbuconazole	ND 0,01 MOC3407
Fenchlorphos oxon (m)	ND 0,01 MOC3407
Fenoxaprop-ethyl	ND 0,01 MOC3407
Fenoxycarbe	ND 0,01 MOC3407
Fenpropidine	ND 0,01 MOC3407
Fenpyrazamine	ND 0,01 MOC3407
Fenpyroximate	ND 0,01 MOC3407
Fensulfothion	ND 0,01 MOC3407
Fensulfothion-oxon	ND 0,01 MOC3407
Fensulfothion-oxon-sulfone	ND 0,01 MOC3407
Fensulfothion-sulfone	ND 0,01 MOC3407
Fenthion(somme)	ND
Fenthion	ND 0,01 MOC3407
Fenthion-sulfone	ND 0,01 MOC3407
Fenthion-sulfoxide	ND 0,01 MOC3407
Fenthion-oxon	ND 0,01 MOC3407
Fenthion-oxon-sulfone	ND 0,01 MOC3407
Fenthion-oxon-sulfoxide	ND 0,01 MOC3407
Fenuron	ND 0,01 MOC3407
Flazasulfuron	ND 0,01 MOC3407
Flonicamide(+TNFA+TNFG)	ND
Flonicamide	ND 0,01 MOC3407
TFNA	ND 0,01 MOC3407
TFNG	ND 0,01 MOC3407
Florasulam	ND 0,01 MOC3407
Fluazifop(free acid) (m)	ND 0,01 MOC3407
Fluazinam	ND 0,01 MOC3407
Flufenacet(somme) (m)	ND
Flufenacet ESA	ND 0,01 MOC3407
Flufenacet FOE 5043	ND 0,01 MOC3407
Flufenacet OA	ND 0,01 MOC3407
Flufenoxuron	ND 0,01 MOC3407
Flumetralin	ND 0,01 MOC3407
Fluometuron	ND 0,01 MOC3407
Fluopyram	ND 0,01 MOC3407
Fluoxastrobine	ND 0,01 MOC3407
Flupyradifurone	ND 0,01 MOC3407
Flupyrsulfuron methyl	ND 0,01 MOC3407
Fluquinconazole	ND 0,01 MOC3407
Fluroxypyr(acide libre) (m)	ND 0,01 MOC3407
Flurtamone	ND 0,01 MOC3407
Fluxapyroxad	ND 0,01 MOC3407
Fomesafen	ND 0,01 MOC3407
Foramsulfuron	ND 0,01 MOC3407
Forchlorfenuron	ND 0,01 MOC3407
Formetanate (hydrochloride)	ND 0,01 MOC3407
Fosthiazate	ND 0,01 MOC3407
Fuberidazole	ND 0,01 MOC3407
Furametpyr	ND 0,01 MOC3407
Furmecyclox	ND 0,01 MOC3407
Halauxifen-methyl	ND 0,01 MOC3407
Halfenprox	ND 0,01 MOC3407
Halosulfuron-methyl	ND 0,01 MOC3407
Haloxyfop(acide libre) (m)	ND 0,01 MOC3407
Hexaconazole	ND 0,01 MOC3407
Hexaflumuron	ND 0,01 MOC3407
Hexythiazox	ND 0,01 MOC3407
Hydramethylnon	ND 0,01 MOC3407
Imazalil	ND 0,01 MOC3407
Imazamox	ND 0,01 MOC3407
Imazaquin	ND 0,01 MOC3407
Imazosulfuron	ND 0,01 MOC3407
Imibenconazole	ND 0,01 MOC3407
Imidachlopride	ND 0,01 MOC3407
Indoxacarb (Σénantiomères)	ND 0,01 MOC3407
Iodosulfuron-methyl	ND 0,01 MOC3407
Ioxynil (m)	ND 0,01 MOC3407
Ipconazole	ND 0,01 MOC3407
Iprobenfos	ND 0,01 MOC3407
Iprovalicarbe	ND 0,01 MOC3407
Isazofos	ND 0,01 MOC3407
Isocarbophos	ND 0,01 MOC3407
Isofetamid	ND 0,01 MOC3407
Isoprocarb	ND 0,01 MOC3407
Isopropaline	ND 0,01 MOC3407
Isoprothiolane	ND 0,01 MOC3407
Isoproturon	ND 0,01 MOC3407
Isopyrazam	ND 0,01 MOC3407
Isoxaben	ND 0,01 MOC3407
Isoxaflutole(somme) (m)	ND
Isoxaflutole	ND 0,01 MOC3407
RPA 202248	ND 0,01 MOC3407
Isoxathion	ND 0,01 MOC3407
Kresoxim-methyl	ND 0,01 MOC3407
Lenacil	ND 0,01 MOC3407
Linuron	ND 0,01 MOC3407
Lufenurone	ND 0,01 MOC3407
Mandipropamide	ND 0,01 MOC3407
MCPA+MCPB (m)	ND
MCPA	ND 0,01 MOC3407
MCPB	ND 0,01 MOC3407
Mecarbam	ND 0,01 MOC3407
Mefenacet	ND 0,01 MOC3407
Mephosfolan	ND 0,01 MOC3407
Meptyldinocap-phenol (2,4-DNOP) (m)	ND 0,01 MOC3407
Mesosulfuron-methyl	ND 0,01 MOC3407
Mesotrione	ND 0,01 MOC3407
Metaflumizone	ND 0,01 MOC3407
Metaldehyde	ND 0,01 MOC3407
Metamitron	ND 0,01 MOC3407
Metazachlor(somme) (m)	ND
Metazachlor ESA	ND 0,01 MOC3407
Metazachlor OA	ND 0,01 MOC3407
Metconazole(Σ des isomères)	ND 0,01 MOC3407
Methabenzthiazuron	ND 0,01 MOC3407
Methamidophos	ND 0,01 MOC3407
Methiocarbe(somme)	ND
Methiocarbe	ND 0,01 MOC3407
Methiocarbe-sulfone	ND 0,01 MOC3407
Methiocarbe-sulfoxide	ND 0,01 MOC3407
Methomyl	ND 0,01 MOC3407
Methoxyfenozide	ND 0,01 MOC3407
Metobromuron	ND 0,01 MOC3407
Metolachlore ESA	ND 0,01 MOC3407

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Metolachlore OA	ND 0,01 MOC3407
Metolcarb	ND 0,01 MOC3407
Metosulam	ND 0,01 MOC3407
Metoxuron	ND 0,01 MOC3407
Metrafenone	ND 0,01 MOC3407
Metribuzine	ND 0,01 MOC3407
Metsulfuron-methyl	ND 0,01 MOC3407
Mevinphos	ND 0,01 MOC3407
Milbemectin(somme)	ND
Milbemectin A3	ND 0,01 MOC3407
Milbemectin A4	ND 0,01 MOC3407
MNBA	ND 0,01 MOC3407
Molinate	ND 0,01 MOC3407
Monalide	ND 0,01 MOC3407
Monocrotophos	ND 0,01 MOC3407
Monolinuron	ND 0,01 MOC3407
Monuron	ND 0,01 MOC3407
NAD(1-naphtyl acetamide) (m	ND 0,01 MOC3407
Naled	ND 0,01 MOC3407
Napropamide	ND 0,01 MOC3407
Neburon	ND 0,01 MOC3407
Nicosulfuron	ND 0,01 MOC3407
Nitenpyram	ND 0,01 MOC3407
Norflurazon	ND 0,01 MOC3407
Novaluron	ND 0,01 MOC3407
Nuarimol	ND 0,01 MOC3407
Ofurace	ND 0,01 MOC3407
Omethoate	ND 0,01 MOC3407
Orthosulfamuron	ND 0,01 MOC3407
Oryzalin	ND 0,01 MOC3407
Oxamyl	ND 0,01 MOC3407
Oxasulfuron	ND 0,01 MOC3407
Oxathiapiprolin	ND 0,01 MOC3407
Paclobutrazol	ND 0,01 MOC3407
Paraoxon-ethyl (m)	ND 0,01 MOC3407
Pebulate	ND 0,01 MOC3407
Pencycuron	ND 0,01 MOC3407
Penflufen	ND 0,01 MOC3407
Penoxsulame	ND 0,01 MOC3407
Penthiopyrad	ND 0,01 MOC3407
pethoxamid	ND 0,01 MOC3407
Phenmediphame	ND 0,01 MOC3407
Phorate(somme)	ND
Phorate	ND 0,01 MOC3407
Phorate-sulfone	ND 0,01 MOC3407
Phorate-sulfoxide	ND 0,01 MOC3407
Phorate-oxon	ND 0,01 MOC3407
Phorate-oxon-sulfone	ND 0,01 MOC3407
Phorate-oxon-sulfoxide	ND 0,01 MOC3407
Phosmet(+oxon)	ND
Phosmet	ND 0,01 MOC3407
Phosmet-oxon	ND 0,01 MOC3407
Phosphamidon	ND 0,01 MOC3407
Phoxim	ND 0,01 MOC3407
Picolinafen	ND 0,01 MOC3407
Picoxystrobine	ND 0,01 MOC3407
Pinoxadene	ND 0,01 MOC3407
Pirimicarb-desmethyl	ND 0,01 MOC3407
Primisulfuron	ND 0,01 MOC3407
Prochloraz(somme) (m)	ND
Prochloraz	ND 0,01 MOC3407
Prochloraz metabolite BTS9608	ND 0,01 MOC3407
Prochloraz metabolite BTS40348	ND 0,01 MOC3407
Prochloraz metabolite (BTS44595)	ND 0,01 MOC3407
Prochloraz metabolite BTS44596	ND 0,01 MOC3407
Promecarb	ND 0,01 MOC3407
Prometon	ND 0,01 MOC3407
Propamocarbe	ND 0,01 MOC3407
Propanil	ND 0,01 MOC3407
Propaphos	ND 0,01 MOC3407
Propaquizafop	ND 0,01 MOC3407
Propargite	ND 0,01 MOC3407
Propoxur	ND 0,01 MOC3407
Propoxycarbazone(somme)	ND
Propoxycarbazone	ND 0,01 MOC3407
2-hydroxy-propoxycarbazon	ND 0,01 MOC3407
Prosulfuron	ND 0,01 MOC3407
Prothioconazole-desthio	ND 0,01 MOC3407
Pymetrozine	ND 0,01 MOC3407
Pyraclofos	ND 0,01 MOC3407
Pyraclostrobine	ND 0,01 MOC3407
Pyraflufen-ethyl (m)	ND 0,01 MOC3407
Pyrethrines(Somme)	ND
Cinerine I	ND 0,01 MOC3407
Cinerine II	ND 0,01 MOC3407
Jasmoline I	ND 0,01 MOC3407
Jasmoline II	ND 0,01 MOC3407
Pyrethrine I	ND 0,01 MOC3407
Pyrethrine II	ND 0,01 MOC3407
Pyridate(+Pyridafol) (m)	ND
Pyridate	ND 0,01 MOC3407
Pyridafol	ND 0,01 MOC3407
Pyrimidifen	ND 0,01 MOC3407
Pyriofenone	ND 0,01 MOC3407
Pyroquilon	ND 0,01 MOC3407
Pyroxsulam	ND 0,01 MOC3407
Quinmerac	ND 0,01 MOC3407
Quizalofop dont quizalofop-P	ND 0,01 MOC3407
Resmethrine	ND 0,01 MOC3407
Rimsulfuron	ND 0,01 MOC3407
Rotenone	ND 0,01 MOC3407
Sedaxane	ND 0,01 MOC3407
Silthiofam	ND 0,01 MOC3407
Simazine	ND 0,01 MOC3407
Simetryn	ND 0,01 MOC3407
Spinetoram XDE-175	ND
Spinetoram XDE-175-J	ND 0,01 MOC3407
Spinetoram XDE-175-L	ND 0,01 MOC3407
Spinosad(A+D)	ND
Spinosyne A	ND 0,01 MOC3407
Spinosyne D	ND 0,01 MOC3407
Spirodiclofen	ND 0,01 MOC3407
Spiromesifen	ND 0,01 MOC3407
Spirotetramate(+4 metabolites	ND
Spirotetramat	ND 0,01 MOC3407
Spirotetramate-enol	ND 0,01 MOC3407
Spirotetramat-enol-glucosid	ND 0,01 MOC3407
Spirotetramat-keto-hydroxy	ND 0,01 MOC3407
Spirotetramat-mono-hydrox	ND 0,01 MOC3407
Spiroxamine	ND 0,01 MOC3407
Sulcotrione	ND 0,01 MOC3407
Sulfosulfuron	ND 0,01 MOC3407
Sulfoxaflor	ND 0,01 MOC3407
TCMTB	ND 0,01 MOC3407
Tebufenozide	ND 0,01 MOC3407
Tebutam	ND 0,01 MOC3407
Tebuthiuron	ND 0,01 MOC3407
Teflubenzuron	ND 0,01 MOC3407
Tembotrione	ND 0,01 MOC3407
Tepraloxydim(somme) (m)	ND
Tepraloxydim	ND 0,01 MOC3407
Tepraloxydim-5-hydroxy	ND 0,01 MOC3407
Terbumeton	ND 0,01 MOC3407
Terbumeton-desethyl	ND 0,01 MOC3407
Tetraconazole	ND 0,01 MOC3407
Thiabendazole	ND 0,01 MOC3407
Thiachlopride	ND 0,01 MOC3407
Thiadone	ND 0,01 MOC3407
Thiamethoxam	ND 0,01 MOC3407
Thiencarbazone-methyl	ND 0,01 MOC3407
Thifensulfuron-methyl	ND 0,01 MOC3407
Thiobencarb (m)	ND 0,01 MOC3407
Thiocyclam	ND 0,01 MOC3407
Thiodicarb	ND 0,01 MOC3407
Thiometon	ND 0,01 MOC3407
Thionazin	ND 0,01 MOC3407
Thiophanate-methyl	ND 0,01 MOC3407
Tolfenpyrad	ND 0,01 MOC3407
Topramezone	ND 0,01 MOC3407
Triasulfuron	ND 0,01 MOC3407
Triazamate	ND 0,01 MOC3407
Tribenuron-methyl	ND 0,01 MOC3407
Trichlorfon	ND 0,01 MOC3407
Triclopyr	ND 0,01 MOC3407
Tricyclazole	ND 0,01 MOC3407
Tridemorphe	ND 0,01 MOC3407
Trifloxystrobine	ND 0,01 MOC3407
Triflumuron	ND 0,01 MOC3407
Triflusulfuron Metabolite IN-M7222	ND 0,01 MOC3407
Triflusulfuron-methyl	ND 0,01 MOC3407
Triforine	ND 0,01 MOC3407
Trinexapac-ethyl	ND 0,01 MOC3407
Triticonazole	ND 0,01 MOC3407
Tritosulfuron	ND 0,01 MOC3407
Vamidothion	ND 0,01 MOC3407
Warfarin	ND 0,01 MOC3407

