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David Edwards, Ph.D.
Director
Division of Animal Feeds, HFV-220
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

June 29, 2017

Subject: **GRAS Notice Filing**
Clinoptilolite as an Anticaking Agent

Dear Dr. Edwards

We respectfully resubmit the attached Notice in support of the determination that clinoptilolite, a natural crystalline aluminosilicate mineral of sedimentary origin, is Generally Recognized as Safe (GRAS) when used as an anticaking agent in animal feed for major food animals (cattle, swine, chicken, turkeys), other minor species (ruminants: goats and sheep, other poultry species) and pet animals (cats, dogs) at levels up to 2%.

G-Science has determined that clinoptilolite produced by Zeocem a.s. is GRAS based on scientific procedures in accordance with 21 CFR 570.30(a) and (b). The enclosed GRAS Notice provides a review of the information related to the intended uses, manufacturing, and safety of the ingredient. The GRAS notice was compiled in accordance with the rules and regulations set out in the Federal Register, Vol. 81, No. 159, Part 570, Subpart E. The analytical data, published studies, and information that are the basis for this GRAS determination are included with this Notice. The GRAS Notice consists of seven parts as required by 21 CFR 570.225 through 570.255. We have included a hard copy of the GRAS Notice and its Attachments.

Certain data and information included in some sections of this notice are exempt from disclosure under the Freedom of Information Act, 5 U.S.C 552 due to being considered a trade secret and/or commercial information that is confidential. Those sections and information/data contained therein which meet these criteria are identified using a "grey" background. They are described in Section 1, part (c)(8). If you disagree with our

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confidential aims, we respectfully request that the Agency notify us, prior to any release of the Notice on FDA´s website or otherwise.

We trust that this resubmission satisfies the Agency´s needs and addresses all deficiencies specified in your letter (May 30th, 2017), and will be deemed accepted and complete. Should any questions arise, please contact us, preferably by telephone (+1 678 925 8015) or e-mail (thomas.berger@g-science.com) so that we can promptly reply.

Sincerely yours,

Thomas Berger
Position: Vice President G-Science, Inc.

Enclosures

Requests for copies of the respective materials may be directed to the person responsible for the submission.

1.8 Exemption from Disclosure under the FOI provisions

Certain data and information included in some sections of this notice are exempt from disclosure under the Freedom of Information Act, 5 U.S.C 552 due to being considered a trade secret and/or commercial information that is confidential. Those sections and information/data contained therein which meet these criteria are identified using a "grey" background.

This GRAS notice is signed by

Thomas Berger
Position: Vice President G-SCIENCE, Inc.

June 29, 2017
Date

Generally Recognized as Safe (GRAS) Notice

for

Clinoptilolite
(CAS Reg. No. 12173-10-3)

Submitted to:

Division of Animal Feeds (HFV-220)
Office of Surveillance and Compliance
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

Notifier:

G-SCIENCE, Inc.
5500 Highlands Parkway
Smyrna, GA, 30082
USA

Part 1

SIGNED STATEMENTS AND CERTIFICATIONS

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1. SIGNED STATEMENTS AND CERTIFICATIONS

1.1 Claim of GRAS Notice

G-SCIENCE, Inc. (hereinafter G-Science or the Notifier) submits the enclosed notice to support the claim that the compound clinoptilolite, a natural crystalline aluminosilicate mineral of sedimentary origin, is generally recognized as safe (GRAS) when used as an anticaking agent in feed products for major food animals (cattle, swine, chicken, turkeys), other minor species (ruminants: goats and sheep, other poultry species) and pet animals (cats, dogs).

1.2 Name and Address of the Notifier

G-SCIENCE, Inc.
5500 Highlands Parkway
Smyrna, GA, 30082
USA
Phone: +1 678 925 8015

1.2.1 Person responsible for the submission

Thomas Berger
Vice President G-SCIENCE, Inc.
Email: thomas.berger@g-science.com

1.3 Name of the Notified Substance

The name of the notified substance is clinoptilolite, a natural crystalline aluminosilicate mineral of sedimentary origin. The Chemical Abstracts Service (CAS) identifies the substance using the registry number 12173-10-3 (CAS, 2016).

1.4 Intended Conditions of Use

Clinoptilolite is intended to be used as an anticaking agent. It is added to complete feed mixtures or feed premixes of diets of major food animals (cattle, swine, chicken, turkeys), other minor species (ruminants: goats and sheep, other poultry species) and pet animals (cats, dogs), regardless of stage of production, at a level not exceeding 2% (20,000 mg/kg feed) by weight of the feed composition in accordance with good manufacturing or feeding practice.

1.5 Basis for Conclusion of GRAS Status

The determination of the GRAS status of clinoptilolite is based on scientific procedures in accordance with the Code of Federal Regulations (CFR) 21 CFR 570.30(a) and (b).

1.6 GRAS Conclusion

The Notifier claims that because the notified substance is GRAS the substance is exempt from the requirement for premarket approval as defined in Chapter III, Sec. 301 [21 U.S.C. 331] (II)(3)(C) of the Federal Food and Drug Cosmetic Act [As Amended Through P.L. 114-146, Enacted April 19, 2016] (OLRC, 2016).

The GRAS notice was complied in accordance with the rules and regulations set out in the Federal Register, Vol. 81, No. 159, Part 570, Subpart E (GPO, 2016a). The Notifier certifies to the best of its knowledge that the GRAS notice is a complete, representative and balanced submission that includes unfavorable information, as well as favorable information, that is known to the Notifier, and pertinent to the evaluation of the safety and GRAS status of the use of the substance

1.7 Availability of Information

This GRAS notice is being submitted in electronic format. The Notifier will retain copies of all data and information that form the basis for the Notifier's conclusion of GRAS status. The Notifier agrees to provide FDA, either during or after its evaluation of the notice, complete copies of the data and information, either in electronic format accessible for evaluation or on paper. FDA can review or copy the data and information during customary business hours at the Notifier's address given above.

PART 2

DETAILED INFORMATION ABOUT THE NOTIFIED SUBSTANCE

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2. DETAILED INFORMATION ABOUT THE NOTIFIED SUBSTANCE

2.1 Identity

Clinoptilolite is a natural zeolite that occurs in sedimentary and volcanic rocks, altered basalts, ores and clay deposits. Zeolites are hydrated aluminosilicates that possess a three dimensional framework structure. They are characterized by their ability to lose and gain water reversibly, absorb molecules of appropriate cross sectional diameter (absorption or acting as molecular sieves) and exchange their extra-framework cations without major change of their structure (ion exchange property) (Ames, 1960; Sheppard, 1971; Mumpton and Fishman, 1977).

Each zeolite species has its own unique crystal structure, thus its own set of physical and chemical properties. Clinoptilolite is one of the most commonly mined zeolites worldwide (USGS, 2015). It belongs to the heulandite group of tectosilicate minerals and includes three species: clinoptilolite Ca, clinoptilolite Na and clinoptilolite K; with the respective chemical symbol indicating the most dominant extraframework cation in the chemical formula (Coombs et al, 1997). Factors affecting clinoptilolite cation selectivity include cation size, charge, electronic structure and, in the presence of Na, temperature. Clinoptilolite has a thermal stability of up to 700°C (without reaction at lower temperatures) and a Si:Al ratio of ≥4. The small amount of Al in clinoptilolite results in a relatively low cation exchange capacity (CEC) (~2.3 meq/g), however, clinoptilolite has a decided preference for larger cations, including NH_4^+ (Ames, 1960; Mumpton, 1960), with absorption capacity increasing with pH (Kithome et al., 1999). The affinity of clinoptilolite for NH_4^+ is the basis for its widespread use in the treatment of animal wastes and municipal/industrial wastewater (Jorgensen et al., 1976; Mumpton, 1985, 1999; Inglezakis, 2005; Jha and Hayashi, 2009). Because of its absorption, cation exchange, catalysis and dehydration properties, clinoptilolite is used in a variety of applications in the fields of agricultural/animal production, construction, industrial technology, environment and human medicine (Mumpton, 1985; Auerbach et al., 2003; Reháková et al., 2004; Colella, 2011).

2.2 Characterization of Zeocem Clinoptilolite

The clinoptilolite which is the subject of this GRAS notice is a natural crystalline aluminosilicate mineral of sedimentary origin that is exclusively sourced at Zeocem's Nižný Hrabovec mine in the Prešov Region of the Slovak Republic.

Natural clinoptilolites are characterized primarily by the content of clinoptilolite and secondly by the presence of clays. A commonly accepted mineralogical analysis for clinoptilolite is X-ray diffraction (XRD) (CRL, 2010). Based on this analysis, the Zeocem clinoptilolite has a minimum clinoptilolite content of 80% and a maximum clay content of 20%, and is free of quartz and fibers of other zeolite minerals. Particle size ranges from 0.05 to 2.5 mm. The clinoptilolite is primarily of the species Ca and K, with low content of Fe, Mg and Na ions (Reháková et al., 2004; Domaraká et al., 2015).

The general physical and chemical properties of Zeocem clinoptilolite are summarized Table 2.1. An overview of the composition is given in Table 2.2. Additional detailed information about its specific qualitative parameters is given in Appendices 2.1 and 2.2.

2.3 Technical Effect

2.3.1 Anticaking agent

Clinoptilolite acts as an anticaking agent that when added to feed keeps it dry and free-flowing. Under normal environmental conditions, clinoptilolite has a stable crystal structure, with mineral - specific ion exchange and adsorption properties and reversible hydration capacity.

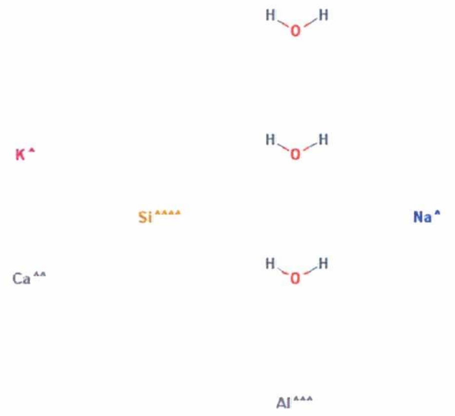
Table 2.1	**Physical and chemical properties of clinoptilolite**
Parameter	Description
Clinoptilolite	A natural crystalline aluminosilicate mineral of sedimentary origin containing ≥80% clinoptilolite and ≤20% clay minerals (free of fibers and quartz)
Chemical formula (as a naturally occurring mineral, the precise composition of clinoptilolite is subject to a degree of variation)	$(Ca, K_2, Na_2, Mg)_4\ Al_8\ Si_{40}\ O_{96}\ 24H_2O$
Molecular weight	211.279 g/mol
Structure	
CAS No.	12173-10-3
EC No.	E568
Synonyms	Clinoptilolite; Aquavital; Klinosorb; Minazel; 1010A
Uses	Anticaking agent
Color/Form	Light grayish-green
Odor	None
Physical state @ 20°C	Solid
Solubility in water	None
Melting point	1340°C
Flow temperature	1420°C
Ignition temperature	Settled dust – neg. up to 600 °C, raised dust – neg. up to 800 °C.
Flash point	Neg. up to 600 °C.
Explosive limits (volume % in air)	Non-explosive
Particle size	0.05 to 2.5 mm
Specific gravity	2200-2440 kg/m^3
Density	1600-1800 kg/m^3
Porosity	24 - 32%
Pore diameter	0.4 nm (4 Å)
Comprehensive strength	33 MPa
Mohs hardness	1.5 – 2.5
Grindability index determination	kVTI = 1.628
Specific surface (BET)	30-60 m^2g
Cation exchange capacity	1.20 – 1.50 mol/kg
Acid stability	79.5%
Thermal stability	up to 400 °C
Source: Appendices 2.1 and 2.2; Vatalová et al (2016); PubChem (2016).	

Table 2.2	Composition of Zeocem clinoptilolite
Parameter	Amount
Purity	86 – 92%
Particle size	0.05 - 2.5 mm
SiO_2	> 62%
Al_2O_3	< 14%
CaO	< 10%
Na_2O	0.2 - 1.3
Fe_2O_3	< 3.3%
K_2O	2.2 - 3.4
MgO	0.6 - 1.2
Si:Al (ratio)	4.8 - 5.4
Pb	20 ppm
Cd	0.1 ppm
As	2.5 ppm
Hg	0.1 ppm
Source: Appendices 2.1 and 2.2.	

2.3.2 Potential safety issues

No information could be found in the scientific literature indicating that the technical effect of using clinoptilolite as an anticaking agent, either in terms of the physical form of the substance or its properties in animal diets, has an impact on the safety and welfare of the target animals consuming the feed to which the substance was added. Experimental studies have demonstrated that clinoptilolite can be added to diets at levels ranging from 1.5 to 3% for ruminants, 2% to 5% for swine and 1.5% to 8% in poultry without encountering any adverse effects on animal heath. Specific studies carried out using the clinoptilolite mined and manufactured by Zeocem show that diets of target animals can be supplemented at levels ranging from 1.5% to 7.5% for ruminants, 3% to 5% in swine and 1% to 2% in poultry without any negative effects of animal health being observed. The overall safety of feeding clinoptilolite is discussed in detail in Part 6 of this notice.