Specific monoresidues

	Result	LOQ	method
Unit ◦ : mg/kg			
Dithiocarbamates (CS2)	ND	0,05	MOC3/11

Heavy metals

	Result	LOQ	method
Unit ◦ : mg/kg			
Lead*	< 0,04	0,04	MOC3/85

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Cadmium*	< 0,01	0,01	MOC3/85
Arsenic*	< 0,03	0,03	MOC3/85
Mercury*	< 0,0050	0,005	MOC3/85
Palladium*	0,42	0,01	MOC3/85

Mycotoxines

	Result	LOQ	method
Unit ◊ : µg/kg			
Aflatoxin B1	ND	1	MOC3111
Aflatoxin B2	ND	1	MOC3111
Aflatoxin G1	ND	1	MOC3111
Aflatoxin G2	ND	1	MOC3111
Aflatoxins (Σ B1,B2, G1,G2)	ND	1	MOC3111

Polycyclic aromatic hydrocarbons (PaH)

	Result	LOQ	method
Unit ◊ : µg/kg			
Benzo(a)pyrene	ND	0,5	MOC3/23
Benzo(a)anthracene	ND	0,5	MOC3/23
Benzo(b)fluoranthene	ND	0,5	MOC3/23
Chrysene	ND	0,5	MOC3/23
Sum of the 4 HAP	ND	0,5	MOC3/23

Other contaminants

	Result	LOQ	method
Unit ◊ : mg/kg			
Melamin	ND	0,1	MOC3134

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GRUPO FERRER
Joaquina, Helena
Raiguero, 143-145
30588 ZENETA (MURCIA)

- This report cancels and replaces the previous version. Please disregard the previous report.

Laboratory reference	19/1-049736		
Customer reference	1010095, 019C045		
Type of sample	NHDC FARMA 5KG	**Weight**	422g
Status	Grind	**Temperature at reception**	Room
Date of reception	03/04/2019 14:08:37	**Expiration date**	03/07/2019
Packaging	Customer	**Transport**	DHL
Quotation reference	DES180463	**Regional agency**	Phytocontrol Alicante

Ordered analysis

Pesticides	Dithiocarbamates (CS2) Multirésidus GC250 + Multirésidus LC350
Heavy metals	5 Métaux
Mycotoxines	Aflatoxins B1 B2 G1 G2
Polycyclic aromatic hydrocarbons (PaH)	4 PAHs
Other contaminants	Melamine

Sample at reception

Results of analysis

	Result	Unit	LOQ	Limit	End of analysis
Pesticides					
Multiresidues GC 250	ND				16/04/2019
Multiresidues LC 350	ND				16/04/2019
Specific monoresidues					
Dithiocarbamates (CS2)	ND	mg/kg	0,05		16/04/2019
Heavy metals					
Lead*	< 0,04	mg/kg	0,04		30/04/2019
Cadmium*	< 0,01	mg/kg	0,01		30/04/2019
Arsenic*	< 0,03	mg/kg	0,03		30/04/2019
Mercury*	< 0,005	mg/kg	0,005		30/04/2019
Palladium*	0,26 ± 0,05	mg/kg	0,01		30/04/2019
Mycotoxines					
Aflatoxin B1	ND	µg/kg	2		17/04/2019
Aflatoxin B2	ND	µg/kg	2		17/04/2019
Aflatoxin G1	ND	µg/kg	2		17/04/2019
Aflatoxin G2	ND	µg/kg	2		17/04/2019
Aflatoxins (Σ B1,B2, G1,G2)	ND	µg/kg	2		17/04/2019
Polycyclic aromatic hydrocarbons (PaH)					
Benzo(a)pyrene	ND	µg/kg	0,5		16/04/2019
Benzo(a)anthracene	ND	µg/kg	0,5		16/04/2019
Benzo(b)fluoranthene	ND	µg/kg	0,5		16/04/2019
Chrysene	ND	µg/kg	0,5		16/04/2019
Sum of the 4 HAP	ND	µg/kg	0,5		16/04/2019
Other contaminants					
Melamin	ND	mg/kg	0,1		16/04/2019

Detail of the analyzed parameters and the methods used in following page(s)

Legend

ND = Not Detected D = Detected LOQ = Limit of Quantification NA = Not Analysed NQ = Not Quantifiable NI = Not Identifiable

(m):determined without its associated analyte(s) for pesticide residue analysis carried out only within the scope of Regulation 396/2005 and its amendments, or Directive 2006/125/EC, or delegated Regulation (EU) 2016/127 supplementing Regulation (EU) No 609/2013, or for drug residue analysis carried out only within the scope of Regulation 37/2010 and CRL/2007.

Used methods mentioned in following page(s) :

MOC3/05(S1) version 0 : Determination of pesticide residue content by GC-MS-MS : internal method.

MOC3/11(S1) version 0 : Determination of the content in dithiocarbamates on fruits and vegetables by GC-MS/HS : internal method.

MOC3/23(S1) version 2 : Determination of the content of PAH by GC-MS/MS : internal method.

MOC3/85(S1) version 14 : Determination of heavy metals elements (metallic and non-metallic) in all product of animal and vegetable origin including babyfood by ICP-MS: internal method.

MOC3111(S1) version 2 : Determination of mycotoxins in product of plant origin LC-MS-MS: internal method.

MOC3134(S1) version 1 : Determination of melamin content in feed and food, including babyfood, by LC-MS/MS : internal method

MOC3407(S1) version 2 : Determination of pesticide residue content by LC-MS-MS : internal method.

(S1) : analysis carried out by Phytocontrol laboratoire d'analyses - 180 rue Philippe Maupas - Parc Georges Besse - 30035 NIMES

Comments

The analytical results are only valid within the perimeter of application of the used method.

The limit values are based on the regulations and / or guidelines and / or recommendations listed below :

Pesticides

• Human and Animal Nutrition (raw materials): Regulation (EC) No 396/2005 and subsequent amendments on maximum residue levels of pesticides in or on food and feed of plant and animal origin.
• Animal Feed: Directive 2002/32 and subsequent amendments on undesirable substances in animal feed. The maximum levels apply to feedingstuffs with a moisture content of 12%.

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Heavy metals

• Food:
Regulation (EC) No 1881/2006 and subsequent amendments setting maximum levels for certain contaminants in foodstuffs.
Copper and Mercury (depending on matrix) : Regulation (EC) No 396/2005 and subsequent amendments on maximum residue levels of pesticides in or on food and feed of plant and animal origin.
• For wine: OIV - Maximum acceptable limits of various elements in wine (2015 edition).
• Animal Feed: Directive 2002/32 and subsequent amendments on undesirable substances in animal feed. The maximum levels apply to feedingstuffs with a moisture content of 12%.
• Food additives: Regulation (EU) n°231/2012 and subsequent amendments laying down specifications for food additives listed in Annexes II and III to Regulation (EC) N°1333/2008 of the European Parliament and of the council.

Mycotoxines

• Food : Regulation (EC) No 1881/2006 and subsequent amendments setting maximum levels for certain contaminants in foodstuffs.
Recommendations 2013/165/UE on the presence of T-2 toxin and HT-2 in cereals and cereal products.
• Animal Feed: Directive 2002/32 and subsequent amendments on undesirable substances in animal feed. The maximum levels apply to feedingstuffs with a moisture content of 12%.

Polycyclic aromatic hydrocarbons (PaH)

• Food: Regulation (EC) No 1881/2006 and subsequent amendments setting maximum levels for certain contaminants in foodstuffs.
Units may vary depending on the matrix: µg/kg (raw) or µg/kg MG (fat).

Report amendment: Adding a new report (language)

more information :

Dinocap(Σ des isomères) : Performed without its phenols. Including le Meptyldinocap.

Melamin : According EC 594/2012, the maximum limit of melamin on food is 2,5 mg/kg unless it can be proven that the level of melamine higher than 2,5 mg/kg is the consequence of authorized use of cyromazine as insecticide. The melamine level shall not exceed the level of cyromazine.

This provision does not apply on baby food. The limit on powdered infant formulae and follow-on formulae is 1mg/kg

Signature

The updating of regulatory information as regard to the European regulation or any other published standard is ensured by our Regulatory Monitoring department.

Report validated by :

Doriane BAUDOUIN
Analytical Validation

- This certificate was electronically produced and validated. The name and the function of the persons in charge on it document were produced on a protected procedure and personalised. This certificate is authentic. A paper version signed of this document can be obtained on simple demand.
- The results of analysis concern only objects subjected to the analysis.
- In absence of accurate and of opposite indication, the Limit of Detection is equal to half of the Limit of Quantification (excluding subcontracted parameters).
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- Comments are not covered by the accreditation (unless otherwise stated).
- PHYTOCONTROL is accredited by the FAVV-AFSCA and is approved by INAO, BNN and by QS, and certified ISO 14001 by Afnor.
- This report cancels and replaces the previous report.

Pesticides

Multiresidues GC 250

FB3/02.c vers. 24 (01/02/2019)

Unit ÷ : mg/kg	Result	LOQ	method
1,4-Dimethylnaphtalene	ND	0,01	MOC3/05
2,4,6 trichlorophenol (TCP) (m	ND	0,01	MOC3/05
2-Phenylphenol(somme)	ND		
2-Methoxybiphenyl	ND	0,01	MOC3/05
2-Phenylhydroquinone	ND	0,01	MOC3/05
2-Phenylphenol	ND	0,01	MOC3/05
3,4-dichloroaniline	ND	0,01	MOC3/05
4,4-Dichlorobenzophenone	ND	0,01	MOC3/05
Acetochlore	ND	0,01	MOC3/05
Acibenzolar-S-methyl (m)	ND	0,01	MOC3/05
Aclonifen	ND	0,01	MOC3/05
Acrinathrine	ND	0,01	MOC3/05
Alachlore	ND	0,01	MOC3/05
Ametryn	ND	0,01	MOC3/05
Amisulbrom	ND	0,01	MOC3/05
Atrazine	ND	0,01	MOC3/05
Benalaxyl dont Benalaxyl-M	ND	0,01	MOC3/05
Bendiocarb	ND	0,01	MOC3/05
Benfluraline	ND	0,01	MOC3/05
Benoxacor	ND	0,01	MOC3/05
Bifenox	ND	0,01	MOC3/05
Bifenthrine (sum of isomers)	ND	0,01	MOC3/05
Biphenyl	ND	0,01	MOC3/05
Bitertanol	ND	0,01	MOC3/05
Bromocyclen	ND	0,01	MOC3/05
Bromophos-ethyl	ND	0,01	MOC3/05
Bromophos-methyl	ND	0,01	MOC3/05
Bromopropylate	ND	0,01	MOC3/05
Butachlor	ND	0,01	MOC3/05
Butraline	ND	0,01	MOC3/05
Captafol	ND	0,01	MOC3/05
Captan(sum)	ND		
Captan	ND	0,01	MOC3/05
Tetrahydrophtalimide (THP	ND	0,01	MOC3/05
Carbaryl	ND	0,01	MOC3/05
Carbofuran(+3-hydroxy) (m)	ND		
Carbofuran	ND	0,01	MOC3/05
Carbofuran-3-Hydroxy	ND	0,01	MOC3/05
Furathiocarbe	ND	0,01	MOC3/05
Carbophenothion	ND	0,01	MOC3/05
Carfentrazone-ethyl	ND	0,01	MOC3/05
Chlorbenside	ND	0,01	MOC3/05
Chlordane(cis+trans)	ND	0,01	MOC3/05
Chlorfenapyr	ND	0,01	MOC3/05
Chlorfenson	ND	0,01	MOC3/05
Chlorfenvinphos	ND	0,01	MOC3/05
Chlorobenzilate	ND	0,01	MOC3/05
Chlorothalonil	ND	0,01	MOC3/05
Chlorpropham	ND	0,01	MOC3/05
Chlorpyrifos	ND	0,01	MOC3/05
Chlorpyrifos-methyl	ND	0,01	MOC3/05
Chlorthal dimethyl	ND	0,01	MOC3/05
Chlorthiophos	ND	0,01	MOC3/05
Chlozolinate	ND	0,01	MOC3/05
Clomazone	ND	0,01	MOC3/05
Coumaphos	ND	0,01	MOC3/05
Cyfluthrine (β+γ)	ND	0,01	MOC3/05
Cyhalofop-butyl	ND	0,01	MOC3/05
Cyhalothrine(∑ des isomères)	ND	0,01	MOC3/05
Cymiazole	ND	0,01	MOC3/05
Cypermethrine(α+β+θ+ζ)	ND	0,01	MOC3/05
Cyproconazole	ND	0,01	MOC3/05
Cyprodinil	ND	0,01	MOC3/05
DDT(Σ des isomères)	ND		
o,p'-DDT	ND	0,01	MOC3/05
p,p'-DDT	ND	0,01	MOC3/05
p,p'-DDE	ND	0,01	MOC3/05
p,p'-TDE(DDD)	ND	0,01	MOC3/05
Deltamethrine	ND	0,01	MOC3/05
Demeton-S-methyl	ND	0,01	MOC3/05
Dialifos	ND	0,01	MOC3/05
Dichlobenil	ND	0,01	MOC3/05
Dichlofenthion	ND	0,01	MOC3/05
Dichlofluanide	ND	0,01	MOC3/05
Dichlorvos	ND	0,01	MOC3/05
Diclofop-methyl (m)	ND	0,01	MOC3/05
Dicofol(Σ des isomères)	ND		
Dicofol o,p'	ND	0,01	MOC3/05
Dicofol p,p'	ND	0,01	MOC3/05
Dicrotophos	ND	0,01	MOC3/05
Dieldrin(sum)	ND		
Aldrin	ND	0,01	MOC3/05
Dieldrin	ND	0,01	MOC3/05
Diethofencarb	ND	0,01	MOC3/05
Difenoconazole	ND	0,01	MOC3/05
Diflufenican	ND	0,01	MOC3/05
Dimetachlor	ND	0,01	MOC3/05
Dinitramine	ND	0,01	MOC3/05
Diphenylamine	ND	0,01	MOC3/05
Disulfoton (m)	ND	0,01	MOC3/05
Ditalimfos	ND	0,01	MOC3/05
Edifenphos	ND	0,01	MOC3/05
Endosulfan(sum)	ND		
Endosulfan α	ND	0,01	MOC3/05
Endosulfan β	ND	0,01	MOC3/05
Endosulfan sulfate	ND	0,01	MOC3/05
Endrin	ND	0,01	MOC3/05
Endrin-ketone	ND	0,01	MOC3/05
EPN	ND	0,01	MOC3/05
Ethalfluraline	ND	0,01	MOC3/05
Ethiofencarb	ND	0,01	MOC3/05
Ethion	ND	0,01	MOC3/05
Ethofumesate (m)	ND	0,01	MOC3/05
Ethoprophos	ND	0,01	MOC3/05
Ethoxyquine	ND	0,01	MOC3/05
Etofenprox	ND	0,01	MOC3/05
Etridiazole	ND	0,01	MOC3/05
Etrimfos	ND	0,01	MOC3/05
Famoxadone	ND	0,01	MOC3/05
Famphur	ND	0,01	MOC3/05
Fenamiphos (m)	ND	0,01	MOC3/05
Fenarimol	ND	0,01	MOC3/05
Fenazaquin	ND	0,01	MOC3/05
Fenchlorphos (m)	ND	0,01	MOC3/05
Fenhexamide	ND	0,01	MOC3/05
Fenitrothion	ND	0,01	MOC3/05
Fenobucarbe	ND	0,01	MOC3/05
Fenpropathrine	ND	0,01	MOC3/05
Fenpropimorphe	ND	0,01	MOC3/05
Fenvalerate (Σ des isomères)	ND	0,01	MOC3/05
Fipronil(sum)	ND		
Fipronil	ND	0,005	MOC3/05
Fipronil-sulfone	ND	0,005	MOC3/05
Fipronil-desulfinyl	ND	0,01	MOC3/05
Fluazifop-p-butyl (m)	ND	0,01	MOC3/05
Fluchloralin	ND	0,01	MOC3/05
Flucythrinate	ND	0,01	MOC3/05
Fludioxonil	ND	0,01	MOC3/05
Flufenacet (m)	ND	0,01	MOC3/05
Fluopicolide	ND	0,01	MOC3/05
Flurochloridone	ND	0,01	MOC3/05
Fluroxypyr-methylheptyl ester (m)	ND	0,01	MOC3/05
Flusilazole	ND	0,01	MOC3/05
Flutolanil	ND	0,01	MOC3/05
Flutriafol	ND	0,01	MOC3/05
Fluvalinate (Tau)	ND	0,01	MOC3/05
Folpet(somme)	ND		
Folpet	ND	0,01	MOC3/05
Phtalimide	ND	0,01	MOC3/05
Fonofos	ND	0,01	MOC3/05
Formothion	ND	0,01	MOC3/05
Furalaxyl	ND	0,01	MOC3/05
Haloxyfop-2-ethoxyethyl (m)	ND	0,01	MOC3/05
Haloxyfop-methyl(R+S) (m)	ND	0,01	MOC3/05
HCB	ND	0,01	MOC3/05
HCH alpha	ND	0,01	MOC3/05
HCH beta	ND	0,01	MOC3/05
HCH gamma	ND	0,01	MOC3/05
Heptachlore(sum)	ND		
Heptachlore	ND	0,01	MOC3/05
Heptachlore epoxyde cis-	ND	0,01	MOC3/05
Heptachlore epoxyde trans-	ND	0,01	MOC3/05
Heptenophos	ND	0,01	MOC3/05
Hexazinone	ND	0,01	MOC3/05
Iodofenphos	ND	0,01	MOC3/05
Iprodione	ND	0,01	MOC3/05
Isobenzan	ND	0,01	MOC3/05
Isodrine	ND	0,01	MOC3/05
Isofenphos-ethyl	ND	0,01	MOC3/05
Isofenphos-methyl	ND	0,01	MOC3/05
Isoxadifen-ethyl	ND	0,01	MOC3/05
Leptophos	ND	0,01	MOC3/05
Malathion(sum)	ND		
Malathion	ND	0,01	MOC3/05
Malaoxon	ND	0,01	MOC3/05
Mepanipyrim	ND	0,01	MOC3/05
Mepronil	ND	0,01	MOC3/05
Metalaxyl dont Metalaxyl-M	ND	0,01	MOC3/05
Metazachlor	ND	0,01	MOC3/05
Methacrifos	ND	0,01	MOC3/05
Methidathion	ND	0,01	MOC3/05
Methoxychlore	ND	0,01	MOC3/05

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S.A.S. au Capital de 1.000.000 euros - SIRET 490 024 049 00028 RCS Nîmes - TVA intracom FR08490024049 - APE 7120B

Metolachlore dont S-Metolachlore	ND	0,01	MOC3/05
Mirex	ND	0,01	MOC3/05
Myclobutanil	ND	0,01	MOC3/05
Nitrofene	ND	0,01	MOC3/05
Nitrothal isopropyle	ND	0,01	MOC3/05
Oxadiazon	ND	0,01	MOC3/05
Oxadixyl	ND	0,01	MOC3/05
Oxyfluorfene	ND	0,01	MOC3/05
Parathion-ethyl	ND	0,01	MOC3/05
Parathion-methyl (m)	ND	0,01	MOC3/05
PCB 028	ND	0,01	MOC3/05
PCB 052	ND	0,01	MOC3/05
PCB 101	ND	0,01	MOC3/05
PCB 118	ND	0,01	MOC3/05
PCB 138	ND	0,01	MOC3/05
PCB 153	ND	0,01	MOC3/05
PCB 180	ND	0,01	MOC3/05
Penconazole	ND	0,01	MOC3/05
Pendimethaline	ND	0,01	MOC3/05
Pentachloroanisole	ND	0,01	MOC3/05
Permethrine(cis + trans)	ND	0,01	MOC3/05
Perthane	ND	0,01	MOC3/05
Phenothrine	ND	0,01	MOC3/05
Phenthoate	ND	0,01	MOC3/05
Phosalone	ND	0,01	MOC3/05
Piperonyl butoxide	ND	0,01	MOC3/05
Pirimicarb	ND	0,01	MOC3/05
Pirimiphos-ethyl	ND	0,01	MOC3/05
Pirimiphos-methyl	ND	0,01	MOC3/05
Plifenate	ND	0,01	MOC3/05
Pretilachlore	ND	0,01	MOC3/05
Procymidone	ND	0,01	MOC3/05
Profenophos	ND	0,01	MOC3/05
Prometryn	ND	0,01	MOC3/05
Propachlore (m)	ND	0,01	MOC3/05
Propazine	ND	0,01	MOC3/05
Propetamphos	ND	0,01	MOC3/05
Prophame	ND	0,01	MOC3/05
Propiconazole	ND	0,01	MOC3/05
Propyzamide	ND	0,01	MOC3/05
Proquinazid	ND	0,01	MOC3/05
Prosulfocarbe	ND	0,01	MOC3/05
Prothiophos	ND	0,01	MOC3/05
Prothoate	ND	0,01	MOC3/05
Pyrazophos	ND	0,01	MOC3/05
Pyridaben	ND	0,01	MOC3/05
Pyridalyl	ND	0,01	MOC3/05
Pyridaphenthion	ND	0,01	MOC3/05
Pyrifenox	ND	0,01	MOC3/05
Pyrimethanil	ND	0,01	MOC3/05
Pyriproxyfen	ND	0,01	MOC3/05
Quinalphos	ND	0,01	MOC3/05
Quinomethionate	ND	0,01	MOC3/05
Quinoxyfen	ND	0,01	MOC3/05
Quintozene(sum)	ND		
Quintozene	ND	0,01	MOC3/05
Pentachloroaniline (PCA)	ND	0,01	MOC3/05
Quizalofop-ethyl	ND	0,01	MOC3/05
S 421	ND	0,01	MOC3/05
Sebuthylazine	ND	0,01	MOC3/05
Secbumeton	ND	0,01	MOC3/05
Sulfotep	ND	0,01	MOC3/05
Sulprofos	ND	0,01	MOC3/05
Tebuconazole	ND	0,01	MOC3/05
Tebufenpyrad	ND	0,01	MOC3/05
Tebupirimphos	ND	0,01	MOC3/05
Tecnazene	ND	0,01	MOC3/05
Tefluthrine	ND	0,01	MOC3/05
Terbacil	ND	0,01	MOC3/05
Terbufos	ND	0,01	MOC3/05
Terbuthylazine	ND	0,01	MOC3/05
Terbutryne	ND	0,01	MOC3/05
Tetrachlorvinphos	ND	0,01	MOC3/05
Tetradifon	ND	0,01	MOC3/05
Tetramethrine	ND	0,01	MOC3/05
Tetrasul	ND	0,01	MOC3/05
Tolclofos-methyl	ND	0,01	MOC3/05
Tolylfluanid (m)	ND	0,01	MOC3/05
Tralomethrine	ND	0,01	MOC3/05
Transfluthrine	ND	0,01	MOC3/05
Triadimefon	ND	0,01	MOC3/05
Triadimenol	ND	0,01	MOC3/05
Triallate	ND	0,01	MOC3/05
Triamiphos	ND	0,01	MOC3/05
Triazophos	ND	0,01	MOC3/05
Trichloronat	ND	0,01	MOC3/05
Trifluraline	ND	0,01	MOC3/05
Valifenalate	ND	0,01	MOC3/05
Vinclozoline	ND	0,01	MOC3/05
Zoxamide	ND	0,01	MOC3/05

Multiresidues LC 350

FB3/02.A vers. 4 (25/03/2019)

Unit ◊ : mg/kg	Result	LOQ	method
2,4 D(free acid) (m)	ND	0,01	MOC3407
6-Benzyladenine	ND	0,01	MOC3407
Abamectine(sum)	ND		
Avermectine B1a	ND	0,01	MOC3407
Avermectine B1b	ND	0,01	MOC3407
8,9-Z-AvermectinB1a	ND	0,01	MOC3407
Acephate	ND	0,01	MOC3407
Acequinocyl	ND	0,01	MOC3407
Acetamipride	ND	0,01	MOC3407
Aldicarb(somme)	ND		
Aldicarb	ND	0,01	MOC3407
Aldicarb sulfone	ND	0,01	MOC3407
Aldicarb sulfoxide	ND	0,01	MOC3407
Ametoctradine	ND	0,01	MOC3407
Amidosulfuron	ND	0,01	MOC3407
Amitraze(somme)	ND		
Amitraze	ND	0,01	MOC3407
2,4-Dimethylaniline	ND	0,01	MOC3407
N-(2,4-Dimethylphenyl)formamide	ND	0,01	MOC3407
N-2,4-Dimethylphenyl-Np-methylformamidine HCl	ND	0,01	MOC3407
Amitrole	ND	0,01	MOC3407
Asulam	ND	0,01	MOC3407
Atrazine desisopropyl	ND	0,01	MOC3407
Atrazine-desethyl	ND	0,01	MOC3407
Azaconazole	ND	0,01	MOC3407
Azadirachtin(somme)	ND		
Azadirachtin A	ND	0,01	MOC3407
Azadirachtin B	ND	0,01	MOC3407
Azamethiphos	ND	0,01	MOC3407
Azimsulfuron	ND	0,01	MOC3407
Azinphos-ethyl	ND	0,01	MOC3407
Azinphos-methyl	ND	0,01	MOC3407
Azoxystrobine	ND	0,01	MOC3407
Beflubutamide	ND	0,01	MOC3407
Bensulfuron-methyl	ND	0,01	MOC3407
Bentazone(somme) (m)	ND		
Bentazone	ND	0,01	MOC3407
Bentazone 8 hydroxy	ND	0,01	MOC3407
Bentazone 6 hydroxy	ND	0,01	MOC3407
Benthiavalicarb-isopropyl (m)	ND	0,01	MOC3407
Benzovindiflupyr	ND	0,01	MOC3407
Bifenazate(sum)	ND		
Bifenazate	ND	0,01	MOC3407
Bifenazate-diazene	ND	0,01	MOC3407
Bispyribac-sodium	ND	0,01	MOC3407
Bixafen	ND	0,01	MOC3407
Boscalide	ND	0,01	MOC3407
Bromacil	ND	0,01	MOC3407
Bromoxynil	ND	0,01	MOC3407
Bromuconazole	ND	0,01	MOC3407
Bupirimate	ND	0,01	MOC3407
Buprofezin	ND	0,01	MOC3407
Butoxycarboxim	ND	0,01	MOC3407
Butoxycarboxim-sulfoxide	ND	0,01	MOC3407
Buturon	ND	0,01	MOC3407
Cadusafos	ND	0,01	MOC3407
Carbendazime(+Benomyl)	ND	0,01	MOC3407
Carbétamide (∑ de la carbétamide et de son isomère)	ND	0,01	MOC3407
Carbofuran(somme LC) (m)	ND		
Benfuracarbe	ND	0,01	MOC3407
Carbosulfan	ND	0,01	MOC3407
Carboxine (m)	ND	0,01	MOC3407
Chlorantraniliprole	ND	0,01	MOC3407
Chlorfluazuron	ND	0,01	MOC3407
Chloridazon(somme)	ND		
Chloridazon	ND	0,01	MOC3407
Chloridazon-desphenyl	ND	0,01	MOC3407
Chloridazon-methyl-despheny	ND	0,01	MOC3407
Chlorotoluron	ND	0,01	MOC3407
Chloroxuron	ND	0,01	MOC3407
Chlorpyrifos-methyl-desméthy (m)	ND	0,02	MOC3407
Chlorsulfuron	ND	0,01	MOC3407
Chromafenozide	ND	0,01	MOC3407
Cinidon-ethyl	ND	0,01	MOC3407
Cinmethylin	ND	0,01	MOC3407
Cinosulfuron	ND	0,01	MOC3407
Clethodim(somme) (m)	ND		
Clethodim	ND	0,01	MOC3407
Clethodim sulfoxide	ND	0,01	MOC3407
Sethoxydim	ND	0,01	MOC3407
Clodinafop-propargyl	ND	0,01	MOC3407