2.4 Efficacy

The efficacy of an additive as an anticaking agent can be demonstrated by measuring the flowability of feed materials or compound feed, without and with the additive (Jenike, 1964). The European Community (EC) Expert Group for Technical Advice on Organic Production reported that the addition of 2% clinoptilolite to feed compounds improves flow properties (EC, 2011).

The European Food Safety Authority (EFSA) assessed the efficacy of clinoptilolite as an anticaking agent when added to feedstuffs for different food producing and companion animals. It was reported that in compound feeds with cohesive proprieties (e.g. smaller particle size and/or after solidification) clinoptilolite has the potential to improve the flowability. However, the effect tends to disappear in feeds that are already free flowing without the addition of an anticaking agent (Appendix 2.3). It was concluded that clinoptilolite is considered to have the potential to be effective as an anticaking agent (EFSA, 2013).

Zeocem clinoptilolite meets the specifications of the clinoptilolite assessed by EFSA. Therefore, the efficacy of the Zeocem clinoptilolite as an anticaking agent will be comparable to the product assessed by EFSA.

2.5 Stability Data

The clinoptilolite is certified by Zeocem as being stable for 24 months from the manufacturing date when stored in original, undamaged and closed containers in dry, hygienically clean, well-aired indoor storage facilities. The product is packaged in paper bags (25 kg) shipped as 40 bags/pallet and BigBag packaging (1,000 kg/1,200 kg/pallet) or shipped as bulk material for storage in silos (Appendix

2.1). Stability data for one a production batch of Zeocem clinoptilolite over a four-year period is given in Table 2.3.

Table 2.3	Stability of Zeocem clinoptilolite over four-year period (Batch M 070103-1)						
Product	Sample no.	Testing date	Humidity[a] (%)	Exchange capacity[b] (mol/kg)	Cumulative oversize[c] (%) (b) (4) [redacted]	(b) (4) [redacted]	Months of storage
Zeocem clinoptilolite (25 kg bags)	1	08.01.2003	(b) (4) [redacted]				
	2	08.07.2003					
	3	09.01.2004					
	4	09.07.2004					
	5	10.01.2005					
	6	08.07.2005					
	7	09.01.2006					
	8	10.07.2006					
	9	08.01.2007					

Standards used:
[a] STN 720102 - Basic analysis of silicates. Determination of loss by drying.
[b] CSN 721076 - Determination of exchange capacity and exchangeable cations of clay soils.
[c] STN 721213 - Physical and mechanical tests of limestone (sieving analysis-wet way).

2.6 Homogeneity Data

The efficacy of clinoptilolite as an anticaking agent was discussed in terms of flowability of feed materials (Section 2.4). The free flow of feed can only be achieved if an anticaking agent is distributed homogenously (otherwise clumps would occur); therefore, homogeneity studies are not necessary.

2.7 Manufacturing Process for the Notified Substance

2.7.1 Mined and processed raw material

The Zeocem clinoptilolite is exclusively sourced at the Nižný Hrabovec mine in the Prešov Region of the Slovak Republic. The raw material is excavated using conventional pit mining techniques. A selected area is blasted and the resulting blocks are broken into sizes that can be transported to an on-site crusher before being transported by bulk in trucks to the manufacturing site in Bystré. There it is dried and further milled. The milled ore is separated according to particle size, stored and later sold in bulk or in bags. A flow diagram depicting the different steps in the manufacturing of Zeocem's ground and granular clinoptilolite products is given in Appendix 2.4. The production process for the granular form of clinoptilolite is described below.

(b) (4) [redacted]

(b) (4) [redacted]

(b) (4) [redacted]

2.7.2 Traceability of product

Traceability of each production batch is carried out according to recognized industry practices. (b) (4) [redacted] (Table 2.4).

Table 2.4. Production batch codes used for products

Code	Definitions of code
(b) (4) [redacted]	(b) (4) [redacted]
(b) (4) [redacted]	

2.7.3 Process controls

(b) (4) [redacted]

(b) (4) [redacted]

2.7.4 Certificates of registration

Code of practice and good feed manufacturing practices certificates issued to Zeocem by the feed industry's quality/safety system for specialty feed ingredients and their mixtures (FAMI-QS) and the Central Controlling and Testing Institute in Agriculture in Bratislava are given in Appendices 2.11 and

2.12. A material safety data sheet (MSDS) for clinoptilolite is given in Appendix 2.13 and an example of a Zeocem ZeoFeed® product label in Appendix 2.14.

PART 3

TARGET ANIMAL AND HUMAN EXPOSURE

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3. TARGET ANIMAL AND HUMAN EXPOSURE

3.1 Target Animals

The Zeocem clinoptilolite is intended to be added to a complete feed mixture or to feed premixes of the diets of major food animals (cattle, swine, chicken, turkeys), other minor species (ruminants: goats and sheep, other poultry species) and pet animals (cats, dogs) at a level not exceeding 2% (20,000 mg/kg feed) by weight of the feed composition in accordance with good manufacturing or feeding practice.

Clinoptilolite is found in sedimentary and volcanic rocks that formed under diverse geological occurrence. Therefore, it also contains minor amounts of other minerals and impurities. These substances are therefore also consumed by the animal when clinoptilolite is added to the diet. An overview of the qualitative parameters of clinoptilolite (oxide minerals, heavy metals, dioxins, radioactive and microbial contamination, etc) is given in Appendices 2.1, 2.2 and 2.10a-d. Examples of detailed analyses carried out are given for the content of dioxins (Appendices 3.1 and 3.2), radionuclides (Appendix 3.3) and constituents of animal origin (Appendix 3.4).

The daily amounts of clinoptilolite and additional oxide mineral substances and heavy metals that would be consumed by target animals when the anticaking agent is added to the diet at the maximum recommended level of 2% are given in Table 3.1. These amounts are then compared to the respective maximum tolerable levels of these substances as recommended by NRC (2005) and AAFCO (2016) (Table 3.2). The data demonstrate that the amounts of mineral substances and heavy metals that animals would ingest when consuming diets containing 2% clinoptilolite are below the recommended tolerable levels, except for aluminum.

The level of aluminum (1482 mg/kg diet) is above the NRC (2005) maximum proposed level of 1000 mg/kg diet). However, it should be noted that this maximum level is derived from studies in lambs (Rosa et al., 1982; Valdivia et al., 1982), steers (Valdivia et al., 1978) and poultry (Wisser et al., 1990) which received aluminum as chloride, the salt with the highest bioavailability. As discussed by NRC (2005), dietary silicates reduce the absorption and retention of free aluminum. Aluminum bound in silicates is considered to be significantly less bioavailable if at all (Section 6.4.1).

3.2 Human Exposure

As is described in detail in Part 6 (Section 6.4.1), there is no evidence that clinoptilolite is degraded during its passage through the gastrointestinal tract of target animals. The physiological and chemical conditions in the animal's digestive system (pH, digestive enzymes, etc) are not enough to decompose clinoptilolite; the substance is essentially not absorbed and is excreted with the feces. No scientific reports were found demonstrating that any impurities (minerals or heavy metals) contained in clinoptilolite were deposited in tissues of animals to which the substance was fed in amounts above maximum permitted levels. Therefore, based on the information available at the time of this submission, it can be stated that human exposure to residues of clinoptilolite in animal tissues is unlikely to pose a potential risk or safety issue (Section 6.5).

Table 3.1		**Target animal exposure to clinoptilolite**										
Animal category[a]		Daily feed intake[b] (kg)	Daily clinoptilolite intake[c] (g)	Daily intake of minerals and heavy metals contained in clinoptilolite[d]								
				Silicon (g)	Aluminum (g)	Iron (g)	Calcium (g)	Lead (mg)	Arsenic (mg)	Cadmium (µg)	Mercury (µg)
Ruminants	Calves (≤15 months, 300 kg)	7.10	142.00	44.67	9.39	1.59	3.15	1.91	0.206	3.6778	1.123
	Dairy cows (≥2 years, 680 kg)	26.90	538.00	169.24	35.59	6.02	11.92	7.22	0.780	13.9342	4.256
	Sheep (≥8 months,140 kg)	1.98	39.60	12.46	2.62	0.44	0.88	0.53	0.057	1.0256	0.313
	Goats (≥8 months, 90 kg)	1.54	30.80	9.69	2.04	0.34	0.68	0.41	0.045	0.7977	0.244
Swine	Piglets (3.5 - 5 kg)	0.25	5.00	1.57	0.33	0.06	0.11	0.07	0.007	0.1295	0.040
	Piglets (5.0 - 10 kg)	0.50	10.00	3.15	0.66	0.11	0.22	0.13	0.015	0.2590	0.079
	Piglets (10 - 20 kg)	1.00	20.00	6.29	0.30	0.05	0.10	0.06	0.006	0.1159	0.035
	Pigs (20 - 50 kg)	1.86	37.10	11.67	2.45	0.42	0.82	0.50	0.054	0.9609	0.293
	Pigs (50 - 80 kg)	2.58	51.50	16.20	3.41	0.58	1.14	0.69	0.075	1.3339	0.407
	Pigs (80 - 120 kg)	3.08	61.50	19.35	4.07	0.69	1.36	0.83	0.089	1.5929	0.486
	Sows (lactating) (175 kg)	5.25	105.00	33.03	6.95	1.18	2.33	1.41	0.152	2.7195	0.831
Poultry	Layers (commercial/breeder)	0.10	2.00	0.63	0.13	0.02	0.04	0.03	0.003	0.0518	0.016
	Broilers (starter, 0-3 weeks)	0.07	1.32	0.42	0.09	0.01	0.03	0.02	0.002	0.0342	0.010
	Broilers (grower, 4-6 weeks)	0.15	3.06	0.96	0.20	0.03	0.07	0.04	0.004	0.0793	0.024
	Broilers (finisher, 7-9 weeks)	0.20	4.04	1.27	0.27	0.05	0.09	0.05	0.006	0.1046	0.032
	Turkeys (starter, 0-8 wk)	0.21	4.20	1.32	0.28	0.05	0.09	0.06	0.006	0.1088	0.033
	Turkeys (grower, 8-16 wk)	0.49	9.80	3.08	0.65	0.11	0.22	0.13	0.014	0.2538	0.078
	Turkeys (finisher, 16-24 wk)	0.75	15.00	4.72	0.99	0.17	0.33	0.20	0.022	0.3885	0.119
Pets	Dogs (adult 15 kg)	0.21	4.19	1.32	0.28	0.05	0.09	0.06	0.006	0.1086	0.033
	Cats (adult 3 kg)	0.04	0.83	0.26	0.06	0.01	0.02	0.01	0.0216	3.6778	0.007

[a,b] Animal categories (age, weight and/or production) and respective daily feed intake are based on NRC (1994, 1998, 2000, 2001, 2006, 2007) and FEDIAF (2013).
[c] Use level of 2% of diet by weight.
[d] Calculated based on data in Appendix 2.1.