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S.A.S. au Capital de 1.000.000 euros - SIRET 490 024 049 00028 RCS Nîmes - TVA intracom FR08490024049 - APE 7120B

Clofentezine	ND 0,01 MOC3407	Etoxazole	ND 0,01 MOC3407	Hexaflumuron	ND 0,01 MOC3407		
Clothianidine	ND 0,01 MOC3407	Fenamidone	ND 0,01 MOC3407	Hexythiazox	ND 0,01 MOC3407		
Cyanazine	ND 0,01 MOC3407	Fenamiphos(sum) (m)	ND	Hydramethylnon	ND 0,01 MOC3407		
Cyantraniliprole	ND 0,01 MOC3407	Fenamiphos-sulfone	ND 0,01 MOC3407	Imazalil	ND 0,01 MOC3407		
Cyazofamide	ND 0,01 MOC3407	Fenamiphos-sulfoxide	ND 0,01 MOC3407	Imazamox	ND 0,01 MOC3407		
Cycloxydime (m)	ND 0,01 MOC3407	Fenbuconazole	ND 0,01 MOC3407	Imazaquin	ND 0,01 MOC3407		
Cycluron	ND 0,01 MOC3407	Fenchlorphos oxon (m)	ND 0,01 MOC3407	Imazosulfuron	ND 0,01 MOC3407		
Cyflufenamid	ND 0,01 MOC3407	Fenoxaprop-ethyl	ND 0,01 MOC3407	Imibenconazole	ND 0,01 MOC3407		
Cymoxanil	ND 0,01 MOC3407	Fenoxycarbe	ND 0,01 MOC3407	Imidachlopride	ND 0,01 MOC3407		
Cyprosulfamide	ND 0,01 MOC3407	Fenpropidine	ND 0,01 MOC3407	Indoxacarb (Σénantiomères)	ND 0,01 MOC3407		
Cyromazine	ND 0,01 MOC3407	Fenpyrazamine	ND 0,01 MOC3407	Iodosulfuron-methyl	ND 0,01 MOC3407		
Daminozide (m)	ND 0,01 MOC3407	Fenpyroximate	ND 0,01 MOC3407	Ioxynil	ND 0,01 MOC3407		
Dazomet (m)	ND 0,01 MOC3407	Fensulfothion	ND 0,01 MOC3407	Ipconazole	ND 0,01 MOC3407		
Demeton-S	ND 0,01 MOC3407	Fensulfothion-oxon	ND 0,01 MOC3407	Iprobenfos	ND 0,01 MOC3407		
Oxydemeton-methyl(somme)	ND	Fensulfothion-oxon-sulfone	ND 0,01 MOC3407	Iprovalicarbe	ND 0,01 MOC3407		
Demeton-S-methyl sulfone	ND 0,01 MOC3407	Fensulfothion-sulfone	ND 0,01 MOC3407	Isazofos	ND 0,01 MOC3407		
Oxydemeton-methyl	ND 0,01 MOC3407	Fenthion(somme)	ND	Isocarbophos	ND 0,01 MOC3407		
Desmediphame	ND 0,01 MOC3407	Fenthion	ND 0,01 MOC3407	Isofetamid	ND 0,01 MOC3407		
Desmetryn	ND 0,01 MOC3407	Fenthion-sulfone	ND 0,01 MOC3407	Isoprocarb	ND 0,01 MOC3407		
Diafenthiuron	ND 0,01 MOC3407	Fenthion-sulfoxide	ND 0,01 MOC3407	Isopropaline	ND 0,01 MOC3407		
Diallate	ND 0,01 MOC3407	Fenthion-oxon	ND 0,01 MOC3407	Isoprothiolane	ND 0,01 MOC3407		
Diazinon	ND 0,01 MOC3407	Fenthion-oxon-sulfone	ND 0,01 MOC3407	Isoproturon	ND 0,01 MOC3407		
Dichlorprop(free acid) (m)	ND 0,01 MOC3407	Fenthion-oxon-sulfoxide	ND 0,01 MOC3407	Isopyrazam	ND 0,01 MOC3407		
Diclobutrazol	ND 0,01 MOC3407	Fenuron	ND 0,01 MOC3407	Isoxaben	ND 0,01 MOC3407		
Dicloran	ND 0,01 MOC3407	Flazasulfuron	ND 0,01 MOC3407	Isoxaflutole(somme) (m)	ND		
Difenacoum	ND 0,01 MOC3407	Flonicamide(sum)	ND	Isoxaflutole	ND 0,01 MOC3407		
Difenamide	ND 0,01 MOC3407	Flonicamide	ND 0,01 MOC3407	RPA 202248	ND 0,01 MOC3407		
Difethialone	ND 0,01 MOC3407	TFNA	ND 0,01 MOC3407	Isoxathion	ND 0,01 MOC3407		
Diflubenzuron	ND 0,01 MOC3407	TFNG	ND 0,01 MOC3407	Kresoxim-methyl	ND 0,01 MOC3407		
Dimethenamid-P(Σ des isomeres)	ND 0,01 MOC3407	Florasulam	ND 0,01 MOC3407	Lenacil	ND 0,01 MOC3407		
Dimethoate	ND 0,01 MOC3407	Fluazifop(free acid) (m)	ND 0,01 MOC3407	Linuron	ND 0,01 MOC3407		
Dimethomorphe(Σ des isomeres)	ND 0,01 MOC3407	Fluazinam	ND 0,01 MOC3407	Lufenurone	ND 0,01 MOC3407		
Dimoxystrobine	ND 0,01 MOC3407	Flufenacet(somme) (m)	ND	Mandipropamide	ND 0,01 MOC3407		
Diniconazole(Σ des isomères)	ND 0,01 MOC3407	Flufenacet ESA	ND 0,01 MOC3407	MCPA(sum) (m)	ND		
Dinocap(Σ des isomères) (m)	ND 0,01 MOC3407	Flufenacet FOE 5043	ND 0,01 MOC3407	MCPA	ND 0,01 MOC3407		
Dinoseb (m)	ND 0,01 MOC3407	Flufenacet OA	ND 0,01 MOC3407	MCPB	ND 0,01 MOC3407		
Dinotefuran	ND 0,01 MOC3407	Flufenoxuron	ND 0,01 MOC3407	Mecarbam	ND 0,01 MOC3407		
Dinoterb	ND 0,01 MOC3407	Flumetralin	ND 0,01 MOC3407	Mefenacet	ND 0,01 MOC3407		
Disulfoton(sum) (m)	ND	Fluometuron	ND 0,01 MOC3407	Mephosfolan	ND 0,01 MOC3407		
Disulfoton-sulfone	ND 0,01 MOC3407	Fluopyram	ND 0,01 MOC3407	Mesosulfuron-methyl	ND 0,01 MOC3407		
Disulfoton-sulfoxide	ND 0,01 MOC3407	Fluoxastrobine	ND 0,01 MOC3407	Mesotrione	ND 0,01 MOC3407		
Dithianon	ND 0,01 MOC3407	Flupyradifurone	ND 0,01 MOC3407	Metaflumizone	ND 0,01 MOC3407		
Diuron	ND 0,01 MOC3407	Flupyrsulfuron methyl	ND 0,01 MOC3407	Metaldehyde	ND 0,01 MOC3407		
DMST (m)	ND 0,01 MOC3407	Fluquinconazole	ND 0,01 MOC3407	Metamitron	ND 0,01 MOC3407		
DNOC	ND 0,01 MOC3407	Fluroxypyr(free acid) (m)	ND 0,01 MOC3407	Metazachlor(somme)	ND		
Dodemorphe	ND 0,01 MOC3407	Flurtamone	ND 0,01 MOC3407	Metazachlor ESA	ND 0,01 MOC3407		
Dodine	ND 0,01 MOC3407	Fluxapyroxad	ND 0,01 MOC3407	Metazachlor OA	ND 0,01 MOC3407		
Emamectine-benzoate B1a	ND 0,01 MOC3407	Fomesafen	ND 0,01 MOC3407	Metazachlor Metabolite 479M16	ND 0,01 MOC3407		
Emamectine-benzoate B1b	ND 0,01 MOC3407	Foramsulfuron	ND 0,01 MOC3407	Metconazole(Σ des isomères)	ND 0,01 MOC3407		
Epoxiconazole	ND 0,01 MOC3407	Forchlorfenuron	ND 0,01 MOC3407	Methabenzthiazuron	ND 0,01 MOC3407		
EPTC	ND 0,01 MOC3407	Formetanate (hydrochloride)	ND 0,01 MOC3407	Methamidophos	ND 0,01 MOC3407		
Ethametsulfuron methyl	ND 0,01 MOC3407	Fosthiazate	ND 0,01 MOC3407	Methiocarbe(somme)	ND		
Ethidimuron	ND 0,01 MOC3407	Fuberidazole	ND 0,01 MOC3407	Methiocarbe	ND 0,01 MOC3407		
Ethiofencarb sulfone	ND 0,01 MOC3407	Furametpyr	ND 0,01 MOC3407	Methiocarbe-sulfone	ND 0,01 MOC3407		
Ethiofencarb sulfoxide	ND 0,01 MOC3407	Furmecyclox	ND 0,01 MOC3407	Methiocarbe-sulfoxide	ND 0,01 MOC3407		
Ethiprole	ND 0,01 MOC3407	Halauxifen-methyl	ND 0,01 MOC3407	Methomyl	ND 0,01 MOC3407		
Ethirimol	ND 0,01 MOC3407	Halfenprox	ND 0,01 MOC3407	Methoxyfenozide	ND 0,01 MOC3407		
Ethoxysulfuron	ND 0,01 MOC3407	Halosulfuron-methyl	ND 0,01 MOC3407	Metobromuron	ND 0,01 MOC3407		
		Haloxyfop(free acid) (m)	ND 0,01 MOC3407	Metolachlore ESA	ND 0,01 MOC3407		
		Hexaconazole	ND 0,01 MOC3407				