Table 3.2 **Levels of minerals and heavy metals in diets supplemented with Zeocem clinoptilolite compared to recommended tolerable levels**[a]
Silica. Insoluble forms of silica can be tolerated by the relevant species at levels as high as 50,000 mg/kg diet (NRC, 2005). Silica dioxide is considered to be GRAS (21 CFR 573.940) and (21 CFR 582.80). Assuming a maximum level of 72% SiO_2, adding clinoptilolite to diets at a level of 2% would result in silica being present at a level of 6,731 mg/kg diet, or 7.4 times less than the maximum tolerable level.
Aluminum. It is estimated that less soluble forms of aluminum can be tolerated at levels of 1000 mg/kg diet (NRC, 2005; AAFCO, 2016). Assuming a maximum level of 14% Al_2O_3, adding clinoptilolite to diets at a level of 2% would result in aluminum being present at a level of 1482 mg/kg diet or approximately 1.5 times greater than the maximum tolerable level.
Iron. The proposed maximum safe level of iron is 500 mg/kg for ruminants and poultry, and 3000 mg/kg for swine (NRC, 2005). EFSA FEEDAP Panel recommended a maximum safe content of iron in complete feed as being 450 mg/kg for cattle, 500 mg/kg for ovines, 600 mg/kg for cats, dogs and poultry, and 3000 mg/kg for pigs (EFSA, 2016). Iron oxide is listed to be GRAS when added to food (21 CFR 186.1374) and feed (21 CFR 582.80) as a nutritional dietary supplement at levels consistent with good feeding practice. Assuming a maximum level of 3.3% Fe_2O_3, adding clinoptilolite to diets at a level of 2% would result in iron being present at a level of 462 mg/kg diet. This amount is within the recommended ranges given by NRC (2005) and EFSA (2016), except for cattle which is slightly above the EFSA safe level.
Calcium. NRC (2005) recommends upper tolerable levels of calcium for ruminants and poultry as being 1.5% of daily diet, for swine 1.0% of daily diet, 2% of daily intake of dogs and 1% for cats. As an example, for an adult dairy cow this would be equivalent to about 404 g/d of Ca or 15000 mg/kg of diet. Calcium oxide is listed to be GRAS when added to food (21 CRF 184.1210) and feed (21 CFR 582.1210) as a nutritional dietary supplement at levels consistent with good feeding practice. Assuming a maximum level of 10% CaO, adding clinoptilolite to diets at a level of 2% would result in calcium being present at a level of 1429 mg/kg diet, or 10 times less than the maximum tolerable level.
Lead. Studies have demonstrated that cattle, sheep and poultry can tolerate 10 mg/kg diet for extended periods without exhibiting adverse effects, however, actual maximum tolerable levels have not been established for the relevant species (NRC, 1980, 2005). It is recommended that of levels of lead in animal diets be limited to 30 mg/kg diet (NRC, 1980; AAFCO, 2016). Zeocem data on the amount of lead present in clinoptilolite mined over the last 15 yr averaged less than 10 mg/kg (Appendix 2.10a-d) or 0.2 mg/kg diet. Even if one assumed that the level of lead in the mined material were to increase to 20 mg/kg clinoptilolite, the amount of lead present in feed when 2% clinoptilolite is added would be 0.4 mg/kg diet. This amount is well below the maximum recommended level of 30 mg/kg.
Cadmium. Dietary levels of cadmium (10 mg/kg) are tolerated chronically by poultry and ruminant species, but these levels result in unacceptable levels of cadmium in tissue and muscle. The World Health Organization has set a 1 mg/kg upper limit for cadmium in complete feeds for animals (NRC, 2005). AAFCO (2016) proposes 0.5 mg/kg diet. Zeocem data on the amount of cadmium present in clinoptilolite mined over the last 15 yr averaged less than 0.1 mg/kg (Appendix 2.10a-d). Adding clinoptilolite at a level of 2% would result in cadmium being present at less than 0.01 mg/kg of diet.
Arsenic. The suggested maximum tolerable levels of arsenic for the relevant species proposed by NRC (2005) and AAFCO (2016) are 30 mg/kg and 50 mg/kg diet, respectively. Zeocem data on the amount of arsenic present in clinoptilolite mined over the last 15 yr averaged less than 1.5 mg/kg (Appendix 2.10a-d). Adding clinoptilolite at a level of 2% would result in arsenic being present at less than 0.1 mg/kg diet.
Mercury. NRC (2005) and AAFCO (2016) recommend a maximum mercury level of 2 mg/kg diet for ruminants, poultry and pigs. Zeocem data on the amount of mercury present in clinoptilolite mined over the last 15 yr averaged less than 0.02 mg/kg (Appendix 2.10a-d). Adding clinoptilolite at a level of 2% would result in mercury being present at less than 0.001 mg/kg of diet.
[a] Amounts of minerals and heavy metals (mg/kg feed) were calculated using the upper ranges of the analytical data for clinoptilolite given in Appendix 2.1 and feed intake data based on NRC (1994, 1998, 2000, 2001, 2006, 2007) and FEDIAF (2013). The levels of minerals and heavy metals presented in the table only reflect those amounts that would be contained in the diet due to the addition of 2% clinoptilolite and do not include any potential impurities in the feed prior to adding the anticaking agent.

PART 4

SELF-LIMITING LEVELS OF USE

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4. SELF-LIMITING LEVELS OF USE 2

4. SELF-LIMITING LEVELS OF USE

As stated in Section 1.4, the levels at which Zeocem clinoptilolite should be added to the diets of major food animals (cattle, swine, chicken, turkeys), other minor species (ruminants: goats and sheep, other poultry species) and pet animals (cats, dogs) should not exceed the recommended guidance level of 2% (20,000 mg/kg feed) by weight of the feed composition in accordance with good manufacturing or feeding practice.

Data reported in studies reviewed in Part 6 (Narrative) demonstrate that clinoptilolite can be added to the diets of major food animals (cattle, swine, chicken, turkeys), other minor species (ruminants: goats and sheep, other poultry species) and pet animals (cats, dogs) at levels ranging from 3% to 8% of the diet by weight without negatively affecting intake. No studies could be found where these species were fed higher levels of clinoptilolite.

In toxicological studies carried out with mice it was reported that feeding clinoptilolite at levels of 25% to normal mice and 25% and 50% to tumor-bearing animals did not illicit a negative effect on feed consumption. Clinoptilolite ingestion was well tolerated as judged by comparable body masses of control and experimental animals (Martin-Kleiner et al., 2001). Similarly, in a study with rats fed diets containing 25% clinoptilolite no adverse effects on feed intake was reported (Pavelić et al., 2001).

There is no established self-limiting level of use. At what level of the diet clinoptilolite would have to be added to make it self-limiting (unpalatable or technologically impractical) is not known.

Part 5

EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

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5. EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958 2

5. EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

This section is not applicable because the GRAS status of clinoptilolite is based on scientific procedures in accordance with the Code of Federal Regulations (CFR) 21 CFR 570.30(a) and (b).as stated in Part 1, Section 1.5.

Part 6

DETAILED SUMMARY OF THE BASIS FOR THE NOTIFIER'S GRAS DETERMINATION

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6. NARRATIVE

This narrative provides a basis for the Notifier's conclusion that the notified substance clinoptilolite, a natural crystalline aluminosilicate mineral of sedimentary origin, mined by Zeocem, is GRAS when used as an anticaking agent in feed products for major food animals (cattle, swine, chicken, turkeys), other minor species (ruminants: goats and sheep, other poultry species) and pet animals (cats, dogs). The scientific data and information presented in the following sections demonstrate that clinoptilolite is safe under the conditions of intended use for both the target animals and for humans consuming human food derived from food-producing animals consuming the substance.

The data and information used to establish this conclusion are referenced within the narrative using an author/date format or appendix number. Full citations for all references are given in Part 7 of the notice; those references that are generally available are listed in Section 1 and those that are not generally available in Section 2.

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

There is no information or data contained in this narrative which is considered by the Notifier to be exempt from the Freedom of Information Act (FIA). Likewise, no non-public, safety-related data or information was used in reaching the conclusion of GRAS status for clinoptilolite.

6.1 Clinoptilolite and Chemically-Related Compounds with GRAS Status

As described in Part 2, clinoptilolite is a natural crystalline aluminosilicate substance belonging to the class of minerals known as silicates. The chemical composition and purity of the clinoptilolite manufactured by Zeocem as an anticaking agent is well defined (Appendices 2.1 and 2.2).

In this section information provided by FDA and other recognized food/feed regulatory bodies/organizations concerning the composition and purity of compounds listed as being GRAS when used as anticaking agents are reviewed; aluminosilicate compounds are emphasized.

6.1.1 Food and Drug Administration

The 1979 report of the FDA Select Committee of GRAS Substances (SCOGS) reevaluated the safety of six silicate compounds authorized for use as anticaking agents in food (LSRO, 1979; FDA, 2015). These compounds had received GRAS status "through experience based on their common use in food" following the passage of the 1958 Food Additives Amendment to the Federal Food, Drug and Cosmetic Act (GPO, 1958). Three of these compounds are aluminosilicates: aluminum calcium silicate (21 CFR 182.2122), sodium aluminosilicate (21 CFR 182.2727) and sodium calcium aluminosilicate, hydrated (21 CFR 182.2729). The SCOGS report gives a description for sodium aluminosilicate as shown below. No information is provided for the other two aluminosilicate compounds.

<u>Sodium aluminosilicate</u>: Composition - SiO_2 (≥66%, but ≤71% after drying), Al_2O_3 (≥9%, but ≤13% after drying), Na_2O (≥4%, but ≤7% after drying). Loss on drying ≤8%. Loss after ignition ≥8%, but ≤11%. Limits of impurities - arsenic ≤3 ppm and heavy metals as lead ≤10 ppm.

The FDA has designated a use tolerance level of 2% in accordance with good manufacturing practice for all three of these anticaking agents when used in food, but no description of the actual composition or purity is given (FDA, 2016a).

The FDA considers these same three aluminosilicate compounds to be GRAS when used as anticaking agents in animal feed at a use tolerance level of 2% in accordance with good manufacturing practice (21 CFR 582.2122, 21 CFR 582.2727 and 21 CFR 582.2729, respectively) (FDA, 2016b). However, definitions of substance composition or purity for these compounds are lacking as shown by the example of 21 CFR 582.2729 given below (GPO, 2016b).

a) Product. Hydrated sodium calcium aluminosilicate (sodium calcium silicoaluminate).
b) Tolerance. This substance is generally recognized as safe for use at a level not exceeding 2% in accordance with good manufacturing or feeding practice.

6.1.2 Food Chemicals Codex

The Food Chemicals Codex (FCC) compendium (developed by the National Academy of Sciences and first published in 1966) includes sodium aluminosilicate (CAS No. 1344-00-9, INS 554) within its listing of chemical description monographs. It gives a general definition of composition as shown below. No information is given for aluminum calcium silicate or hydrated sodium calcium aluminosilicate (FCC, 2010).

Sodium aluminosilicate:
Composition - occurs as a fine powder, or as beads. It is a series of hydrated sodium aluminum silicates having Na_2O: Al_2O_3: SiO_2 molar ratios of approximately 1:1:13, respectively.
Solubility - insoluble in water and in alcohol and other organic solvents, but at 80°C to 100°C, it is partially soluble in strong acids and solutions of hydroxides.

6.1.3 Association of American Feed Control Officials

The Official Publication of the Association of American Feed Control Officials (AAFCO) contains the most complete listing of feed ingredients and their definitions commonly used in the animal food manufacturing industry (AAFCO, 2016). Under FDA's Center for Veterinary Medicine (CVM) Compliance Policy Guide CPG 665.100 (Common or Usual Names for Animal Feed Ingredients), the definitions, as they appear in the Official Publication, are generally regarded as constituting the common or usual name for animal food ingredients, including pet food (FDA, 1995). AAFCO lists the same three aluminosilicates used as anticaking agents in feed as the FDA (21 CFR 582.2122, 21 CFR 582.2727 and 21 CFR 582.2729, respectively). Again, no information is given regarding their composition or purity (AAFCO, 2016).

6.1.4 FAO/WHO

The Food and Agriculture Organization (FAO) and World Health Organization (WHO) joint international body for food standards - Codex Alimentarius (Food Code) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) list sodium aluminosilicate (INS 554) and calcium aluminium silicate (INS 556) as anticaking agents in food (WHO, 1984; FAO, 2005a,b; CODEX, 2016). The criteria for composition and purity for these two compounds are given as follows:

Sodium aluminosilicate: Composition - a series of hydrated sodium aluminium silicates. The article of commerce may be specified further to silicon dioxide, aluminium oxide, and sodium oxide content, loss on drying, loss on ignition and pH slurry in water. Limits of impurities - lead (≤5 mg/kg). Solubility - insoluble in water and ethanol, partially soluble in strong acids and alkali hydroxides.
Aluminium calcium silicate: Composition - SiO_2 (≥44%, but ≤50%), Al_2O_3 (≥3%, but ≤5%), CaO (≥32%, but ≤38%), Na_2O (≥ 0.5%, but ≤4%). Loss on ignition ≥14%, but ≤18%. Loss on drying ≤10%. Limits of impurities - fluoride ≤50 mg/kg and lead ≤5 mg/kg. Solubility - insoluble in water and ethanol.

6.1.5 European Food Safety Authority

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) issued a scientific opinion on the additive clinoptilolite of sedimentary origin that has by specification at least 80% clinoptilolite (hydrated calcium aluminosilicate) and a maximum of 20% clay minerals (EFSA, 2013). The main chemical composition and purity of the clinoptilolite reported in the scientific opinion (based on eight batches) is shown below.

Clinoptilolite: Composition - SiO_2 (67%), Al_2O_3 (12%), CaO (3%), Na_2O (0.7%) and Fe_2O_3 (1.3%). Limits of impurities - concentration of heavy metals (mg/kg): Cd (<0.04), Pb (<7.4), Hg (<0.005) and As (<1.4). Dioxins in four batches analysed did not exceed 0.1 ng WHO-PCDD/F-PCB-TEQ/kg. Physical data - Laser diffraction analysis of one batch of the additive identified 90% (v/v) of the particles with a diameter of ≤0.186 μm, 50% with a diameter ≤0.72 μm and 31% with a diameter ≤0.50 μm. Laser diffraction analysis of three other batches identified 50% of the particles falling within the respirable fraction (≤8 μm) and 10% of the particles being ≤1 μm.

EFSA concluded that clinoptilolite is considered to be safe for all animal species when used as an binder/anticaking agent in organic animal feed, subject to the limit of 10,000 mg/kg (1%) of complete feeding stuff and the animal classes (pigs, for fattening, chickens for fattening, turkeys for fattening, bovines and salmon) as specified in EU Regulation 651/2013 (EFSA, 2013; EU, 2013). Clinoptilolite is also listed under the category technological additive, functional group binder/anticaking agent, code 1g568 in the European Union Register of Feed Additives (EU, 2016).

6.1.6 Supportive Data for Clinoptilolite

As can be seen from the information reviewed above, data on the composition of the three aluminosilicate compounds listed as GRAS when used as anticaking agents is limited. Sodium aluminosilicate is relatively well described and some information exists for aluminium calcium silicate, but not for sodium calcium aluminosilicate. Interestingly, composition data for sodium aluminosilicate presented in the SCOGS report was not included in the later FDA GRAS listing. To date, a description of the composition, purity and related parameters for the three aluminosilicate compounds does not exist (FDA, 2016a,b). A detailed description of the composition and purity of clinoptilolite authorized as an anticaking agent in the EU is given by EFSA (2013).