Metolachlore OA	ND 0,01 MOC3407	Pirimicarb-desmethyl	ND 0,01 MOC3407	Spiromesifen	ND 0,01 MOC3407
Metolcarb	ND 0,01 MOC3407	Prallethrin	ND 0,01 MOC3407	Spirotetramate(sum)	ND
Metosulam	ND 0,01 MOC3407	Primisulfuron	ND 0,01 MOC3407	Spirotetramat	ND 0,01 MOC3407
Metoxuron	ND 0,01 MOC3407	Prochloraz(somme) (m)	ND	Spirotetramate-enol	ND 0,01 MOC3407
Metrafenone	ND 0,01 MOC3407	Prochloraz	ND 0,01 MOC3407	Spirotetramat-enol-glucosid	ND 0,01 MOC3407
Metribuzine	ND 0,01 MOC3407	Prochloraz metabolite BTS9608	ND 0,01 MOC3407	Spirotetramat-keto-hydroxy	ND 0,01 MOC3407
Metsulfuron-methyl	ND 0,01 MOC3407			Spirotetramat-mono-hydrox	ND 0,01 MOC3407
Meptyldinocap-phenol (2,4-DNOP) (m)	ND 0,01 MOC3407	Prochloraz metabolite BTS40348	ND 0,01 MOC3407	Spiroxamine	ND 0,01 MOC3407
Mevinphos	ND 0,01 MOC3407	Prochloraz metabolite (BTS44595)	ND 0,01 MOC3407	Sulcotrione	ND 0,01 MOC3407
Milbemectin(somme)	ND			Sulfosulfuron	ND 0,01 MOC3407
Milbemectin A3	ND 0,01 MOC3407	Prochloraz metabolite BTS44596	ND 0,01 MOC3407	Sulfoxaflor	ND 0,01 MOC3407
Milbemectin A4	ND 0,01 MOC3407	Promecarb	ND 0,01 MOC3407	TCMTB	ND 0,01 MOC3407
MNBA	ND 0,01 MOC3407	Prometon	ND 0,01 MOC3407	Tebufenozide	ND 0,01 MOC3407
Molinate	ND 0,01 MOC3407	Propamocarbe	ND 0,01 MOC3407	Tebutam	ND 0,01 MOC3407
Monalide	ND 0,01 MOC3407	Propanil	ND 0,01 MOC3407	Tebuthiuron	ND 0,01 MOC3407
Monocrotophos	ND 0,01 MOC3407	Propaphos	ND 0,01 MOC3407	Teflubenzuron	ND 0,01 MOC3407
Monolinuron	ND 0,01 MOC3407	Propargite	ND 0,01 MOC3407	Tembotrione	ND 0,01 MOC3407
Monuron	ND 0,01 MOC3407	Propoxur	ND 0,01 MOC3407	Tepraloxydim(somme) (m)	ND
NAD(1-naphtyl acetamide) (m	ND 0,01 MOC3407	Propoxycarbazone(somme)	ND	Tepraloxydim	ND 0,01 MOC3407
Naled	ND 0,01 MOC3407	Propoxycarbazone	ND 0,01 MOC3407	Tepraloxydim-5-hydroxy	ND 0,01 MOC3407
Napropamide	ND 0,01 MOC3407	2-hydroxy-propoxycarbazon	ND 0,01 MOC3407	Terbumeton	ND 0,01 MOC3407
Neburon	ND 0,01 MOC3407	Prosulfuron	ND 0,01 MOC3407	Terbumeton-desethyl	ND 0,01 MOC3407
Nicosulfuron	ND 0,01 MOC3407	Prothioconazole-desthio	ND 0,01 MOC3407	Tetraconazole	ND 0,01 MOC3407
Nitenpyram	ND 0,01 MOC3407	Pydiflumetofen	ND 0,01 MOC3407	Thiabendazole	ND 0,01 MOC3407
Norflurazon	ND 0,01 MOC3407	Pymetrozine	ND 0,01 MOC3407	Thiachlopride	ND 0,01 MOC3407
Novaluron	ND 0,01 MOC3407	Pyraclofos	ND 0,01 MOC3407	Thiadone	ND 0,01 MOC3407
Nuarimol	ND 0,01 MOC3407	Pyraclostrobine	ND 0,01 MOC3407	Thiamethoxam	ND 0,01 MOC3407
Ofurace	ND 0,01 MOC3407	Pyraflufen-ethyl (m)	ND 0,01 MOC3407	Thiencarbazone-methyl	ND 0,01 MOC3407
Omethoate	ND 0,01 MOC3407	Pyrethrines(Somme)	ND	Thifensulfuron-methyl	ND 0,01 MOC3407
Orthosulfamuron	ND 0,01 MOC3407	Cinerine I	ND 0,01 MOC3407	Thiobencarb (m)	ND 0,01 MOC3407
Oryzalin	ND 0,01 MOC3407	Cinerine II	ND 0,01 MOC3407	Thiocyclam	ND 0,01 MOC3407
Oxamyl	ND 0,01 MOC3407	Jasmoline I	ND 0,01 MOC3407	Thiodicarb	ND 0,01 MOC3407
Oxasulfuron	ND 0,01 MOC3407	Jasmoline II	ND 0,01 MOC3407	Thiometon	ND 0,01 MOC3407
Oxathiapiprolin	ND 0,01 MOC3407	Pyrethrine I	ND 0,01 MOC3407	Thionazin	ND 0,01 MOC3407
Paclobutrazol	ND 0,01 MOC3407	Pyrethrine II	ND 0,01 MOC3407	Thiophanate-methyl	ND 0,01 MOC3407
Paraoxon-ethyl (m)	ND 0,01 MOC3407	Pyridate(+Pyridafol) (m)	ND	Tolfenpyrad	ND 0,01 MOC3407
Pebulate	ND 0,01 MOC3407	Pyridate	ND 0,01 MOC3407	Topramezone	ND 0,01 MOC3407
Pencycuron	ND 0,01 MOC3407	Pyridafol	ND 0,01 MOC3407	Triasulfuron	ND 0,01 MOC3407
Penflufen	ND 0,01 MOC3407	Pyrimidifen	ND 0,01 MOC3407	Triazamate	ND 0,01 MOC3407
Penoxsulame	ND 0,01 MOC3407	Pyriofenone	ND 0,01 MOC3407	Tribenuron-methyl	ND 0,01 MOC3407
Penthiopyrad	ND 0,01 MOC3407	Pyroquilon	ND 0,01 MOC3407	Trichlorfon	ND 0,01 MOC3407
pethoxamid	ND 0,01 MOC3407	Pyroxsulam	ND 0,01 MOC3407	Triclopyr	ND 0,01 MOC3407
Phenmediphame	ND 0,01 MOC3407	Quinmerac	ND 0,01 MOC3407	Tricyclazole	ND 0,01 MOC3407
Phorate(somme)	ND	Quizalofop dont quizalofop-	ND 0,01 MOC3407	Tridemorphe	ND 0,01 MOC3407
Phorate	ND 0,01 MOC3407	Propaquizafop	ND 0,01 MOC3407	Trifloxystrobine	ND 0,01 MOC3407
Phorate-sulfone	ND 0,01 MOC3407	Resmethrine	ND 0,01 MOC3407	Triflumuron	ND 0,01 MOC3407
Phorate-sulfoxide	ND 0,01 MOC3407	Rimsulfuron	ND 0,01 MOC3407	Triflusulfuron Metabolite IN-M7222	ND 0,01 MOC3407
Phorate-oxon	ND 0,01 MOC3407	Rotenone	ND 0,01 MOC3407	Triflusulfuron-methyl	ND 0,01 MOC3407
Phorate-oxon-sulfone	ND 0,01 MOC3407	Sedaxane	ND 0,01 MOC3407	Triforine	ND 0,01 MOC3407
Phorate-oxon-sulfoxide	ND 0,01 MOC3407	Silthiofam	ND 0,01 MOC3407	Trinexapac-ethyl	ND 0,01 MOC3407
Phosmet(sum)	ND	Simazine	ND 0,01 MOC3407	Triticonazole	ND 0,01 MOC3407
Phosmet	ND 0,01 MOC3407	Simetryn	ND 0,01 MOC3407	Tritosulfuron	ND 0,01 MOC3407
Phosmet-oxon	ND 0,01 MOC3407	Spinetoram XDE-175	ND	Vamidothion	ND 0,01 MOC3407
Phosphamidon	ND 0,01 MOC3407	Spinetoram XDE-175-J	ND 0,01 MOC3407	Warfarin	ND 0,01 MOC3407
Phoxim	ND 0,01 MOC3407	Spinetoram XDE-175-L	ND 0,01 MOC3407		
Picaridin	ND 0,01 MOC3407	Spinosad(A+D)	ND		
Picolinafen	ND 0,01 MOC3407	Spinosyne A	ND 0,01 MOC3407		
Picoxystrobine	ND 0,01 MOC3407	Spinosyne D	ND 0,01 MOC3407		
Pinoxadene	ND 0,01 MOC3407	Spirodiclofen	ND 0,01 MOC3407		

Specific monoresidues

	Result	LOQ	method
Unit ⊙ : mg/kg			
Dithiocarbamates (CS2)	ND	0,05	MOC3/11

Phytocontrol Analytics France, Parc Scientifique Georges BESSE II - 180 rue Philippe Maupas - CS 20009 - 30035 Nîmes Cedex 1
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S.A.S. au Capital de 1.000.000 euros - SIRET 490 024 049 00028 RCS Nîmes - TVA intracom FR08490024049 - APE 7120B

Heavy metals

	Result	LOQ	method
Unit ◊ : mg/kg			
Lead*	< 0,04	0,04	MOC3/85
Cadmium*	< 0,01	0,01	MOC3/85
Arsenic*	< 0,03	0,03	MOC3/85
Mercury*	< 0,005	0,005	MOC3/85
Palladium*	0,26	0,01	MOC3/85

Mycotoxines

	Result	LOQ	method
Unit ◊ : µg/kg			
Aflatoxin B1	ND	2	MOC3111
Aflatoxin B2	ND	2	MOC3111
Aflatoxin G1	ND	2	MOC3111
Aflatoxin G2	ND	2	MOC3111
Aflatoxins (Σ B1,B2, G1,G2)	ND	2	MOC3111

Polycyclic aromatic hydrocarbons (PaH)

	Result	LOQ	method
Unit ◊ : µg/kg			
Benzo(a)pyrene	ND	0,5	MOC3/23
Benzo(a)anthracene	ND	0,5	MOC3/23
Benzo(b)fluoranthene	ND	0,5	MOC3/23
Chrysene	ND	0,5	MOC3/23
Sum of the 4 HAP	ND	0,5	MOC3/23

Other contaminants

	Result	LOQ	method
Unit ◊ : mg/kg			
Melamin	ND	0,1	MOC3134

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TEST REPORT

INTERQUIM, S.A.
Avda. Diagonal, 549, 5ª Planta - . 08029 - Barcelona

Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: **A-02364170020 [MR-F]-EN** **Sample Sent by:** Helena Montijano

Date collected/Entry:	28/03/2017 - 28/03/2017	**Date of issue:**	25/04/2017
Date start/End:	28/03/2017 - 10/04/2017	**Time collected/Entry:**	14:20 - 19:05
Sample quantity:	500 g		
Type of sample:	Citrosa		

Requested test: Multi-residue by GC/MS/MS - LC/MS/MS

ANALYTICAL RESULTS (Multi-residues GC/MS/MS - LC/MS/MS)

Resource	Units	QL	Result
Method: (MET-CR-Multi-GC/MSMS) - (MET-CR-Extraccion-Multi)			
Pesticides GC/MS/MS	**mg/kg**		**<QL**
Method: (MET-CR-MULTI-LC/MSMS) (MET-CR-Extraccion-Multi)			
Pesticides LC/MS/MS	**mg/kg**		**<QL**

In the tested sample, no active substances were detected, according to the quantification limits established in the following pages of this report.

1

Q.L.: Quantification Limit

Methods: (MET-CR-Multi-GC/MS/MS) - (MET-CR-Extraccion-Multi) / (MET-CR-Multi-LC/MS/MS) - (MET-CR-Extraccion-Multi)

The results of this report only affect to the tested samples. It is not permitted the total or partial reproduction of this report without approval of Ecosur laboratory.

The samples will be preserved according the specific requirements established by the Ecosur Quality System except specific demands of the clients. The uncertainties of the test have been calculated and are available for the client.

Estando mas cerca llegamos mas lejos.

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Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: A-02364170020 [MR-F]-EN

RELATION OF ACTIVE ANALYZED MATTERS (PESTICIDES GC/MS/MS)

Resource	Units	Q.L.
1,1-dichloro-2,2-bis-(4-ethyl-phenyl-) ethane (Pertan)	mg/kg	0,01
2-phenylphenol	mg/kg	0,01
3,5-dichloraniniline	mg/kg	0,01
Aclonifen	mg/kg	0,01
Acrinathrin	mg/kg	0,01
Alachlor	mg/kg	0,01
Aldrin	mg/kg	0,01
Aldrin and Dieldrin (Aldrin and dieldrin combined expressed as dieldrin)	mg/kg	0,01
Anthraquinone	mg/kg	0,01
Atrazine	mg/kg	0,01
Azoxystrobin	mg/kg	0,01
Benalaxyl including other mixtures of constituent isomers including benalaxyl-M (sum of isomers)	mg/kg	0,01
Benfluralin	mg/kg	0,01
Bentazone methyl	mg/kg	0,01
Bifenazate	mg/kg	0,01
Bifenox	mg/kg	0,01
Bifenthrin	mg/kg	0,01
Biphenyl	mg/kg	0,01
Bitertanol	mg/kg	0,01
Bromacil	mg/kg	0,01
Bromocyclen	mg/kg	0,01
Bromophos etyl	mg/kg	0,01
Bromophos methyl	mg/kg	0,01
Bromopropylate	mg/kg	0,01
Bupirimate	mg/kg	0,01
Buprofezin	mg/kg	0,01
Butachlor	mg/kg	0,01
Cadusafos	mg/kg	0,01
Captan	mg/kg	0,01

Resource	Units	Q.L
Carbophenothion ethyl	mg/kg	0,01
Chinomethionat	mg/kg	0,01
Chlordane (sum of cis- and trans-chlrodane)	mg/kg	0,01
Chlorfenapyr	mg/kg	0,01
Chlorfenprop methyl	mg/kg	0,01
Chlorfenvinphos	mg/kg	0,01
Chlorobenzilate	mg/kg	0,01
Chlorofenson	mg/kg	0,01
Chloroneb	mg/kg	0,01
Chlorothalonil	mg/kg	0,01
Chlorpropham	mg/kg	0,01
Chlorpyrifos	mg/kg	0,01
Chlorpyrifos-methyl	mg/kg	0,01
Chlorthal-dimethyl	mg/kg	0,01
Chlozolinate	mg/kg	0,01
Cyanazine	mg/kg	0,01
Cyfluthrin (cyfluthrin including other mixtures of constituent isomers (sum of isomers))	mg/kg	0,01
Cyhalothrin-lambda	mg/kg	0,01
Cypermethrin (cypermethrin including other mixtures of constituent isomers (sum of isomers))	mg/kg	0,01
Cyproconazole	mg/kg	0,01
Cyprodinil	mg/kg	0,01
DDD-o,p'	mg/kg	0,01
DDD-p,p'	mg/kg	0,01
DDE-o,p'	mg/kg	0,01
DDE-p,p'	mg/kg	0,01
DDT (Sum p,p'-DDT, o,p'-DDT, p,p'-DDE and p,p'-TDE (DDD) expresed in DDT)	mg/kg	0,01
DDT-o,p'	mg/kg	0,01
DDT-p,p'	mg/kg	0,01

Resource	Units	Q.L
DEET (Diethyl-m-toluamid, N,N-)	mg/kg	0,01
Deltamethrin	mg/kg	0,01
Demeton-S	mg/kg	0,01
Diazinon	mg/kg	0,01
Dichlobenil	mg/kg	0,01
Dichlofenthion	mg/kg	0,01
Dichlofuanid	mg/kg	0,01
Dichlorvos	mg/kg	0,01
Diclofop methyl	mg/kg	0,01
Dicloran	mg/kg	0,01
Dicofol (sum of p, p' and o,p' isomers)	mg/kg	0,01
Dieldrin	mg/kg	0,01
Diethofencarb	mg/kg	0,01
Difenoconazole	mg/kg	0,01
Dimethomorph (sum of isomers)	mg/kg	0,01
Diniconazole (sum of isomers)	mg/kg	0,01
Diphenylamine	mg/kg	0,01
Disulfoton	mg/kg	0,01
Endosulfan (sum of alpha- and beta-isomers and endosulfan-sulphate expresses as endosulfan)	mg/kg	0,01
Endosulfan Beta	mg/kg	0,01
Endosulfan Sulfate	mg/kg	0,01
Endrin	mg/kg	0,01
Ensodulfan Alpha	mg/kg	0,01
Esfenvalerate	mg/kg	0,01
Etaconazole	mg/kg	0,01
Ethiofencarb	mg/kg	0,01
Ethion	mg/kg	0,01
Ethoprophos	mg/kg	0,01
Ethoxyquin	mg/kg	0,01

Q.L.: Quantification Limit RESULTS IN PAGE 1 OF REPORT
Methods: (MET-CR-Multi-GC/MSMS) - (MET-CR-Extraccion-Multi)

Estando mas cerca llegamos mas lejos.

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TEST REPORT

Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: **A-02364170020 [MR-F]-EN**

RELATION OF ACTIVE ANALYZED MATTERS (PESTICIDES GC/MS/MS)

Resource	Units	Q.L.
Etridiazole	mg/kg	0,01
Etrimfos	mg/kg	0,01
Fenamiphos	mg/kg	0,01
Fenarimol	mg/kg	0,01
Fenazaquin	mg/kg	0,01
Fenbuconazole	mg/kg	0,01
Fenchlorphos	mg/kg	0,01
Fenflutrin	mg/kg	0,01
Fenhexamid	mg/kg	0,01
Fenitrothion	mg/kg	0,01
Fenobucarb	mg/kg	0,01
Fenoxaprop-P-ethyl	mg/kg	0,01
Fenpropathrin	mg/kg	0,01
Fenpropimorph	mg/kg	0,01
Fensulfothion	mg/kg	0,01
Fenthion	mg/kg	0,01
Fenvalerate	mg/kg	0,01
Fenvalerate (any ratio of constituent isomers (RR, SS, RS & SR) including esfenvalerate) (F) (R)	mg/kg	0,01
Fipronil	mg/kg	0,005
Fipronil sulfide	mg/kg	0,005
Fluazifop-P-butyl	mg/kg	0,01
Fluchloralin	mg/kg	0,01
Flucythrinate	mg/kg	0,01
Fludioxonil	mg/kg	0,01
Flufenacet	mg/kg	0,01
Flufenoxuron	mg/kg	0,01
Fluotrimazole	mg/kg	0,01
Flusilazole	mg/kg	0,01
Fluvalinate Tau	mg/kg	0,01

Resource	Units	Q.L
Fonofos	mg/kg	0,01
Formothion	mg/kg	0,01
Halfenprox	mg/kg	0,01
heptachlor	mg/kg	0,01
Heptachlor (sum of heptachlor and heptachlor epoxide -cis and trans - expressed as heptachlor)	mg/kg	0,01
Heptachlor epoxid cis	mg/kg	0,01
Heptachlor epoxid trans	mg/kg	0,01
Heptehophos	mg/kg	0,01
Hexachlorobenzene	mg/kg	0,01
Hexachlorocyclohexane (HCH) beta isomer	mg/kg	0,01
Hexachlorocyclohexane (HCH) (sum of isomers, except the Gamma isomer)	mg/kg	0,01
Hexachlorocyclohexane (HCH) alpha isomer	mg/kg	0,01
hexachlorocyclohexane (HCH) delta isomer	mg/kg	0,01
Hexacloro-Butadiene	mg/kg	0,01
Iprodione	mg/kg	0,01
Isocarbophos	mg/kg	0,01
Isodrin	mg/kg	0,01
Isofenphos	mg/kg	0,01
Isofenphos-methyl	mg/kg	0,01
Kresoxim-methyl	mg/kg	0,01
Lenacil	mg/kg	0,01
Leptofos	mg/kg	0,01
Lindan (hexachlorocyclohexane (HCH) gamma isomer	mg/kg	0,01
Malathion	mg/kg	0,01
Metalaxyl and metalaxyl-M (metalaxyl including other mixtures of constituent isomers including metalaxyl-M (sum of isomers))	mg/kg	0,01
Metazachlor	mg/kg	0,01
Metconazole	mg/kg	0,01

Resource	Units	Q.L
Methidathion	mg/kg	0,01
Methoxychlor	mg/kg	0,01
Metolachlor and metolachlor-S (metolachlor including other mixtures of constituent isomers including S-metolachlor (sum of isomers))	mg/kg	0,01
Metrafenone	mg/kg	0,01
Mevinphos (sum of E- and Z-isomers)	mg/kg	0,01
Mirex	mg/kg	0,01
Molinate	mg/kg	0,01
Myclobutanyl	mg/kg	0,01
Naled	mg/kg	0,01
Napropamide	mg/kg	0,01
Nitrofen	mg/kg	0,01
Norflurazon	mg/kg	0,01
Nuarimol	mg/kg	0,01
Ofurace	mg/kg	0,01
Oxadixyl	mg/kg	0,01
Oxyfluorfen	mg/kg	0,01
Parathion	mg/kg	0,01
Parathion-methyl	mg/kg	0,01
Pebulate	mg/kg	0,01
Penconazole	mg/kg	0,01
Pendimethalin	mg/kg	0,01
Pentachloranisole	mg/kg	0,01
Pentachloro-aniline	mg/kg	0,01
Pentaclhorobenzene	mg/kg	0,01
Permethrin (sum of isomers)	mg/kg	0,01
Phentoate	mg/kg	0,01
Phosalone	mg/kg	0,01
Phosphamidon	mg/kg	0,01
Pirimicarb	mg/kg	0,01

Q.L.: Quantification Limit RESULTS IN PAGE 1 OF REPORT
Methods: (MET-CR-Multi-GC/MSMS) - (MET-CR-Extraccion-Multi)

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Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: **A-02364170020 [MR-F]-EN**

RELATION OF ACTIVE ANALYZED MATTERS (PESTICIDES GC/MS/MS)

Resource	Units	Q.L.
Pirimiphos methyl	mg/kg	0,01
Pirimiphos-ethyl	mg/kg	0,01
Procymidone	mg/kg	0,01
Profenofos	mg/kg	0,01
Profluralin	mg/kg	0,01
Prometryn	mg/kg	0,01
Propachlor	mg/kg	0,01
Propargite	mg/kg	0,01
Propetamphos	mg/kg	0,01
Propham	mg/kg	0,01
Propiconazole (sum of isomers)	mg/kg	0,01
Propyzamide	mg/kg	0,01
Prothiofos	mg/kg	0,01
Pyrazophos	mg/kg	0,01
Pyridaben	mg/kg	0,01
Pyridaphenthion	mg/kg	0,01
Pyrifenox	mg/kg	0,01
Pyrimethanil	mg/kg	0,01
Pyriproxyfen	mg/kg	0,01
Quinalphos	mg/kg	0,01
Quinoxyfen	mg/kg	0,01
Quintozene	mg/kg	0,01
Quintozene (sum of quintozene and pentachloro-aniline expressed as quintozene)	mg/kg	0,01
Resmethrin	mg/kg	0,01
S-421	mg/kg	0,01
Silaneophan	mg/kg	0,01
Simazine	mg/kg	0,01
Spiromesifen	mg/kg	0,01
Sulfotep	mg/kg	0,01

Resource	Units	Q.L
Sulprofos	mg/kg	0,01
Tebuconazole	mg/kg	0,01
Tebufenpyrad	mg/kg	0,01
Tecnazene	mg/kg	0,01
Teflubenzuron	mg/kg	0,01
Terbufos	mg/kg	0,01
Terbufos sulfone	mg/kg	0,01
Terbumeton	mg/kg	0,01
Terbuthylazine	mg/kg	0,01
Terbutol	mg/kg	0,01
Terbutryn	mg/kg	0,01
Tetrachlorvinphos	mg/kg	0,01
Tetraconazole	mg/kg	0,01
Tetradifon	mg/kg	0,01
Tetramethrin	mg/kg	0,01
Tetrasul	mg/kg	0,01
Thiocyclam Hidrogen Oxalate	mg/kg	0,01
Thiometon	mg/kg	0,01
Tolclofos-methyl	mg/kg	0,01
Tolylfluanid	mg/kg	0,01
Transfluthrin	mg/kg	0,01
Triadimefon	mg/kg	0,01
Triadimenol	mg/kg	0,01
Triazophos	mg/kg	0,01
Trichlorfon	mg/kg	0,01
Triclhoronat	mg/kg	0,01
Trifloxystrobin	mg/kg	0,01
Triflumizole	mg/kg	0,01
Trifluralin	mg/kg	0,01
Vinclozolin	mg/kg	0,01

Resource	Units	Q.L
Zoxamide	mg/kg	0,01

Q.L.: Quantification Limit RESULTS IN PAGE 1 OF REPORT
Methods: (MET-CR-Multi-GC/MSMS) - (MET-CR-Extraccion-Multi)

Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: **A-02364170020 [MR-F]-EN**

RELATION OF ACTIVE ANALYZED MATTERS (PESTICIDES LC/MS/MS)

Resource	Units	Q.L.
1-(2,4 dichlorophenyl)-2-Imidazol (imazalil metabolite)	mg/kg	0,01
2,4-D (Free acid)	mg/kg	0,01
3-hydroxycarbofuran	mg/kg	0,001
Abamectin	mg/kg	0,01
Acephate	mg/kg	0,01
Acetamiprid	mg/kg	0,01
Ametoctradin	mg/kg	0,01
Ametryn	mg/kg	0,01
Azadirachtin	mg/kg	0,01
Azinphos-methyl	mg/kg	0,01
Azoxystrobin	mg/kg	0,01
Bendiocarb	mg/kg	0,01
Benfuracarb	mg/kg	0,01
Bentazone (Free acid)	mg/kg	0,01
Benthiavalicarb-isopropyl	mg/kg	0,01
Boscalid	mg/kg	0,01
Bromoxynil (Free acid)	mg/kg	0,01
Bromuconazole (sum of diasteroisomers)	mg/kg	0,01
Carbaryl	mg/kg	0,01
Carbendazim (sum of benomyl and carbendazim expressed as carbendazim)	mg/kg	0,01
Carbofuran	mg/kg	0,001
Carbofuran (sum of carbofuran and 3-hydroxycarbofuran expressed as carbofuran)	mg/kg	0,001
Carbosulfan	mg/kg	0,01
Carboxin	mg/kg	0,01
Chlorantraniliprole	mg/kg	0,01
Clodinafop-propargyl	mg/kg	0,01
Clofentezine	mg/kg	0,01
Clomazone	mg/kg	0,01
Clothianidin	mg/kg	0,01
Cyazofamid	mg/kg	0,01
Cycloxydim (parental)	mg/kg	0,01
Cyflufenamid (Sum of isomer Z and E Ciflufenamid)	mg/kg	0,01
Cymoxanil	mg/kg	0,01
Cyromazine	mg/kg	0,01
Desmedipham	mg/kg	0,01
Desmethyl pirimicarb	mg/kg	0,01
Diafenthiuron	mg/kg	0,01

Resource	Units	Q.L.
Dichlormid	mg/kg	0,01
Dichlorprop (Free acid)	mg/kg	0,01
Diethofencarb	mg/kg	0,01
Difenoconazole	mg/kg	0,01
Diflubenzuron	mg/kg	0,01
Diflufenican	mg/kg	0,01
Dimethoate	mg/kg	0,01
Dimethomorph (sum of isomers)	mg/kg	0,01
Dinocap	mg/kg	0,01
Dinoseb	mg/kg	0,01
Ditalimfos	mg/kg	0,01
Diuron	mg/kg	0,01
DNOC	mg/kg	0,01
Dodine	mg/kg	0,01
Emamectin benzoate (As Emamectin)	mg/kg	0,01
Epoxiconazole	mg/kg	0,01
Ethiofencarb	mg/kg	0,01
Ethiofencarb (sum of Ethiofencarb,its sulfoxide and its sulfons, exp as Ethiofencarb)	mg/kg	0,01
Ethiofencarb-sulfone	mg/kg	0,01
Ethiofencarb-sulfoxide	mg/kg	0,01
Ethirimol	mg/kg	0,01
Ethofenprox	mg/kg	0,01
Ethofumesate	mg/kg	0,01
Etoxazole	mg/kg	0,01
Famoxadone	mg/kg	0,01
Fenamidone	mg/kg	0,01
Fenbutatin oxide	mg/kg	0,01
Fenhexamid	mg/kg	0,01
Fenoxycarb	mg/kg	0,01
Fenpirazamina	mg/kg	0,01
Fenpropidin	mg/kg	0,01
Fenpropimorph	mg/kg	0,01
Fenpyroximate	mg/kg	0,01
Fenthion oxon sulfone	mg/kg	0,01
Flazasulfuron	mg/kg	0,01
Flonicamid (sum of flonicamid, TNFG and TNFA, expresed as flonicamid)	mg/kg	0,01
Fluazifop P (Free acid)	mg/kg	0,01
Fluazinam	mg/kg	0,01
Flubendiamide	mg/kg	0,01

Resource	Units	Q.L.
Flufenoxuron	mg/kg	0,01
Fluometuron	mg/kg	0,01
Fluopicolide	mg/kg	0,01
Fluopyram	mg/kg	0,01
Fluquinconazole	mg/kg	0,01
Fluroxypyr (Free acid)	mg/kg	0,01
Flutriafol	mg/kg	0,01
Formetanate (Sum of formetanate and its salts expressed as formetanate(hydrochloride))	mg/kg	0,01
Fosthiazate	mg/kg	0,01
Halosulfuron methyl	mg/kg	0,01
Haloxyfop (Free acid)	mg/kg	0,01
Haloxyfop metyl	mg/kg	0,01
Hexaconazole	mg/kg	0,01
Hexythiazox	mg/kg	0,01
Imazalil	mg/kg	0,01
Imidacloprid	mg/kg	0,01
Indoxacarb (sum of indoxacarb and its R enantiomer)	mg/kg	0,01
Ioxynil (Free acid)	mg/kg	0,01
Iprovalicarb	mg/kg	0,01
Linuron	mg/kg	0,01
Lufenuron	mg/kg	0,01
Malaoxon	mg/kg	0,01
Mandipropamid	mg/kg	0,01
MCPA (Free acid)	mg/kg	0,01
Mecarbam	mg/kg	0,01
Mepanipyrim	mg/kg	0,01
Mepronil	mg/kg	0,01
Metaflumizone (sum E,Z isomers)	mg/kg	0,01
Metamitron	mg/kg	0,01
Metazachlor	mg/kg	0,01
Methamidophos	mg/kg	0,01
Methiocarb	mg/kg	0,01
Methiocarb (sum of methiocarb and methiocarb sulfoxide and sulfone, expressed as methiocarb)	mg/kg	0,01
Methiocarb sulfone	mg/kg	0,01
Methiocarb sulfoxide	mg/kg	0,01
Methomyl	mg/kg	0,01
Methoxyfenozide	mg/kg	0,01
Metoxuron	mg/kg	0,01

Q.L.: Quantification Limit RESULTS IN PAGE 1 OF REPORT
Methods: (MET-CR-MULTI-LC/MSMS) (MET-CR-Extraccion-Multi)

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Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: **A-02364170020 [MR-F]-EN**