A common property of these anticaking agents is that they belong to the mineral class of aluminosilicates, which contain the same three main elements: SiO_2, Al_2O_3 and Na_2O. Clinoptilolite, as per its chemical composition meets this criterion of being an aluminosilicate anticaking agent. In this regard, the safety of adding clinoptilolite to the diets of food-producing animals is addressed in detail in the next section.

6.2 Feeding Studies with Clinoptilolite

Clinoptilolite has been used in animal nutrition since the mid-1960s (Mumpton and Fishmann, 1977). The literature contains numerous studies in which ruminant, swine and poultry diets were supplemented with this mineral substance as an additive (Ramos and Hernández, 1997; Papaioannou et al., 2005; Karamanlis et al., 2008, Pourliotis et al., 2012; Karatzia et al., 2013; Subramaniam and Kim, 2015). However, the adding of clinoptilolite to feed as a binder for mycotoxins or any use other than as an anticaking agent is not considered as being GRAS (IDALS, 1999; FDA, 2016c).

The scientific data and information presented in Sections 6.2.1 through 6.3.4 demonstrate that clinoptilolite can be safely fed to food-producing animals. Emphasis is given to studies where the amount of clinoptilolite added to diets was equal to or greater than the proposed GRAS allowable tolerance of 2%. The main study parameters reviewed are the number and type of animals used, length of the trial and whether adverse effects on performance or general health were observed. Any additional parameters that may have been concurrently measured or compared (statistically or otherwise) as part of a cited study are included only as relevant.

6.2.1 Ruminants

Cattle

McCollum and Galyean (1983) conducted a 148 d feedlot experiment with clinoptilolite. Forty-eight cross-bred steers (average BW 304 kg) were randomly divided into three groups and fed a 70% sorghum diet with clinoptilolite substituted at 0, 1.25 and 2.5% of the diet dry matter (DM). Because the steers had recently been removed from a grazing trial, they were allowed a 2 wk period for environmental and dietary adaptation. Once the steers were on full feed, the experimental diets were offered and the feeding trial commenced. During the experiment, fresh feed was offered once daily in amounts sufficient to allow free choice consumption. On days 1, 37, 66, 93 and 148, all steers were weighed and fecal grab samples were collected from four randomly selected steers/pen. All steer weights were adjusted using a 4% shrink. The pH of fecal grab samples was determined and the samples were frozen until completion of the trial. Steers were slaughtered at a commercial packing plant after 148 d on feed and yield of lean cuts and USDA quality grades were determined by a federal grader. No differences (P>0.05), were found among treatments in dry matter intake (DMI), average daily gain (ADG), feed to gain ratio, carcass weight or dressing percentage. Likewise, dietary clinoptilolite had no significant effect (P>0.05) on fecal starch, pH or DM.

Katsoulos et al (2005a) investigated whether the long term supplementation of 1.25 and 2.5% clinoptilolite in the concentrate feed of dairy cows had any effect on their hematological parameters. Fifty-two clinically healthy Holstein cows were randomly assigned to one of three groups according to their age and parity. Group 1 (control, n = 18) received concentrate feed. Group 2 (n = 17) and Group 3 (n = 17) received concentrate feed supplemented with 1.25 and 2.5% clinoptilolite, respectively. The experiment started 30 d before the expected parturition and lasted up to the end of lactation. Blood samples from individual animals were collected just before the start of experiment, at the day of calving and, thereafter, at monthly intervals. All samples were tested for packed cell volume (PCV), hemoglobin (Hb) and leukocyte count (WBC) values.

Results showed that PCV values and Hb concentrations were unaffected by clinoptilolite supplementation (P>0.05), either among groups or for individual sampling. Likewise, no differences (P>0.05) in WBC were observed between groups. Overall, the results showed that the 1.25 and 2.5% supplementation of clinoptilolite had no adverse effect on the hematological parameters tested. The authors reported that the results were similar to those obtained in former studies in steers receiving 3% clinoptilolite for 56 d (Hutcheson, 1984).

Katsoulos and co-workers also evaluated a wide range of other parameters as part of this same study. The results from these studies are summarized here. Katsoulos et al (2005b) investigated whether the long-term supplementation in the concentrate feed of dairy cows receiving diets supplemented with 1.25 and 2.5% clinoptilolite had any effect on the serum concentrations of ßcarotene and vitamins A and E. Results showed that clinoptilolite supplementation at both levels had no effect (P>0.05) on serum concentration levels of the three parameters measured.

Katsoulos et al (2005c) examined the effect of the percentage of clinoptilolite fed to the two groups of dairy cows on the incidence of parturient paresis and serum concentrations of total calcium (tCa), inorganic phosphorus (PO_4^{2-}), magnesium (Mg^{2+}), potassium (K^+) and sodium (Na^+). Results showed that the incidence of parturient paresis in cows receiving 2.5% clinoptilolite was lower (P<0.05 than for the control animals. However, serum concentrations of tCa, PO_4^{2-}, Mg^{2+}, K^+ and Na^+ were not different (P>0.05) in cows receiving either 1.25 or 2.5% clinoptilolite over a 30 d experimental period.

Katsoulos et al (2005d) investigated the effect of feeding two levels (1.5% and 2.5%) of clinoptilolite on serum copper, zinc and iron concentrations. Fifty-two clinically healthy Holstein cows were randomly assigned to one of three groups according to their age and parity. The first group (group A) comprised 17 cows fed a ration supplemented with 1.25% clinoptilolite, the second group (group B) comprised also 17 cows was given a ration with 2.5% clinoptilolite, and the third group (group C, the control), comprised 18 cows fed the basal ration that did not contain any clinoptilolite. The experiment started when the cows entered the fourth week before the expected parturition and lasted until the end of lactation. All cows were fed the above concentrates during the entire experimental period. Blood samples were collected from each animal at the starting day of the experiment, at the day of calving, and at monthly intervals thereafter. All samples were tested for serum Cu, Zn, and Fe concentrations. The results showed that the 1.25 and 2.5% supplementation of clinoptilolite did not have any adverse effects on serum concentrations of Cu, Zn, and Fe.

Katsoulos et al (2006) analyzed blood samples monthly for serum glucose, ketone bodies, liver enzymes, blood urea nitrogen (BUN) and total proteins. The milk yield of each cow was also recorded monthly. The cows receiving 2.5% clinoptilolite had significantly fewer (P<0.05) cases of clinical ketosis during the first month after calving and a higher total milk yield. Feeding the cows with clinoptilolite for a long period had no apparent adverse effects on their liver function, and did not significantly affect (P>0.05) the concentrations of glucose, ketone bodies, BUN and total proteins in their serum.

Bosi et al (2002) assessed the effect of the dietary clinoptilolite addition on production and milk composition of dairy cows, on rumen fluid composition, and on the content of certain minerals in the blood over 76 d. Thirty-two lactating Holstein cows (142 d average lactation length) were blocked according to milk production, parity, and days of lactation and fed a control diet based on corn and alfalfa silages, hay and concentrates, or the control diet plus clinoptilolite (200 g/d). The clinoptilolite supplementation had no significant effect on milk yield, milk protein contents, fat contents and somatic cell count. The dietary addition of clinoptilolite did not change pH, ammonia content and VFA molar percentages in the rumen. No dietary effect on mineral contents of blood plasma (Na, K, Zn, and Ca) was observed.

The results reported from several other studies also demonstrate that supplementing cattle diets with clinoptilolite does not have any detrimental impact on animal growth or health parameters; for example, at levels of 2% (Mohri et al.,2008; Mojzis et al., 2008; Step et al.,2008; Zarcula et al., 2010; Pourliotis et al., 2012) or 5% (Sweeney et al., 1983).

Sheep

Pond et al (1984) carried out a study with 54 growing male lambs to determine the effect of dietary clinoptilolite on growth, feed utilization and concentrations of several nitrogen and ionic constituents in blood plasma and of selected elements in body tissues. The treatments consisted of a basal (low protein) diet containing no nitrogen supplement, plus vitamins and minerals, and a similar diet fortified with urea as a nonprotein nitrogen source or with soybean meal as an intact protein source added to the diet isonitrogenously with urea, all fed for 9 wk. Clinoptilolite was added to each of these three diets at 3% at the expense of corn. Mean daily weight gain was depressed during the first 4 wk and at 9 wk in lambs fed diets containing corn or urea when clinoptilolite was added (P<0.05). However, when clinoptilolite was added to the corn-soybean meal diet there was no growth depression for either period. Clinoptilolite did not affect plasma concentrations of protein, Ca, P, Mg, Na or K at 9 wk. The pH of the gastrointestinal tract contents was not affected, except for an increase in pH of cecal contents due to clinoptilolite. There was no evidence of changes in liver, kidney, testes and muscle concentrations of major or minor elements in lambs fed clinoptilolite.

Norouzian et al (2010) examined the effects of feeding clinoptilolite on hematology, performance, and health of 30 newborn Balouchi lambs allocated to three groups: Group 1 (control basal diet) and Groups 2 and 3 (basal diet plus 1.5 and 3% clinoptilolite, respectively for 6 wk (3 wk before and 3 wk after weaning). Blood samples were taken from all lambs, at the time when the animals were allocated to the experimental diet and at the end of each week of experiment, and analyzed for hematology, plasma fibrinogen, and total protein. Performance and health of all lambs were measured. Fecal consistency score and diarrhea severity were evaluated. There was no difference between lambs in case of hematological parameters. Lambs fecal consistency score and severity of diarrhea were lowest (P<0.05) for Groups 2 and 3 lambs and highest for control animals. Feed conservation ratio and DMI were similar between the groups of lambs fed the different diets, but ADG of lambs differed significantly (P<0.05) and was higher in Group 2 animals. It was concluded that addition of 3% clinoptilolite to starter diet of newborn lamb can reduce incidence and severity of diarrhea, although its effect on hematology and performance was negligible.

Other studies confirm that that feeding clinoptilolite at levels ranging from 2 to 4% of the diet has no adverse effect on performance and health of sheep (Pond, 1989; Kovac et al., 1995; Deligiannis et al., 2005; Alcala-Canto et al., 2011) or goats (Katsoulos et al., 2009).

6.2.2 Swine

Shurson et al (1984) carried out several trials in which growing pigs were fed diets containing various levels of clinoptilolite. In one growth trial, two groups of 18 crossbred pigs (averaging 25 kg BW) were assigned to diets containing 0 or 5% clinoptilolite for a 6 wk growing phase trial. It was found that ADG, average daily feed intake (ADFI) and F/G ratio were unaffected by clinoptilolite supplementation. A second growth trial utilized the same crossbred pigs (averaged 65 kg BW) assigned to diets containing 0 or 5% clinoptilolite for an 8 wk finishing phase trial. No effect was observed for ADG, ADFI or metabolizable energy (ME) utilization with the clinoptilolite diet, although the F/G ratio increased (P<0.02). In a nutrient balance trial, 16 crossbred pigs (averaging 7 kg BW) were fed diets (4 pigs per diet) containing 0, 2.5, 5.0 or 7.5% clinoptilolite. Digestible energy, ME, N-corrected ME and ME corrected for N-balance and clinoptilolite levels were linearly reduced (P<0.01) as increasing amounts of clinoptilolite were fed. Daily fecal-N increased and apparent digestibility of N was linearly reduced by feeding increasing amounts of clinoptilolite. Likewise, phosphorus retention was linearly reduced (P<0.05), but Ca, Mg, Na, K, Fe and Zn retention were not linearly affected. The authors stated that this indicated the stability of clinoptilolite in the acid environment of the stomach.

Sardi et al (2002) carried out two trials in which pigs were fed diets containing clinoptilolite. In the first trial (growing-finishing) 40 pigs (average 55 kg BW) were homogeneously allocated to two groups (4 replicates of 5 animals each) and fed either a standard diet or the same diet supplemented with 2% clinoptilolite. Pigs were slaughtered at about 160 kg BW. Blood samples were taken to determine BUN. In the second trial (piglets from birth to post-weaning) a total of 116 piglets from 12 litters were used. Sows were homogeneously chosen with respect to farrowing order (second parity-dams) and genetics (Duroc x Large White). Piglets were weighed at birth. Litters were equalized to assign to each sow the same number of piglets of the same sex. Litters were allotted to two groups: Group A (control) in which the 6 litters received feed without clinoptilolite and Group B (experimental) in which the remaining 6 litters received the control diet with 2% clinoptilolite. Animals were fed until attaining 33 kg BW. The ADG, ADFI and health of the pigs were regularly recorded in both trials. Results from both trials showed that the inclusion of clinoptilolite did not affect growing performance. Animals fed the clinoptilolite diet showed a significant (P<0.05) improvement of fecal DM content. It was observed at slaughtering that the dietary inclusion of clinoptilolite resulted in a trend towards an improvement in yield of lean cuts and in an increase

(P<0.05) of the ratio between lean and fat cuts. The authors stated that clinoptilolite did not impair pig growing performances, resulted in a higher dry matter content of feces and improved carcass quality of heavy pigs, particularly in regard to yield of lean cuts and ratio of lean/fat cuts.