RELATION OF ACTIVE ANALYZED MATTERS (PESTICIDES LC/MS/MS)

Resource	Units	Q.L.
Metribuzin	mg/kg	0,01
Milbemectin (sum of milbemycin A4 and milbemycin A3, expressed as milbemectin)	mg/kg	0,01
Monocrotophos	mg/kg	0,01
Nitenpyram	mg/kg	0,01
Norflurazon	mg/kg	0,01
Novaluron	mg/kg	0,01
Omethoate	mg/kg	0,01
Oxadiargyl	mg/kg	0,01
Oxamyl	mg/kg	0,01
Paclobutrazol	mg/kg	0,01
Paraoxon	mg/kg	0,01
Paraoxon-methyl	mg/kg	0,01
Pencycuron	mg/kg	0,01
Phenmedipham	mg/kg	0,01
Phorate	mg/kg	0,01
Phosmet	mg/kg	0,01
Pirimicarb	mg/kg	0,01
Prochloraz	mg/kg	0,01
Procloraz (sum of prochloraz and its metabolites containing 2,4,6-trichlorophenol, expressed as prochloraz)	mg/kg	0,01
Promecarb	mg/kg	0,01
Propamocarb	mg/kg	0,01
Propargite	mg/kg	0,01
Propoxur	mg/kg	0,01
Proquinazid	mg/kg	0,01
Prosulfocarb	mg/kg	0,01
Pymetrozine	mg/kg	0,01
Pyraclostrobin	mg/kg	0,01
Pyridate	mg/kg	0,01
Quizalofop P ethyl	mg/kg	0,01
Rimsulfuron	mg/kg	0,01
Rotenone	mg/kg	0,01
Silthiofam	mg/kg	0,01
Spinosad: sum of spinosyn A and spinosyn D, expressed as spinosad	mg/kg	0,01
Spirodiclofen	mg/kg	0,01
Spirotetramat	mg/kg	0,01
Spirotetramat and its 4 metabolites expressed as spirotetramat R	mg/kg	0,01
Spirotetramat, BYI 03380-Enol	mg/kg	0,01
Spirotetramat, BYI 03380-Enol-Glucoside	mg/kg	0,01
Spirotetramat, BYI 03380-Ketohydroxy	mg/kg	0,01
Spirotetramat, BYI 03380-Monohydroxy	mg/kg	0,01
Spiroxamine	mg/kg	0,01
Sulfentrazone	mg/kg	0,01
Tebufenozide	mg/kg	0,01
Terbufos oxon sulfone	mg/kg	0,01
Terbufos sulfoxide	mg/kg	0,003
Thiabendazole	mg/kg	0,01
Thiacloprid	mg/kg	0,01
Thiamethoxam	mg/kg	0,01
Thifensulfuron methyl	mg/kg	0,01
Thiobencarb	mg/kg	0,01
Thiodicarb	mg/kg	0,01
Thiofanox sulfoxide	mg/kg	0,01
Thiophanate-methyl	mg/kg	0,01
Triadimenol	mg/kg	0,01
Tricyclazole	mg/kg	0,01
Trifloxystrobin	mg/kg	0,01
Triflumuron	mg/kg	0,01
Triforine	mg/kg	0,01

Resource	Units	Q.L.

Q.L.: Quantification Limit RESULTS IN PAGE 1 OF REPORT
Methods: (MET-CR-MULTI-LC/MSMS) (MET-CR-Extraccion-Multi)

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ANNEX TO THE TEST - TRACES

INTERQUIM, S.A.
Avda. Diagonal, 549, 5ª Planta - . 08029 - Barcelona

Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: **A-02364170020 [ANX]-EN** **Sample Sent by:** Helena Montijano

Date collected/Entry:	28/03/2017 - 28/03/2017	**Date of issue:**	25/04/2017
Date start/End:	28/03/2017 - 10/04/2017	**Time collected/Entry:**	14:20 - 19:05
Sample quantity:	500 g		
Type of sample:	Citrosa		

Parameter	Units	Result	LMRs
Carbendazim (sum of benomyl and carbendazim expressed as carbendazim) (MET-CR-MULTI-LC/MSMS) (MET-CR-Extraccion-Multi)	**mg/kg**	**0,008**	

Comment: This Annex affects to parameter detected below the limit of quantification expressed in the test report.

Armonized MRL

The results of this report only affect to the tested samples. It is not permitted the total or partial reproduction this report without approval of Ecosur laboratory.

The samples will be preserved according the specific requirements established by the Ecosur Quality Syste except specific demands of the clients. The uncertainties of the test have been calculated and are available f

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TEST REPORT

INTERQUIM, S.A.
Avda. Diagonal, 549, 5ª Planta - . 08029 - Barcelona

Your Ref:
CITROSA (2044486) LOTE 016K007

Ecosur Ref: **A-02364170020 [P]-EN-MI** **Sample Sent by:** Helena Montijano

Date collected/Entry:	28/03/2017 - 28/03/2017	**Date of issue:**	25/04/2017
Date start/End:	28/03/2017 - 10/04/2017	**Time collected/Entry:**	14:20 - 19:05
Sample quantity:	500 g		
Type of sample:	Citrosa		

Requested test:

Total dithiocarbamates, Melamine, Crysene, POLYCYCLIC HYDROCARBONS AROMATIC (PHAs) (Sum of Benzo (a) Pyrene, Benzo (a) Anthracene, Benzo (b) Fluoranthene y Crysene), Benzo (a) Pyrene, Benzo (b) Fluoranthene, Benzo (a) Anthracene, Aflatoxin B1, Aflatoxin B2, Aflatoxin G1, Aflatoxin G2, Total Aflatoxins (Sum of B1,B2,G1 y G2), Pyrethrins (sum isomers), Cinerin I, Cinerin II, Jasmolin I, Jasmolin II, Piretrin I and Piretrin II.

Parameter	Units	Q.L.	Result
Crysene (MET-CR-HPA-cond / MET-CR-HPA-extr)	**µg/kg**	**1,0**	**< 1,0**
Melamine (MET-CR-MULTI-LC/MSMS) (MET-CR-Extraccion-Multi)	**mg/kg**	**0,05**	**< 0,05**
Total dithiocarbamates (MET-CR-Ditiocarbamatos totales;GC/PFPD)	**mg CS2/kg**	**0,01**	**< 0,01**
POLYCYCLIC HYDROCARBONS AROMATIC (PHAs) (Sum of Benzo (a) Pyrene, Benzo (a) Anthracene, Benzo (b) Fluoranthene y Crysene) (MET-CR-HPA-cond / MET-CR-HPA-extr)	**µg/kg**	**4,0**	**< 4,0**
Benzo (a) Pyrene (MET-CR-HPA-cond / MET-CR-HPA-extr)	**µg/kg**	**1,0**	**< 1,0**
Benzo (b) Fluoranthene (MET-CR-HPA-cond / MET-CR-HPA-extr)	**µg/kg**	**1,0**	**< 1,0**
Benzo (a) Anthracene (MET-CR-HPA-cond / MET-CR-HPA-extr)	**µg/kg**	**1,0**	**< 1,0**
Aflatoxin B1 (MET-CR-Aflatoxinas-Al;HPLC-FLD)	**µg/kg**	**0,5**	**< 0,5**
Aflatoxin B2 (MET-CR-Aflatoxinas-Al;HPLC-FLD)	**µg/kg**	**0,5**	**< 0,5**
Aflatoxin G1 (MET-CR-Aflatoxinas-Al;HPLC-FLD)	**µg/kg**	**0,5**	**< 0,5**
Aflatoxin G2 (MET-CR-Aflatoxinas-Al;HPLC-FLD)	**µg/kg**	**0,5**	**< 0,5**
Total Aflatoxins (Sum of B1,B2,G1 y G2) (MET-CR-Aflatoxinas-Al;HPLC-FLD)	**µg/kg**	**0,50**	**< 0,5**
Pyrethrins (sum isomers) (MET-CR-MULTI-LC/MSMS) - (MET-CR-Extraccion-Multi)	**mg/kg**	**0,06**	**< 0,06**

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Ref. Ecosur: **A-02364170020 [P]-EN-MI**

Su Ref: CITROSA (2044486) LOTE 016K007

ANALYTICAL RESULTS

Parameter	Units	Q.L.	Result
Cinerin I (MET-CR-MULTI-LC/MSMS) - (MET-CR-Extraccion-Multi)	**mg/kg**	**0,01**	**< 0,01**
Cinerin II (MET-CR-MULTI-LC/MSMS) - (MET-CR-Extraccion-Multi)	**mg/kg**	**0,01**	**< 0,01**
Jasmolin I (MET-CR-MULTI-LC/MSMS) - (MET-CR-Extraccion-Multi)	**mg/kg**	**0,01**	**< 0,01**
Jasmolin II (MET-CR-MULTI-LC/MSMS) - (MET-CR-Extraccion-Multi)	**mg/kg**	**0,01**	**< 0,01**
Piretrin I (MET-CR-MULTI-LC/MSMS) - (MET-CR-Extraccion-Multi)	**mg/kg**	**0,01**	**< 0,01**
Piretrin II (MET-CR-MULTI-LC/MSMS) - (MET-CR-Extraccion-Multi)	**mg/kg**	**0,01**	**< 0,01**

This report modifies and cancels to A-02364170020 [P]-EN - 10/04/2017. By change of LC of aflatoxins and breakdown of natural pyrethrins.

Q.L.: Quantification Limit

The results of this report only affect to the tested samples. It is not permitted the total or partial reproduction of this report without approval of Ecosur laboratory.

The samples will be preserved according the specific requirements established by the Ecosur Quality System except specific demands of the clients. The uncertainties of the test have been calculated and are available for the client.

AIBMR
Life Sciences, Inc.

May 26, 2020

Molly Harry
Regulatory Review Scientist/Chemistry Reviewer
U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients

Re: Responses to GRN 902 questions

Dear Ms. Harry,
Please find our responses to your questions for GRN 902 below. The original FDA questions are in black, and responses to the questions are in red.

1. Please provide additional details on the manufacturing process for the starting crystals of neohesperidin.

   Dry, immature bitter oranges are milled and extracted in a hot hydroalcoholic medium. The extract which contains neohesperidin is separated from solids by centrifugation. The supernatant is filtered. The filtrate is concentrated by evaporation of the alcohol where upon neohesperidin precipitates from the solution. The precipitate is washed with water.

   Neohesperidin is purified with a hydroalcoholic solution and washed with water. The washed purified neohesperidin is dried and milled.

2. You indicate that an unknown impurity exists, and it has been tentatively identified as dihydrochalcone or a flavonoid present at no more than 0.4%.
   Can this impurity be identified and confirmed by using mass spectrometry?
   A tentative identification might be carried out by Liquid Chromatography coupled to Mass Spectrometry (MS). According to the used MS detector, several options are available:
   QQQ / Ion trap: This detector would provide the main ion of the molecule, as well as its fragmentation pattern.
   This would allow the identification of its main structural features, such as functional groups. However, these techniques would not provide any information regarding the structural arrangement of the fragments. Therefore, taking into account the structural similarities between flavonoids, an unequivocal identification would not be feasible.

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TOF: This detector would provide the accurate mass of the compound, as well as its isotopic distribution. This data would allow the assignation of a series of tentative molecular formulas, with different degree of agreement. However, this technique would not provide any structural information. Thus, taking into account that many flavonoids share molecular formula, identification would not be possible.

This technique would give us more information about the unknown impurity but, at the end of the day, the internal library of the software would provide a certain number of possible structures. For this reason, the identification would not be unequivocal.

What is the potential source of this impurity and what is the significance of discussing an impurity that is present at such a low level?

As the production of NHDC is a chemical reaction, very low levels of other flavonoids (with various side chains and arrangements) are naturally created in manufacturing. These are in accordance with the impurities listed in the monograph for NHDC in USP-NF.[1] The significance of discussing the impurity present at such a low level is to characterize, as best as possible, the entirety of the product. Additionally, as identified in the USP-NF monograph, there is specific acceptance criteria listed for "other" impurities (i.e. impurities other than impurities A through G). The monograph defines "other" impurities as composing no more than 0.5% of the final product. Impurity H was found to compose no more than 0.4% of the batches tested. Therefore, its mention in the GRAS dossier also reflects HealthTech BioActives' compliance with accepted monographs.

3. Please provide batch analyses data for residual contaminant and pesticide in three non-consecutive batches of the NHDC ingredient.

   Please see attached.

4. In section 2.3.6 (page 18) of the notice, you state that heavy metal contamination of NHDC is not expected. However, you provide batch results for heavy metal analysis on page 19.
   - Please provide specifications for heavy metals in the NHDC.

   Please find the table below regarding the specifications for heavy metals.

Metal	Specification	Method
Lead	≤ 2 ppm	USP <730>
Mercury	≤0.1 ppm	USP <730>
Arsenic	≤ 3 ppm	USP <730>
Cadmium	≤ 1 ppm	USP <730>

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5. Please verify that the analytical methods have been validated for their intended purpose.
   The analytical methods have been validated for their intended purposes.

6. There is a specification for assay of 96-102% for the NHDC ingredient and a moisture specification of up to 12%. Based on your batch analyses, the results show 10-11% moisture content with assay levels of approximately 98%. This results in a mass balance of greater than 100%.
   - Please clarify and/or explain this discrepancy.
     The result of assay is calculated on dried basis.