Papaioannou et al (2002) carried out a field study using weanling Large White x Landrace sows to evaluate the effect of long-term consumption of diets supplemented with 2% clinoptilolite on vitamin and macro/trace element concentrations in blood liver and kidney tissues. Twenty-four pigs, randomly assigned to a control or experimental group, received diets containing either 0% or 2% clinoptilolite. Diets were provided ad libitum from weaning, during the service, gestation and lactation periods and up until the date of the next service. Blood samples were collected at the starting day of the trial, on the 30th and 90th day of each pregnancy, and on the days of parturition and weaning for measures of mineral status. Kidney and liver mineral status were also obtained at the end of the study. It was concluded that dietary supplementation of clinoptilolite during pregnancy and lactation is not associated with any adverse effect on vitamin (A and E) and mineral (K, Na, P, Ca, Mg, Cu, and Zn) uptake and/or distribution in sows which are on diets adequately fortified with these vitamins and minerals.

Fokas et al (2004) carried out a study to measure the retention coefficient of lead (Pb) from clinoptilolite in a balance trial with growing pigs. Twelve weaned pigs of 45 days of age were divided into two equal groups. Group 1 was fed a control (C) diet and Group 2 (experimental, E) the same diet supplemented with 2% clinoptilolite. The Pb content of the clinoptilolite used was 46 ppm, and the dietary contents were 1.1 and 2.1 ppm for diets C and E, respectively. Feed intake, growth rate and feed conversion efficiency, as well as digestibility and nitrogen (N) retention were measured to investigate any effects of the dietary inclusion of clinoptilolite in pigs. Pb concentration was measured in whole blood and edible parts of the carcass (muscles, liver, heart and kidneys), and Pb retention coefficient was determined. The results showed that digestibility did not differ between diets C and E, apart from that of ether extract, which was lower ($P < 0.01$) for the C diet, whereas, N retention was higher in pigs of group E. No significant differences were observed for feed intake, growth rate and feed efficiency over the 52-day feeding period. The inclusion of clinoptilolite in the diet of Group E pigs did not result in a significant increase in the Pb concentration in the whole blood and the edible tissues, except for liver (P <0.001). However, the Pb retention coefficient between diets was not significant.

Prvulovic et al (2007) carried out a study to determine the effects of clinoptilolite on growth performance and selected blood serum biochemical components in Landrace × Yorkshire pigs. Sixty animals of both sexes were divided into two groups and fed either a basal diet without clinoptilolite or the same diet supplemented with 5% clinoptilolite. Feed and water were available ad libitum. Individual live weights were recorded on days 45, 90 and 135 of the experiment. Feed consumption was recorded weekly. Blood was drawn from the anterior vena cava of each pig at day 135 for the determination of serum biochemical parameters. During the first 90 d of the experiment, pigs from the clinoptilolite group had higher BW gain (P<0.05) compared with the control group, but growth parameters in the finishing phase were significantly lower (P<0.05). This decrease was attributed to possible effects of the concentration, purity and type of clinoptilolite used, as well as the growth phase of animals. Blood serum biochemical parameters from all experimental pigs were reported as being generally within the normal range, although higher (P<0.05) triglyceride concentration, lower total cholesterol concentration and increased activity of aspartate amino transferase were recorded in the serum of the clinoptilolite supplemented group. Dietary addition of clinoptilolite had no adverse effects on other serum biochemical parameters and did not affect the normal physiological homeostasis of the animals.

The literature contains several additional studies that support the safety of adding 2% clinoptilolite to swine diets. For example, see the reviews by Pond et al (1989), Papaioannou et al (2005), Alexopoulos et al (2007) and Subramaniam and Kim (2015).

6.2.3 Poultry

Olver (1989) carried out a study with 120 single combed pullets (6 wk old) of three strains (20 hens per treatment) that were fed on a diet containing 160 g protein/kg with or without 5% clinoptilolite. Sterile river sand replaced clinoptilolite in the control diet in order to keep the diets isoenergetic. The hens were individually caged in a naturally-ventilated laying house and fed on one of the two diets for ten 28-d periods. No significant dietary effects between treatments were observed with respect to BW, age at first egg, egg weight, Haugh scores or food intake/hen. Significant dietary effects in favor of clinoptilolite feeding were noticed with the number of eggs laid per hen, shell thickness, efficiency of food utilization, droppings moisture content and mortality. Significant differences between strains were observed with respect to all measurements taken except food intake/hen/d.

Öztürk et al (1998) conducted an experiment to study the effects of clinoptilolite on the performance of laying hens. A total of one hundred and eighty 37-week-old Babcock B-300 layers with similar egg production capabilities and live weight were divided into 5 treatment groups (12 replicates and 36 hens per treatment) and fed a diet containing 0, 2, 4, 6 and 8% clinoptilolite over a 112 d experimental period. All feeding programs were isocaloric and isonitrogenous. No significant dietary effects were observed in terms of body weight, feed consumption, feed efficiency ratio, number of eggs laid per hen, shell thickness, mortality or other criteria of egg quality ($P>0.05$). Significant dietary effects of clinoptilolite feeding were observed in the form of a decrease in fecal moisture content ($P<0.05$).

The lack of adverse effects on feeding clinoptilolite to poultry is well-supported by numerous other studies where clinoptilolite was added to diets for broilers at 1.5 to 10% (Nakaue and Koelliker, 1981; Oguz and Kurtoglu, 2000; Oguz et al., 2002; Ortatatli et al., 2005; Kavan et al., 2013; Parizadian et al., 2013; Wu et al., 2013a-d), layers at 1.5 to 4.5% (Utlu et al., 2007; Moghaddam et al., 2008; Gezen et al., 2009; Macháček et al., 2010), and quail at 5% (Parlat et al., 1999).

6.2.4 Cats and Dogs

Roque et al (2011) evaluated the effect of adding clinoptilolite to diets of cats at levels of 0.5%, 0.75% and 1.0% of dry matter on the digestibility and blood parameters of domestic cats. Twenty-one mongrel, adult, vaccinated and dewormed male and female cats (average age of 3 ± 0.84 yr old, average BW 3.71 ± 0.84 kg) were housed in metabolism room and kept in individual metabolism cages. No differences ($P>0.05$) in apparent digestibility were observed between diets for dry matter, crude protein and mineral matter. The mean values for hemoglobin, indirect bilirubin and urea in blood samples of cats receiving diets containing the different additive levels were not significantly different.

Santos et al (2013) carried out a study in which the effect of feeding clinoptilolite on the acceptability/dry matter intake of feed and apparent indigestibility coefficient (AIC) for calcium, phosphorus, magnesium, sodium, potassium, mineral excretion in dogs were measured.. Fourteen adult beagle dogs (7 animals per group, average 4.5 yr and BW of 12.5±1.46 kg), were fed a with a standard control diet and the same diet supplemented with 1% clinoptilolite for 10 d (5 d adaption and 5 d feces collection). No effect on feed intake/acceptability was observed and there were no differences ($P>0.05$) on the production of feces (g/day) and the percentage of water in the feces. Differences were observed between the control and clinoptilolite supplemented diets for the AIC of calcium and phosphorous, but they were not significant ($P<0.02$). The AIC for magnesium in the clinoptilolite diet was less than the control ($P<0.001$). It was postulated that the reduced absorption might have occurred because the increase in the excretion of phosphorus may have led to the formation of complexes with magnesium. The AIC for potassium and sodium in both diets was similar. Similar results for palatability/digestibility and mineral excretion of diets containing 0.5%, 0.75% and 1% clinoptilolite are reported for cats and dogs (Maia et al., 2010; Santos et al., 2011).

Santos et al (2016) also provide data on the apparent digestibility and urinary pH of adult dogs fed a commercial diet supplemented with 1% clinoptilolite. Twenty-one healthy male and female Beagles (average 4.5 yr and BW 12.5±1.5 kg) and were used. No significant differences ($P>0.05$) were observed in the apparent digestibility coefficients of dry matter, organic matter, crude protein, gross energy, or apparent digestible energy of the control and clinoptilolite diets. Likewise, the addition of clinoptilolite to the diet had no effect on urinary pH, a finding similar to that reported for cats by Roque et al (2011).

6.3 Feeding Studies with Zeocem Clinoptilolite

The first part of this section reviews studies in target animals that were carried using clinoptilolite sourced from the Zeocem mine in Nižný Hrabovec, Slovak Republic. The second part presents data from trials in which clinoptilolite sourced from the same mine was fed as a designated Zeocem ZeoFeed® product for poultry.

6.3.1 Ruminants

Cattle

The effects of supplementing rations with 2 to 7.5% clinoptilolite from Slovakia were studied in beef cattle and dairy cows (reviewed by Bartko et al., 1995). Long-term supplementation revealed no significant differences in weight gain, feed efficiency, or milk yield between supplemented and control animals. Similar results were reported by the same authors for lambs supplemented across this range.

Vrzgula et al (1988) carried out an experiment to determine the effect of adding clinoptilolite to the colostrum given to calves in the control/treatment of diarrhea. A total of 43 calves (23 controls and 20 treated) from Slovak spotted and Black spotted breeds were kept on two farms. The calves individually received 2 L of maternal colostrum within the first 3 hr of life and 3x daily for 15 d. The colostrum for the treated calves was enriched with 1% clinoptilolite. General health and incidence of diarrhea were monitored daily. Blood was taken immediately after birth and at 24 hr, and on days 5, 10 and 15 after parturition. Total protein and immunoglobulin levels, and serum concentrations of Ca, Cu, Fe and Zn were measured.

The results showed that clinoptilolite added to the colostrum given to the calves produced an increase in the concentration of total immunoglobulin in the blood serum of the treated groups, but the increase was significant only on one farm on days 5 and 10. An increase in the serum levels of total proteins in treated calves compared with the controls was observed in each collection beginning 24 hr after birth. This difference was statistically significant ($P<0.01$) on day 10. Calcium concentration increased ($P<0.05$) in the treated groups on the day 10 and it persisted until day 15 on Farm 2. Different results were noted in both farms in the analysis of serum P which was higher in the treated groups in each collection than in the control groups on Farm 2; the situation was similar in the first collections in Farm 1, but on day 15 there was a statistically significant $P< 0.01$) decrease in the mean concentration of the serum P in the treated groups compared with the controls. Serum Fe level of treated calves increased markedly 24 hr after parturition on both farms. There were significant differences in favor of the treated groups in the level of copper, showing the highest concentrations on days 10 and 15. At the same time, there was an increase in the concentration of the total proteins which are the biological carriers of trace elements, forming together protein metal enzymatic complexes. There were no significant differences in serum zinc on either farm due to clinoptilolite. Throughout the course of the experiment the occurrence of the diarrhea syndrome was recorded on both farms in the treated and control groups; in the latter diarrhea developed in 13 calves. In 5 cases it was complicated by respiratory syndrome ending in death. In the treated groups the course of the diarrhea was moderate and lasted only 2 d. These results confirm an earlier trial (Vrzgula, 1986) where feeding clinoptilolite (1% of diet) twice daily to calves for 10 to 14 d reduced the incidence of diarrhea. Adding clinoptilolite (2% of diet twice daily) was found to have a positive effect on animals already affected with the syndrome.

Sheep

Bartko et al (1983a) studied the effect of clinoptilolite on the health condition of 10 sheep of the Merino breed; a control group (5 animals) fed a basic diet and experimental group (5 animals) given the same diet with 1.5% clinoptilolite for 3 mo. No significant differences were observed in the health condition and general behavior of the control animals and those fed clinoptilolite. Differences observed in content of volatile fatty acids in rumen contents, blood chemistry, micro/macro elements, transaminase activity and acid-base homeostasis were also not significant.

6.3.2 Swine

Vrzgula et al (1984) carried out a feeding trial with clinoptilolite in a large-scale fattening facility with 450 pigs in both the control and treatment groups. The pigs (crossbreed Slovak white pedigree x Landrace) weighed an average 22 kg in the control and 20 kg in the experimental group. Animals were fed a starter ration until reaching about 45 kg and then a finisher ration. Clinoptilolite was added to both rations of the experimental group at a level of 3%. The feeding mixtures were given in troughs 3x daily in granulated form ad libitum. Animals were weighed on days 70 and 166. General observations of behavior and sensory evaluation of feces was carried out during the 167 d fattening period. At the beginning of fattening the-average pig weight in the experimental group was about 2 kg lower than in the control group. However, after 70 d, it was 4.14 kg higher in the experimental group than in the control. At the end of the fattening the average weight of the experimental group was 3.96 kg lower than the control. The ADG in the experimental group over 70 d, was 13.5% higher than in the control, however during the remaining 96 d (until the end of fattening), the ADG was 5.8% lower in the experimental group than in the control. Overall, the ADG of the entire period of fattening was only about 1% higher in the experimental group. The mortality rate of the pigs receiving clinoptilolite was 2.9% lower than the control animals. The feces of pigs receiving clinoptilolite were denser, lighter and smelled less than the feces of control animals.

Vrzgula et al (1982, 1984) and Bartko et al (1983b, 1995) also report data from large-scale commercial studies in which experimental groups of 100 to 600 swine were fed diets supplemented with 5% clinoptilolite for 30 to 45 d. No detrimental effects on animal performance and health were reported for any of the studies.

6.3.3 Poultry

Herzig et al (2008) conducted a study to find out the impact of a long-term application of clinoptilolite on the chemical composition of long bones (femur, tibiotarsus) and eggshell of layers. A total of 120 birds of the hybrid breed Bovans Goldline were divided into a control group fed a standard feed mixture and an experimental group in which the diet was supplemented with 1% Zeocem clinoptilolite (ZeoFeed®). The layers were raised in a three-floor cage structure with automatic watering and manual feeding in an environment with a regulated lighting and thermal schedule. The actual experimental period started in the 22nd week and ended in the 68th week of age of the layers. Layers receiving the clinoptilolite had higher average egg weights ($P<0.05$) and the consumption of feed mixture per one egg was 4 g lower compared to the control birds. The eggshell of layers receiving clinoptilolite had a higher ($P<0.01$) content of crude protein, calcium and magnesium than the controls. The values of the same indicators were higher in the femur and tibiotarsus ($P<0.05$ and $P<0.01$, respectively) of layers fed clinoptilolite. The health condition of the layers was monitored daily and no clinical symptoms of a disease were registered. It was reported that the long-term application of clinoptilolite favorably influenced the lodgment of Ca, P, Mg and crude protein in the eggshell, as well as in both long bones, increased egg production and reduced the consumption of feed mixture per/egg, while maintaining health of the layers.

Suchý et al (2006) carried out trials to determine the effect of supplementing broiler diets with Zeocem clinoptilolite (ZeoFeed®) at levels of 1 and 2% on growth performance. The average liveweight of supplemented birds was higher ($P<0.01$) than for the control group at 40 d of age. There were no differences in water consumption between groups at either level of supplementation. Chickens in all groups showed very good health and a very low rate of mortality.

Other studies where Zeocem clinoptilolite (ZeoFeed®) was fed to layers include Straková et al (2008) who examined selected production, hematological and biochemical parameters of hepatic and renal function. No negative effects were observed when supplementing layer diets at a level of 1% clinoptilolite.

6.3.4 Similarities in clinoptilolite composition

The studies reviewed in Sections 6.2 and 6.3 demonstrate that clinoptilolite can be added to the diets of ruminants, swine and poultry under normal production conditions at levels ranging from 1 to 7.5% without eliciting detrimental effects on animal health or overall performance.

A comparison between the composition of the Zeocem clinoptilolite which is the subject of this GRAS notice and the composition of the clinoptilolite used in some of the feeding studies cited in Section 6.2 is given in Table 6.1. The data demonstrate that the purity and mineral composition of the oxides of the Zeocem clinoptilolite is very similar to that of the clinoptilolite used in the reported animal feeding trials, and for which no safety concerns were indicated for animal performance or health.

Table 6.1.	**Similarities between Zeocem clinoptilolite and clinoptilolite in feeding studies**						
Reference	Zeocem[a]	Katsoulos et al (2005a,b,c)	Karatzia et al (2011)	Pourliotis et al (2012)	Papaioannou et al (2002)	Sardi et al (2002)	Herzig et al (2008)[b]
Animals	Ruminants, swine, poultry and pets	Dairy cows	Dairy cows	Calves	Swine	Swine	Poultry
Parameter							
Purity (%)	86 - 92	92	92	92	88[c]	≥85	>80
Composition (%)[d]							
SiO_2	65.0 - 71.3	68.9	69.9	68.9	68.26	68.20	62
Al_2O_3	11.5 - 13.1	11.3	11.3	11.3	13.30	12.3	14
CaO	2.7 - 5.2	3.0	3.0	3.0	4.34	4.34	5.5
Na_2O	0.2 - 1.3	0.75	0.75	0.75	0.26	0.26	NG
Fe_2O_3	0.7 - 2.1	0.11	0.11	0.11	0.08	0.08	2.3
K_2O	2.2 - 3.4	2.23	2.23	2.23	0.94	0.94	NG
MgO	0.6 - 1.2	0.6	0.6	0.6	1.05	1.05	NG
Si:Al (ratio)	4.8 - 5.4	6.1	6.1	NG	5.1	5.5	4.4
Particle size (mm)	0.05 - 2.5	0.80	NG	<0.80	NG	0-1	0.2 - 0.5

[a] Clinoptilolite sourced from Zeocem's mine in Nižný Hrabovec, Slovak Republic (Appendices 2.1 and 2.2).
[b] Clinoptilolite used in the study was a Zeocem clinoptilolite ZeoFeed® product.
[c] Estimated amount; calculation based on data provided in study.
[d] Mineral composition of reported oxides.
NG - Not given.

6.4 Animal Safety

6.4.1 Bioavailability and Absorption

Clinoptilolite is chemically highly stable under acidic conditions due the abundance of high energy silicon-oxygen bonding throughout the tectosilicate structure (Cotton, 2008). Li et al (2008) estimated the stability of clinoptilolite by the leaching of Al, Si, K and Na ions from the clinoptilolite after acid treatment (pH ranging from 1.0 to 5.0) over periods of 24 hr to 6 days. They reported that clinoptilolite is chemically stable at low pH environments. Akkoca et al (2013) also treated clinoptilolite with acids (hydrochloric, phosphoric and bromic) and alkalies (potassium hydroxide and sodium hydroxide). X-ray diffraction (XRD) analysis indicated that the structure of clinoptilolite is not altered by either of the treatments.

Available evidence indicates that clinoptilolite resists degradation by gastric and intestinal juices. In studies using simulated body fluids, the crystal structure of clinoptilolite is reported as remaining stable (Rivera et al., 1998; Ceyhan et al., 2007), even up to 40 days (Martin-Kleiner et al., 2001).

Kavak and Ülkü (2012) also investigated the structural stability of clinoptilolite in simulated digestion conditions and their interactions with digestive media and human colon adenocarcinoma cells. Analyses (XRD, fourier transform infrared spectroscopy, scanning electron microscopy and inductively coupled plasma atomic emission spectroscopy) of the clinoptilolite samples showed that the substance preserved its structural stability during in vitro digestion. Leung et al (2007) conducted laboratory tests to determine the stability of a zeolite (containing 90% clinoptilolite, high in Al, Fe, Pb) under acidic conditions (pH 1.5) similar to those found in the stomachs of swine. It was reported that after 25 hr the amounts of the heavy metals released were well below the toxic levels as recommended by NRC (1998).

Demirel et al (2011) conducted a study to determine the effects of dietary natural clinoptilolite (95%) on serum contents, health status and feeding performance of rats. Adult male Sprague–Dawley rats (n=24) were randomly divided into four groups with three replicates including a control group (without zeolite) and three levels of natural zeolite (2%, 4% and 6%) added to balanced nutritive diets. All rats were fed the above diets during 56-d experimental period. Blood samples were collected from each animal at the end of the experiment. Dietary clinoptilolite increased in serum albumin, triglyceride and VLDL levels ($P<0.05$). However, the differences among treatment groups were not significant for serum minerals (Ca, P, Mg, K, Na, Cl, Fe), urea, Fe binding, LDL, alkaline phosphatase, glucose, uric acid, total Fe, total protein, globulin, cholesterol, HDL cholesterol, creatinin; metabolizable energy and crude protein consumption for 1g live weight gain of rats ($P>0.05$). The results showed that the supplementation of clinoptilolite did not have positive effect on serum concentrations of the investigated parameters apart from albumin, triglyceride and VLDL, but they had no negative effect on the health status of animals.

Studies of the bioavailability of clinoptilolite minerals in porcine models have been conducted by numerous investigators. Pond and Yen (1983a) reported that the concentrations of liver and kidney ash, Cd, Zn, Fe, Mn, Cu, Ca, M, P, K, and N were unchanged in growing pigs fed a diet containing 3% clinoptilolite, thereby indicating that clinoptilolite is considered to be stable at physiological pH and at the acidic pH (<2) of the stomach. Shurson et al (1984) fed pigs diets containing up to 7.5% clinoptilolite. Analysis of feces and urine samples for mineral retention indicated a reduction in levels of P, but no changes in the levels of Ca, Mg, Na, K, Fe and Zn. The authors stated that this indicated the stability of clinoptilolite in the acid environment of the stomach. In another study Pond et al (1989) reported that feeding growing pigs 2% clinoptilolite for 12 wk had no consequence on the concentrations of P, Fe, Zn, or Al in either kidney or liver tissue. The authors stated that the failure of liver or kidney Al to be affected by supplemental clinoptilolite in the diet suggests that clinoptilolite is stable in the milieu of the digestive tract contents and therefore that the absorption of Al or Si contained in the crystalline matrix of the molecule is nil or low.

Papaioannou et al (2002) reported that supplementing sow diets with 2% clinoptilolite had no significant effect on vitamin (A and E), and mineral (K, Na, P, Ca, Mg, Cu, and Zn) uptake and/or distribution. Fokas et al (2004) reported that supplementing the diets of castrated male pigs with 2% clinoptilolite did not lead to a significant increase of Pb concentration in blood or edible tissues, except for liver ($P <0.001$). However, the Pb retention coefficient between diets was not significant. The retention coefficient of Pb in the clinoptilolite used was practically negligible (0.009). The amount of Pb contained in the supplemented diet (2.1 ppm) was below the allowable EC limit of 5 ppm for complete feeds (EU, 1999) and well below the level of 30 ppm given by NRC (2005) for mineral feeds.

Alexopoulos et al (2007) studied the effect of long-term use of clinoptilolite on certain biochemical and hematological parameters in piglets. Forty-eight piglets (24 females and 24 males), equally allocated in two experimental groups were fed a control diet or the control diet with 2% clinoptilolite continuously from weaning to slaughter. All pigs were individually weighed and blood samples taken upon commencement of the study (25 days of age) and subsequently at the end of the weaning, growing and fattening stages (70, 112 and 161 days of age, respectively. The diet had no effect on serum K, Na, Ca, P, total protein, albumin and total bilirubin concentrations throughout the study

($P<0.05$). Likewise, no significant alteration was noticed concerning the hematocrit, leucocyte count and hemoglobin concentration ($P<0.05$).

Dwyer et al (1997) conducted a study in which day-old broiler chicks were fed a diet containing 1% clinoptilolite until 3 wk of age. No significant differences were observed in hematology, serum biochemical values and enzyme activities. Similar results for blood serum biochemical parameter are reported by Miles and Henry (2007) who fed broilers diets containing 2% hydrated sodium calcium aluminosilicate for 21 d and Safameher et al (2008) and Eleroglu et al (2011) who fed broiler chicks diets containing 2% and 5% clinoptilolite, respectively for 42 d.

In summary, available research indicates that clinoptilolite is not soluble and is resistant to the physiological and chemical conditions in the digestive systems of monogastric and ruminant animals; it passes through the gastro-intestinal tract essentially unabsorbed and is excreted with the feces. No studies could be found in the scientific literature demonstrating that clinoptilolite is degraded or absorbed after being consumed, and thereby posing a health risk for animals. As previously noted, it is already authorized for use as an anticaking agent in Europe (EC, 1999, 2011; EFSA, 2013).

6.4.2 Carcinogenicity

Studies lasting up to one year with Sprague-Dawley rats have demonstrated that intratracheal injection of 10 to 15 mg of clinoptilolite dust (50% clinoptilolite content, particle size of <2 μ) did not lead to significant damage of macrophage cell membranes. Mild fibrosis was detected, but no significant rise in tumor incidence. None of the doses applied caused heavy fibrosis or mesothelioma (Adamis et al., 2000). Likewise, no significant dose-related increase was found in the incidence of tumors in any organ or tissue of Wistar rats given intratracheal doses of clinoptilolite (0, 30, or 60 mg/animal) to groups of 60 or 50 male and 50 female rats on one occasion (Tátrai and Ungváry, 1993; WHO, 1997). In vitro cell culture studies have shown that clinoptilolite, unlike other zeolites, caused no aleveolar macrophage cytotoxicity due to the shape of its dust particles (Dong et al., 2006).

At present, clinoptilolite is placed in Group 3, being not classifiable as to its carcinogenicity in humans due to inadequate evidence in humans and experimental animals (WHO, 1997; Elmore, 2003).

6.4.3 Toxicity

Pavelić et al (2001) conducted a series of studies in mice using 4-mo-old male and female CBA/HZgr mice administered diets containing 0 or 25% clinoptilolite for a period of 1, 3, or 6 mo. During the course of study, the animals were monitored daily for clinical signs, changes in behavior, and survival, changes in body weight were monitored weekly, and food and water consumption measured at days 14 and 28 when the mice were housed for 24 hr in metabolic cages (5 mice per cage). Changes in hematological and serum clinical chemistry parameters (erythrocytes, leukocytes, platelets, hematocrit, hemoglobin, glucose, alkaline phosphatase, AST, ALT, bilirubin, inorganic phosphorus, and calcium) were obtained at t = 1, 3, and 6 mo and 24 hr urinalyses (glucose, proteins, urobilinogen, bilirubin, nitrites, erythrocytes, leukocytes, pH and specific gravity) obtained monthly. Histopathological analyses of liver, spleen, kidney, brain, lung, testes, ovary, duodenum, eye, stomach, large and small intestine, muscles, myocardium, pancreas, thymus, auxiliary lymph node were carried out on all animals at the end of the 1, 3, or 6 mo time-points. The investigators reported that no changes were observed that could be considered a toxic effect of the treatment. The results of this feeding study with clinoptilolite suggest a NOAEL of 25% in the diet (~37,500 mg/kg body weight/day), the highest dose tested.