7. On page 44 section 6.7.1 of the notice (4th bullet), you state that data from Gumbmann et al., (1978) (e.g. 1-year oral toxicity study in rats and 2-year oral toxicity study in dogs) were used to establish safety. Since FDA could not obtain this publication using publicly available sources, we could not determine whether it was peer-reviewed and whether or not the discussed information satisfies the "*generally available and accepted* scientific data" requirement as outlined in the GRAS final rule. We note that in your synopsis of those studies, you described some toxicological endpoints of potential concern that JECFA evaluated (summarized in Table 12). Yet, the European Commission's Scientific Committee for Food (Reports of the Scientific Committee for Food (Twenty-first series), pg. 23) clearly noted deficiencies in those studies:
   "The Committee could not determine a no-effect level for NHDC using the studies carried out by the USDA up to 1978 because the results found during the various tests were variable and sometimes contradictory."
   - Please clarify which studies and data were pivotal to your GRAS conclusions and discuss the findings of Gumbmann et al. in their context.
     While AIBMR was able to obtain this article (please find it attached), we understand the FDA's concern that it may not be easily available and satisfy the requirement of a GRAS conclusion. We believe that a GRAS conclusion can still be made with Gumbmann as a corroborative reference and, therefore, our pivotal studies are:
     - Lina et al., (1990), an oral, repeated-dose rat study, establishing a NOAEL in rats at 750 mg/kg bw/day,[2]
     - Various published genotoxicity studies summarized in Table 10 of the GRAS dossier,
     - Waalkens-Berendsen et al., (2004) reproductive study establishing a NOAEL of 3100 mg/kg bw/day,[3]
     - The determination of a safe ADI of 5 mg/kg bw/day by the European Commission's Scientific Committee for Food in 1989.[4]

     In 1989, European Commission's Scientific Committee for Food (Reports of the Scientific Committee for Food) noted that they could not determine a no-effect level for NHDC using the studies carried out by the USDA up to 1978 because the results found during the various tests were "variable and sometimes contradictory" due to nutritional deficiencies noted in some of the reviewed studies, specifically within the various toxicologic studies performed by Gumbmann et al., (1978).[4] However, based on the totality of evidence, the committee determined the substance was safe and recommended an ADI of 5 mg/kg bw/day.

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Gumbmann et al., (1978) was published in the book Sweeteners and Dental Caries and the report is attached to this communication.[5] The publication was listed as pivotal data (specifically the 1-year repeated dose rat and 2-year repeated dose dog studies) due to findings of lack of adverse effects at elevated doses (up to 10% NHDC in diet) for long periods of time (up to 1 year). The Joint Expert Committee on Food Additives (JECFA) determined the NOAEL of the study to be 2500 mg/kg bw/day (1-year rat study) and 1000 mg/kg bw/day (2-year dog study).[6] In addition to the 1- and 2-year repeated dose studies, the authors completed 122–170 day repeated dose trials on rats with NHDC comprising of 0% and 5% of the animals' diet. As noted in the GRAS dossier, the contradictory findings within this study include an increase in thyroid weights in rats fed NHDC at 5% of their diet for 122–170 days, which was not found in rats fed NHDC at 5% of their diet for 1 year or in rats fed NHDC at 10% of their diet for 11 months. Other findings from this publication have been noted in the GRAS conclusion. In summary, much of the data from Gumbmann et al., (1978) corroborates the safety of HealthTech BioActives' NHDC for its intended use.

8. Please provide a brief narrative as to why NHDC from your intended use is not a safety concern for sensitive sub-populations, such as diabetics.

Non-nutritive sweeteners (NNS), including NHDC, are low calorie sweeteners that do not have an effect on glycemic response in those that ingest them. A study by Dewinter et al., (2016) examined non-nutritive sweetener consumption habits of pediatric patients with type 1 diabetes and found that while diabetics are considered a population with high consumption patterns of NNS (due to a lack of effect on blood glucose levels), this population did not exceed the EFSA ADI for NHDC. The authors also determined that there is little chance that NNS ADIs in general would be exceeded by this population.[7]

Animal models can inform on the effects of NHDC and similar flavonoid structures with regard to glucose homeostasis. In healthy mice, the ingestion of NHDC in combination with a bolus of glucose did not cause a change in 30-minute post-prandial blood glucose levels or gastric emptying compared to vehicle control.[8] In diabetic mice, neohesperidin was shown to have no negative effect on blood glucose levels.[9] Though it was neohesperidin and not NHDC, the study is suggestive that a similar lack of blood sugar effects could be found in NHDC as it is composed of the same flavonoid. Diabetic animal model studies using other NNS compounds have similarly shown a lack of concerning results.[10, 11]

Other studies monitoring various glycemic parameters on people with diabetes given NNS showed a lack of adverse effects on blood sugar regulation compared to the controls.[12-15] Three independent reviews of research on individuals with both T1DM and T2DM did not find a difference in diabetic control between those consuming various NNS and controls.[16-18] Lohner, et al. (2016) performed a scoping review of 372 human studies on any health outcome, including on subjects with diabetes, using NNS as the intervention.[16] In diabetics, most of the reviewed studies showed no effects of NNS on diabetic control. Olivier et al., (2015) examined 1,616 studies on overall health effects of NNS, of which 5 trials were specifically on blood glucose homeostasis in diabetics, showing that overall there were no acute or chronic effects of NNS consumption on blood glucose in diabetes.[17] Behnen et al., (2013) specifically reviewed studies on NNS effects in diabetics. They included 9

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clinical trials (490 diabetic subjects) and found no significant difference in glycemic control in those consuming NNS.[18] Though NHDC was not included in any of these reviews examining NNS effects on diabetic subjects, the results from the studied NNS do not suggest possible concern related to NHDC consumption by diabetic individuals. EFSA did not identified any at risk subpopulations in their ADI determination for NHDC, either in their original report, or in mentions of the ADI since.[4, 19, 20] Additionally, the FDA has allowed the addition of many NNS (as seen, for example, in 21 CFR 180.37, 172.804, 172.800, 172.830, 172.829 and GRNs 858, 839, 838, 821, 795, 790, 768, 759, 745, 744, 733, 702, 662, 656, 638, 626, 619, 607, 555, etc.) into the food supply without limitation to sub-populations such as diabetics. Therefore, though there are authoritative opinions that state there is insufficient evidence either for or against the recommendation of consumption of NNS in place of nutritive sweeteners to individuals with diabetes,[21, 22] there is no reason to suspect NHDC would pose any increased safety concern in this or other sub-populations compared to other NNS with GRAS status. Lastly, the very large margin of safety for the ingredient as relates to its estimated exposure also provides some safety assurance with regard to various sub-populations.

We hope that these responses are adequate with regard to your questions. Please don't hesitate to let us know if there are any further questions or comments or would like for us to expand on any of the responses above during your continued GRN evaluation process. We will be happy to discuss and/or provide any additional written responses.

Sincerely,

Dr. Kayla Preece
Agent of the notifier
Regulatory and Scientific Consultant at AIBMR Life Sciences, Inc.

References:

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2. Lina BA, Dreef-van der Meulen HC, et al. Subchronic (13-week) oral toxicity of neohesperidin dihydrochalcone in rats. *Food Chem Toxicol*. 1990;28(7):507-13
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fattening, dairy sheep, ewes for reproduction, salmonids and dogs. *EFSA Journal*. 2011;9(12):2444
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Ten pages have been removed in accordance with copyright laws. The removed reference is:

M.R. Gumbmann, “Toxicity of neohesperidin dihydrochalcone”, Toxicology and Biological Evaluation Research Unit, Western Regional Research Center, ARS, US Department of Agriculture, Berkeley, California 94710

From:	John Endres
To:	Harry, Molly
Cc:	Kayla Preece; Amy Clewell
Subject:	AIBMR: FDA GRN 902: Neohesperidin dihydrochalcone (NHDC)
Date:	Wednesday, June 24, 2020 2:29:11 PM

Dear Ms. Harry-
We understand from previous discussions we have had with the FDA why OFAS has concerns over Pb and As levels (specifically concentrations) in various foods–especially for the most sensitive populations such as infants. We have also discussed with the FDA that it makes more sense to consider absolute exposure to Pb and As rather than relative concentration. Of course, it is the EDI at the 90th percentile of the foods that matters most (the greater the daily mass consumed, the greater the exposure based upon the concentration). We don't believe that it is scientifically appropriate to limit the concentration without considering the EDI.

Below are 2 examples of significant bodies that have established safe harbor levels for these 2 elements.
–California Proposition 65
–ICH FDA Guideline (March 2020) Elemental Impurities: Guidance for Industry

Prop 65 has set the NSRL for Pb at 15 µg/day and the MADL at 0.5 µg/day and set the NSRL for As at 10 µg/day. ICH FDA Guideline (March 2020) Elemental Impurities: Guidance for Industry Appendix A.2.1 (pg 31) sets the limit of Pb at 5 µg/day and As at 15 µg/day. The EDI for Neohesperidin dihydrochalcone of our GRAS Notification 902 at the 90th percentile is 19.3 mg NHDC/day.

With the Pb specification of ≤ 2 ppm, the absolute maximum exposure to Pb would be 0.0386 µg/day, which is 389 times lower than the NSRL and 13 times lower than the MADL. With the As specification of ≤ 3 ppm, the absolute maximum exposure to As would be 0.0579 µg/day, which is 173 times lower than the NSRL.

As illustrated above, these exposures are exceedingly low and in our opinion of little, if any, concern. Importantly, these respective specifications are also the same limits for NHDC listed in the Food Chemical Codex/USP monograph.

Therefore, based on the above calculations and exposures, we would like to respectfully leave the specification as is. Thank you in advance for your consideration and feedback.

Best Regards,
Dr. Kayla Preece
Dr. Amy Clewell
&
John R. Endres, ND
Chief Scientific Officer
AIBMR Life Sciences, Inc.
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From:	Kayla Preece
To:	Harry, Molly
Cc:	John Endres; Amy Clewell; Jared Brodin
Subject:	AIBMR: GRN 902: NHDC: Clarification of intended use for NHDC (GRN 000902)
Date:	Monday, September 28, 2020 1:10:48 PM
Attachments:	image001.png

Dear Ms. Harry-

NHDC is intended to be used as a sweetener in the foods listed in GRN 902. Please let us know if you have any further questions we can assist with.

Best regards,
Kayla

Kayla Preece, ND

Scientific and Regulatory Consultant

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On Fri, Sep 25, 2020 at 9:20 AM Harry, Molly <Molly.Harry@fda.hhs.gov> wrote:

> Dear Dr. Preece,
>
> In GRN 000902, you state that the intended use of neohesperidin dihydrochalcone (NHDC) is as an "ingredient." However, you also provide information regarding its relative sweetness to sucrose and its use as a sugar substitute. Please clarify that NHDC is being used as a sweetener in the foods listed in the GRN and not as an ingredient.
>
> **Molly A. Harry**
> *Regulatory Review Scientist*
>
> **Office of Food Additive Safety, Division of Food Ingredients**
> **Center for Food Safety and Applied Nutrition**
> **U.S. Food and Drug Administration**
> Molly.Harry@fda.hhs.gov
>
> Tel: 240-402-1075

--

Best regards,
Kayla

Kayla Preece, ND

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From: Kayla Preece
To: Harry, Molly
Cc: John Endres; Amy Clewell; Jared Brodin
Subject: AIBMR: HealthTech BioActives-FDA GRN 000902 - NHDC- Updated Pt 1
Date: Friday, October 9, 2020 2:04:06 PM
Attachments: image001.png
Part 1UPDATEDwithsig.pdf

Hello Ms. Harry-

Thank you again for taking the time to speak with us the other day.

Please find the attached signed and updated Pt 1 that specifies NHDC as a sweetener. Per our phone discussion, our client does not wish to describe the intended use in GRN 902 as a flavor enhancement or modifier.

Please let me know if you have any questions and we look forward to hearing from the FDA soon.

Best regards,
Kayla

Kayla Preece, ND

Scientific and Regulatory Consultant

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On Fri, Oct 2, 2020 at 9:07 AM Harry, Molly <Molly.Harry@fda.hhs.gov> wrote:

> Dear Dr. Preece,
>
> In your September 28, 2020 email, you stated that NHDC is intended for use as a sweetener in the food categories listed in the notice. This means that the intended use in food has changed and that NHDC would have a technical effect in the food. For the record, please provide an updated "Part 1: Signed Statements and Certification" for GRN 000902 that is signed by the notifier.
>
> Sincerely,
>
> **Molly A. Harry**

Part 1: Signed Statements and Certification

1.1 Submission of GRAS Notice

HealthTech BioActives, S.L.U. (the notifier) is submitting a new GRAS notice in accordance with 21 CFR Part 170, Subpart E, regarding the conclusion that neohesperidin dihydrochalcone (NHDC) is Generally Recognized as Safe (GRAS) for its intended use, consistent with section 201(s) of the Federal Food, Drug and Cosmetic Act.

1.2 Name and Address of the Notifier and Agent of the Notifier

Notifier

Francisco Borrego Ríos
HealthTech BioActives, S.L.U.
Ctra. Beniel a Zeneta, 143-145
El Raiguero-La Villa
30130 Beniel (Murcia)
Spain
Tel: +34 968 012 006
pborrego@ferrer.com

Agent of the Notifier

Kayla Preece, ND
Scientific and Regulatory Consultant
AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
Seattle, WA 98112
Tel: (253) 286-2888
kayla@aibmr.com

1.3 Name of the Substance

Neohesperidin dihydrochalcone

1.4 Intended Conditions of Use

NHDC is intended to be used as a sweetener in various food categories (as listed in Part 3) at maximum levels of 10–1000 ppm, depending upon the specific food category. NHDC is not intended for use in foods where standards of identity would preclude such use, infant formula, or any products that would require additional regulatory review by USDA.

1.5 Statutory Basis for GRAS Conclusion

The conclusion of GRAS status of NHDC for its intended conditions of use, stated in Part 1.4 of this notice, has been made based on scientific procedures.

1.6 Not Subject to Premarket Approval

We have concluded that NHDC is GRAS for its intended conditions of use, stated in Part 1.4 of this notice, and, therefore, such use of NHDC is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act.

1.7 Data and Information Availability Statement

The data and information that serve as the basis for this GRAS conclusion will be available for review and copying during customary business hours at the office of Ctra. Beniel a Zeneta 143-145, El Raiguero-La Villa 30130 Beniel (Murcia) – Spain or will be sent to FDA upon request.

1.8 Exemption from Disclosure under the Freedom of Information Act

None of the data and information in Parts 2 through 7 of this GRAS notice are considered exempt from disclosure under the Freedom of Information Act (FOIA) as trade secret or commercial or financial information that is privileged or confidential.

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1.9 Certification of Completion

We hereby certify that, to the best of our knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of NHDC.

10/08/2020

_____ _____

Francisco Borrego Ríos — Date
Director
HealthTech BioActives, S.L.U. – Beniel (Murcia)

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