Pavelić et al (2001) also conducted a study using Wistar rats administered diets containing 0, 25, or 50% clinoptilolite for a period of 1, 3, or 12 mo. The protocol used for these studies was similar to that presented for mice as described above. During the course of the study rats were monitored daily for clinical changes in behavior and incidence of mortality, body weight and water consumption were measured every 4 d and feed consumption measured daily. Hematological and serum clinical chemistry parameters (as per mice) were measured monthly. Histopathological examinations of liver, spleen, lung, kidney, testes ovary and brain, were performed on experimental and control rats euthanized after 1, 6, and 12 mo of feeding. The investigators reported that no changes were observed that could be considered a toxic effect of the treatment. The results of this feeding study in rats with clinoptilolite suggest a NOAEL of 50% in the diet (~25,000 mg/kg body weight/day), the highest dose tested.

6.4.4 Reproductive and Developmental Toxicology

In a multi-generation study Pond and Yen (1983b) investigated the effects of long-term ingestion of clinoptilolite on growth and reproduction in Sprague-Dawley rats. Female rats were administered a basal diet or a diet containing 5% clinoptilolite at weaning through week 13, at which point the females were mated and the dams continued on the same feeding regimen. Parameters such as BW after parturition and at 1, 2, and 3 wk postpartum, number of pups born per litter, live birth weight and average total litter birth weight were recorded. At 1, 2, and 3 wk postnatal, the number of live pups and total litter weight were recorded. The pups were weaned at 3 wk and the dams were euthanized. Blood samples were collected from the dams for determination of hemoglobin, hematocrit and plasma urea nitrogen. Fresh and dry weights of livers and kidneys were recorded. Pups (2/sex) from each litter were randomly selected at weaning (3 wk) and placed in a single cage. Individual body weights were recorded weekly for 4 wk, after which males were euthanized, blood collected for hematocrit and liver, kidneys and testes removed and weighed. The females were mated with young adult fertile males. Pregnant females continued on their respective diets during gestation and were weighed immediately after parturition and 1 d postpartum. Numbers of total and live pups per litter were recorded, and total weight of each litter at birth and at one day of age was determined. Dams were euthanized in the same manner as the first generation, blood hemoglobin and hematocrit were determined and liver and kidneys weighed. The authors reported that ingestion of clinoptilolite over 2 generations had no adverse effects on growth or reproduction in the animals. There was no evidence of toxicity of feeding clinoptilolite (5% in diet) during the growing period of the dams or throughout pregnancy and lactation. Reproduction was not affected by clinoptilolite consumption and no teratogenic effects or adverse effects on development or growth of the offspring were observed.

Pavelić et al (2001) investigated the reproductive toxicity of clinoptilolite in mice. In these experiments, clinoptilolite was mixed with standard feed at a ratio of 25:75 and was administered to 10 male and 10 female CBA/HZgr mice for 50 d, starting at least 14 d prior to mating. The treatment continued during the pre-pregnancy and pregnancy period (one cycle) and until weaning. The same pair of animals was fed clinoptilolite diets and monitored during four consecutive cycles (approximately 4 to 5 mo). The same schedule was applied for control animals. The parental generation was monitored for duration of the cycle period (pre- pregnancy and pregnancy period), fertility (presence or absence of litter in a particular cycle), delivery incidence, mortality, and histological changes of the ovaries, after the fourth cycle. The number of total and viable pups born, as well as gain in pup BW and mortality until weaning also was recorded. The pre-pregnancy period was shorter in the clinoptilolite-treated mice. The number of pups per litter was increased in clinoptilolite-treated mice. The authors postulated that probably for this reason the gain in body weight until weaning was decreased and a higher rate of mortality between days 8 and 21 of the neonatal period was observed. However, there were no differences between control and treated animals that would suggest reproductive toxicity attributable to the clinoptilolite administration.

Kyriakis et al (2002) conducted a study with 240 crossbred gilts and sows divided equally into two groups, and 2% clinoptilolite incorporated into the feed of one group. The sows and gilts of each group were offered the experimental diets from weaning (or from age of 6 mo for the gilts), during service, pregnancy and lactation and up to the date of service of the next reproductive cycle. All sows and gilts and their litters were monitored daily. No adverse or side effects were noted in the sows that were on the clinoptilolite-enriched diet. They showed normal estrus behavior during the breeding period, and gave rise to a slightly better farrowing rate (92.5%) compared to the control group (85.8%). No teratogenic effects were reported.

In a second study (Kyriakis et al, 2002), twenty-four crossbred sows (Large White x Landrace) were divided into two equal groups, the experimental group being offered feed incorporating 2% clinoptilolite. The study was maintained for a complete reproductive cycle (day of weaning up to the day of weaning of the next reproductive cycle). Blood samples were collected from each sow on the first day of the study, on days 30 and 90 of pregnancy, at parturition and at weaning. Serum parameters measured included vitamins A and E, inorganic phosphorus, potassium, copper and zinc. The dietary use of clinoptilolite at the inclusion rate of 2% did not provoke any adverse effect on sows/gilts health status and did not provoke any interactive effect on the availability of the dietary mineral elements and vitamins, although the level of vitamin E was found to be slightly lower in the experimental group.

6.4.5 Supplementary Animal Safety Information

The clinoptilolite used in several of the animal safety studies reviewed above is similar in purity and chemical composition to the Zeocem clinoptilolite which is the subject of this GRAS notice (Table 6.2). In addition, the Zeocem clinoptilolite contained in ZeoFeed® products is considered to be safe when used as an anticaking agent according to the criteria set forth in the EC/EU Commission Regulations for the addition of clinoptilolite to animal feed (EC, 1999, 2005; EU, 2013, 2016).

Table 6.2.	**Comparison of Zeocem clinoptilolite and clinoptilolite used in animal safety studies**		
Reference	Zeocem[a]	Pond and Yen (1983a,b)[b]	Pavelic et al (2001)
Animals	Ruminants, swine, poultry and pets	Rats	Mice and rats
Parameter	Composition (%)[c]		
Purity	86 - 92	85 - 87[d]	85[d]
SiO_2	65.0 - 71.3	63.4 - 63.6	50 - 55
Al_2O_3	11.5 - 13.1	12.2 - 12.6	9.3 - 11.4
CaO	2.7 - 5.2	3.0 - 3.4	13.7 - 17.2
Na_2O	0.2 - 1.3	1.4 - 2.5	0.8 - 1.1
Fe_2O_3	0.7 - 2.1	1.3 - 1.9	2.2 - 2.8
K_2O	2.2 - 3.4	1.1 - 2.3	2.9 - 4.3
MgO	0.6 - 1.2	1.5 - 1.7	0.8 - 1.2
TiO_2	0.1 - 0.3	0.1 - 0.3	0.14 - 0.22
Si:Al (ratio)	4.8 - 5.4	4.0 - 4.1	4.8 - 5.4
Particle size	0.05 - 2.5 mm	NG	1.5 - 3.0 µ

[a] Clinoptilolite sourced from Zeocem's mine in Nižný Hrabovec, Slovak Republic (Appendices 2.1 and 2.2).
[b] Pond et al (1983b) stated that the composition of the clinoptilolite used in the toxicity study was analyzed by Sheppard and Gude III (1982); the same analytical data is reported in Gude III and Sheppard (1988).
[c] Mineral composition of reported oxides.
[d] Estimated amount; calculation based on dated provided in the respective study.
NG - Not given.

6.5 Consumer Safety

Ordinarily, a GRAS notice will address the human dietary consumption of a component of animal feed because of the potential risk to human health due to consumption of animal products and tissues in which the component could be present. However, as the studies reviewed in Section 6.4.1 make evident, there is no need to determine the estimated daily intake for human consumption for clinoptilolite because the substance is excreted by the animal as part of its normal physiological and digestive processes. No data could be found in the scientific literature that would indicate any potential acute or chronic health risks to humans who have consumed animal products from animals that were fed diets containing clinoptilolite. The use of clinoptilolite as an anticaking agent in animal feed in the EU was authorized over 15 years ago. To date, there have been no reports of any adverse effects on consumer safety.

Moreover, because clinoptilolite is a natural crystalline aluminosilicate mineral of sedimentary origin it belongs to the same category of silicates that are classified as GRAS when used as anticaking agents in animal feeds (Sections 6.1.1 -6.1.3) and is considered safe for use in animal feeds in Europe, (Sections 6.1.4 and 6.1.5) no safety concerns for consumers need to be addressed.

6.6 Summary and Conclusions

The data and scientific information presented in this document demonstrate that the clinoptilolite which is the subject of this notice has similar physiochemical properties as those silicates (aluminosilicates) listed to be GRAS when used as anticaking agents.

An extensive review of the scientific literature on feeding studies has shown that animal data for poultry and monogastric, ruminant and laboratory animals fed clinoptilolite at levels above 2% of the diet did not indicate any safety issues that could have a negative impact on the health and performance. The data reviewed strongly support the premise that the purity and mineral composition of Zeocem clinoptilolite is similar to the purity and composition of other sources of clinoptilolite used in past animal feeding and safety trials for which no safety concerns were indicated for animal performance or health.

Thus, based on the information provided in this GRAS notice and the scientific procedures discussed herein, the Notifier submits that the Zeocem clinoptilolite of sedimentary origin contained in ZeoFeed® animal products fully meets the criteria of being GRAS when it is used as an anticaking agent at levels not exceeding 2% of the diet, in accordance with good manufacturing practices.

Part 7

DATA AND INFORMATION USED IN THE NOTICE

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7. DATA AND INFORMATION USED IN THE NOTICE

As stated in Part 6, the data and information used in this GRAS notice are listed separately according to those documents which are generally available and those which are not. Documents that are generally available are listed below in Section 7.1 using standard bibliographic citations.

Those documents that are not generally available are listed in Section 7.2 using the respective names of the Appendices.

7.1 Documentation Generally Available

21 CFR 25.32(f). Foods, food additives, and color additives (see GRAS environmental exclusions).

21 CFR 182.2122. Subpart C, Anticaking agents. Aluminum calcium silicate.

21 CFR 182.2727. Subpart C, Anticaking agents. Sodium aluminosilicate.

21 CFR 182.2729. Subpart C, Anticaking Agents. Sodium calcium aluminosilicate, hydrated.

21 CFR 184.1210. Calcium oxide.

21 CFR 186.1374. Iron oxides.

21 CFR 570.30. Eligibility for classification as generally recognized as safe (GRAS).

21 CFR 573.940. Silicon dioxide.

21 CFr 582.80. Trace minerals added to animal feeds.

21 CFR 582.1210. Calcium oxide.

21 CFR 582.2122. Subpart C, Anticaking agents. Aluminum calcium silicate.

21 CFR 582.2727. Subpart C, Anticaking agents. Sodium aluminosilicate.

21 CFR 582.2729. Subpart C, Anticaking Agents. Hydrated sodium calcium aluminosilicate.

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7.2 Documentation Not Generally Available

Appendix 2.1_Zeocem_2014_ZeoFeed Clinoptilolite 1g568

Appendix 2.2_Zeocem_2015b_Zeolite Data Sheet

Appendix 2.3_EFSA_2013_Clinoptilolite Flowability

Appendix 2.4_Zeocem_2015c_Manufacturing Process

Appendix 2.5_Internal_External Control Processes

Appendix 2.6a

EL. 2015a. Test Report 15/02461 Clinoptilolite of sedimentary origin - Batch M 181214-1. Ekologické laboratorià, Spisska Nova Ves, Slovakia.

Appendix 2.6b

EL. 2015b. Test Report 15/16295 Clinoptilolite of sedimentary origin - Batch M 300615-1. Ekologické laboratorià, Spisska Nova Ves, Slovakia.

Appendix 2.7a

EL. 2016. Test Report 16/01348 Clinoptilolite of sedimentary origin - Batch M 181215-1. Ekologické laboratorià, Spisska Nova Ves, Slovakia.

Appendix 2.7b

ICT. 2015a. Report of XRD analysis of clinoptilolite in the sample of Clinoptiolite of sedimentary origin -batch M 231214-1. Central Laboratories, Institute of Chemical Technology, Prague.

Appendix 2.8a

ICT. 2015b. Report of XRD analysis of clinoptilolite in the sample of Clinoptiolite of sedimentary origin -batch M 300615-1. Central Laboratories, Institute of Chemical Technology, Prague.

Appendix 2.8b

ICT. 2016. Report of XRD analysis of clinoptilolite in the sample of Clinoptiolite of sedimentary origin - batch M 181215-1. Central Laboratories, Institute of Chemical Technology, Prague.

Appendix 2.9_Zeocem_2016_Clinoptilolite Percent_2001_2015

Appendix 2.10a_Zeocem_2016_Levels of Heavy Metals: As Content in ZeoFeed_2001-2015

Appendix 2.10b_Zeocem_2016_Levels of Heavy Metals: Cd Content in ZeoFeed_2001-2015

Appendix 2.10c_Zeocem_2016_Levels of Heavy Metals: Hg Content in ZeoFeed_2001-2015

Appendix 2.10d_Zeocem_2016_Levels of Heavy Metals: Pb Content in ZeoFeed_2001-2015

Appendix 2.11_Zeocem_2016b_GMP Certificate

Appendix 2.12_Zeocem_2013_Certificate of Feed Registration

Appendix 2.13_Zeocem_2015g_Clinoptilolite 1g568 MSDS

Appendix 2.14_Zeocem_2016c_ZeoFeed Product label

Appendix 3.1_Dioxins

Appendix 3.2_Dioxins_2001-2016

Appendix 3.3_Radionuclides

Appendix 3.4_Constituents of Animal Origin

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Appendix 2.1

ZeoFeed®

Clinoptilolite of sedimentary origin (1g568)

DEFINITION:
An additive for the production of feed mixtures.
Category: "Technological additives",
Function group: g) „Binders",
i) „Anti-caking agents"

COMPOSITION:
Clinoptilolite (hydrated sodium calcium aluminosilicate) of sedimentary origin ≧80% and clay minerals ≦20% (free of fibres and quartz)

CAS NUMBER: 12173-10-3

MANUFACTURER REGISTRATION NUMBER: SK 100139

DECLARED QUALITATIVE PARAMETER:

Qualitative parameter	Legislative	Validity	Limit value	Praktice Year 2014 ∅ (min., max.)
Content of active materials *				
Clinoptilolite content (%)	Commission Regulation (EC) No 651/2013	Clinoptilolite of sedimentary origin	≧Min. 80.0	92,0 - 92,0
Dioxin content*				
Amount of dioxins such as PCDD/F (ng WHO- TEQ/kg)	Directive 2002/32/EC as amended	Clinoptilolite of sedimentary origin	Max. 0.75	0,094 (0,094-0,096)
Amount of dioxins such as PCBs (ng WHO-TEQ/kg)	*		*	0,032 (0,031-0,033)
Amount of PCDD/F and PCBs (ng WHO-PCDD/F-PCB-TEQ/kg)	Directive 2002/32/EC as amended	Feed additive from functional group binders, anti-caking agents, and coagulants	Max. 1.5	0,126 (0,125-0,129)
Heavy metal content				
Pb content (mg/kg)	Directive 2002/32/EC as amended	Feed additive from functional group binders, anticaking agents, and coagulants	Max. 30	12,32 (11,37-13,42)
Cd content (mg/kg)	Directive 2002/32/EC as amended	Feed additive from functional group binders, anticaking agents, and coagulants	Max. 2.0	0,0211 (0,0140-0,0259)
As content (mg/kg)	Directive 2002/32/EC as amended	Complete feed	Max. 2.0	1,24 (0,90-1,45)
Hg content (mg/kg)*	Directive 2002/32/EC as amended	Complete feed	Max. 0.1	0,00791 - 0,00560
Mycological evaluation *				
All kinds of blight	Slovak Government regulation Nr. 438/2006	Feed mixture for pig fattening and beef cattle	Max. 150,000 blight spores in 1 g of feed	Negative

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Clinoptilolite of sedimentary origin (1g568)

Qualitative parameters		Legislative	Validity	Limit value	Reality Year 2014 Ø(min., max.)
Microbiological evaluation *	Salmonella	Slovak Government Regulation Nr. 438/2006	All kinds of feed	0	Negat.
	E.coli	Slovak Governmenr regulation Nr. 438/2006	Feed mixtures		<MDA <1.0. 10^1
Radioactive contamination (Cs^{134} and Cs^{137}) (Bq/kg)		Slovak Government regulation Nr. 438/2006	Feed for pigs, lambs, and other kinds of animals	1,250-5,000	1.3±0.50
Animal proteins *					Negat.
Chemical analysis					
SiO_2 content (%)		PNR 08/13		Min. 62.0	64.6 (62.4- 67.3)
Al_2O_3 content (%)		PNR 08/13		Max. 14.0	12.4 (12.2- 12.5)
Fe_2O_3 content (%)		PNR 08/13		Max. 2.30	1.4 (1.1- 1.6)
CaO content (%)		PNR 08/13		Max. 5.50	3.1 (2.9- 3.1)

* External analysis

Property		ZeoFeed 50		ZeoFeed 200		ZeoFeed 0-0.2 mm		ZeoFeed 0-1mm	
		PNR 08/13	Year 2014 Ø (min., max.)	PNR 08/13	Year 2014 Ø (min., max.)	PNR 08/13	Year 2014 Ø (min., max.)	PNR 08/13	Year 2014 Ø (min., max.)
Granularity (oversize) (%)	0.05 mm	Max. 25.0	15.8 (11.8-19.5)						
	0.09 mm			Max. 25.0	13.5 (7.1-18.9)				
	0.1 mm	Max. 5.0	3.38 (2.2-4.7)						
	0.2 mm			Max. 10.0	1.5 (0.5-2.6)	Max. 20.0	4.2 (0.9 – 9.4)	Min. 50.0	63.2 (53.8-73.1)
	0.5 mm								
	1.0 mm							Max. 30.0	11.9 (5.4-20.4)
	2.5 mm								
Ion-exchange capacity (mol/kg)		Min. 0.70	0.83 (0.76-0.92)	Min. 0.70	0.82 (0.75-0.90)	Min. 0.60	0.82 (0.74-0.91)	Min. 0.70	0.82 (0.74-0.91)
Wetness (%)		Max. 6.0	3.5 (3.1-3.9)	Max. 6.0	3.8 (3.3-4.3)	Max. 8.0	4.46 (3.9-5.1)	Max. 8.0	4.46 (3.9-5.1)

Property		ZeoFeed 0.2-0.5 mm		ZeoFeed 0.5-1 mm		ZeoFeed 1-2.5 mm		ZeoFeed 0.2-1 mm	
		PNR 08/13	Year 2014 Ø (min., max.)	PNR 08/13	Year 2014 Ø (min., max.)	PNR 08/13	Year 2014 Ø (min., max.)	PNR 08/13	Year 2014 Ø (min., max.)
Granularity (oversize) (%)	0.05 mm								
	0.09 mm								
	0.1 mm								
	0.2 mm	Min. 70.0	80.1 (70.4-90.7)					Min. 80.0	91.2 (82.1- 97.5)
	0.5 mm	Max. 25.0	8.9 (4.2-15.8)	Min. 80.0	90.9 (85.1- 96.6)			-	
	1.0 mm			Max. 30.0	19.4 (7.3- 29.3)	Min. 80.0	96.1 (89.5 -99.2)	Max. 5.0	1.9 (0.2-4.6)
	1.25 mm							Max. 0.0	0
	2.5 mm					Max. 25.0	3.8 (0.7 - 9.7)	-	
Ion-exchange capacity (mol/kg)		Min. 0.70	0.82 (0.74-0.91)	Min. 0,70	0.82 (0.74-0.91)	Min. 0,70	0.82 (0.74-0.91)	Min. 0.70	0.82 (0.74-0.91)
Wetness (%)		Max. 8.0	4.46 (3.9-5.1)	Max. 8.0	4.46 (3.9-5.1)	Max. 8.0	4.46 (3.9-5.1)	Max. 8.0	4.46 (3.9-5.1)

ZEOCEM® SGS FAMI-QS

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ZeoFeed®

Clinoptilolite of sedimentary origin (1g568)

Property		ZeoFeed 0,2-1 Plus 0,2-1mm		ZeoFeed 0,5-1 Plus 0,5-1 mm	
		PNR 08/13	Year 2014 ∅ (min., max.)	PNR 08/13	Year 2014 ∅ (min., max.)
Granularity (oversize) (%)	0.05 mm				
	0.09 mm				
	0.1 mm				
	0.2 mm	Min. 70.0	82.7 (70.5- 97.3)		
	0.5 mm			Min. 80.0	95.4 (90.9- 98.8)
	1.0 mm	Max. 30.0	14.9 (4.0- 26.1)	Max. 50.0	35.4 (22.2-48.3)
	1.25 mm				
	2.5 mm				
Ion-exchange capacity (mol/kg)		Min. 0.70	0.82 (0.74-0.91)	Min. 0.70	0.82 (0.74-0.91)
Wetness (%)		Max. 8.0	4.46 (3.9-5.1)	Max. 8.0	4.46 (3.9-5.1)

APPLICATION:
ZeoFeed is recommended for all feeds for all animal species.

DOSAGE:
Mix ZeoFeed homogeneously into the feed.
Maximum permissible content 10,000 mg/kg of the complete feed.

STORAGE:
The product must be stored in original, undamaged and closed containers in dry, hygienically clean, well-aired indoor storages, away from foodstuffs, beverages and medicines. Unused ZeoFeed (remains without other additives) can be worked into the soil, since clinoptilolite is a certified soil adjuvant. Clinoptilolite is not a water contaminant - it can also be disposed of in the sewage system. Clinoptilolite does not result in hazardous waste! Any used ZeoFeed packaging or containers, once empty, are to be disposed of as separated waste.

LIFETIME:
If storage conditions are observed, granular ZeoFeed remains usable for up to 2 years.

DELIVERY:
25 kg paper bags (40 pcs / pallet)
BigBag packaging (1,000 kg / 1,200 kg / pallet)
bulk material, silo

ZEOCEM®

ZEOCEM, a. s., 094 34 Bystré 282, Slovak Republic
tel.: +421 57 4492643 • fax: +421 57 4452679
e-mail: zeocem@zeocem.sk • www.zeocem.com

AGRO

ZeoFeed®

Clinoptilolite of sedimentary origin (1g568)

CONTACT: Agro-line Project manager
MVDr. Jar oslav Tall
tall@zeocem.sk
tel.: +421 577862 033
fax: +421 574 452 679
mob.: +421 905 903 380

MANUFACTURER: ZEOCEM, a.s., 094 34 Bystré 282, Slovak Republic
Holder of certificate ISO 9001 and FAMI -QS
tel.: 00421/57/4492643, fax: 00421/57/4452679
e-mail: zeocem@zeocem.sk, www.zeocem.com

Version: XF/BXAD

AGRO

Appendix 2.2

Zeolite Data Sheet

Material name	Natural zeolite			
Chemical name	Hydrated aluminosilicate of alkaline metals and alkaline earth metals			
Mineral form	Clinoptilolite			
Empirical formula	$Ca_{1,8} K_{1,8} Na_{0,2} Mg_{0,2} Al_6 Si_{30} O_{72}.24H_2O$ [1] $(Na_{0,21} K_{1,74}) (Ca_{1,71} Mg_{0,31}) (H_2O)_{18,28} \| [Al_{6,11} Si_{29,90} O_{72}]$ [2] $(Na_{0,08} K_{0,35}) (Ca_{0,44} Mg_{0,08}) [Al_{1,47} Si_{7,53} O_{18}] . 4,34 H_2O$ [3]			
General formula	$(Ca, K_2, Na_2, Mg)_4 Al_8 Si_{40} O_{96}.24H_2O$			
CHEMICAL COMPOSITION				
SiO_2	65.00 – 71.30 %		MgO	0.60 – 1.20 %
Al_2O_3	11.50 – 13.10 %		Na_2O	0.20 – 1.30 %
CaO	2.70 – 5.20 %		TiO_2	0.10 – 0.30 %
K_2O	2.20 – 3.40 %			
Fe_2O_3	0.70 – 1.90 %		Si/Al	4.80 – 5.40
MINERAL COMPOSITION				
Clinoptilolite	84 %		Plagioclase	3 - 4 %
Cristobalite	8 %		Rutile	0,10 – 0,30 %
Clay mica	4 %		Quartz	Traces
ION EXCHANGEABILITY PROPERTIES				
Total exchange	Ca^{2+} 0.64 – 0.98 $mol.kg^{-1}$		Mg^{2+} 0.06 – 0.19 $mol.kg^{-1}$	
	K^+ 0.22 – 0.45 $mol.kg^{-1}$		Na^+ 0,01 – 0,19 $mol.kg^{-1}$	
Cation exchange capacity (CEC)			1.20 – 1.50 $mol.kg^{-1}$	
H_2O vapours sorbed by dehydrated rock at a relative moisture of 52 %			7,50 – 8,50 g $H_2O.100g^{-1}$	
at a relative moisture of 98 %			13,50 – 14,50 g $H_2O.100g^{-1}$	
SELECTIVITY				
$Cs^+ > Pb^{2+} > NH_4^+ > Cu^{2+} > Zn^{2+}, Sr^{2+}, Cd^{2+} > Ni^{2+} > Co^{2+}$ [4] $NH_4^+ > K^+ > Mg^{2+} > Ca^{2+}$ [4] $Cs^+ > NH_4^+ > Pb^{2+} > K^+ > Na^+ > Ca^{2+} > Mg^{2+} > Ba^{2+} > Cu^{2+} > Zn^{2+}$				
PHYSICAL AND MECHANICAL PROPERTIES				
Softing point	1260° C		Porosity	24 – 32 %
Melting point	1340° C		Effective Diameter of Pores	0.4 nm (4 Å)
Flow temperature	1420° C		Compactness	70 %
Compressive strength	33 MPa		Whiteness	70 %
Specific gravity	2200-2440 $kg.m^{-3}$		Mohs hardness	1.5 – 2.5
Volume density	1600-1800 $kg.m^{-3}$		Gridability as per VTI	kVTI = 1.628
Appearance and odour	Grey-green with no odour		Physical state (20° C)	solid
DATA ON REACTIVITY				
Acid stability	79.50 %		No dangerous decomposition	
Thermal stability	up to 400° C		No dangerous polymerisation	
Specific surface (BET)	30 – 60 m^2/g			
Solubility in water	none			

[1] Technology of Zeolites production, Final Report, reg. No. K12-526-056
[2] http://www.iza-online.org/natural/Catalog/Slovakia/SlovakiaFrame.htm, Carmine Colella
[3] Nižný Hrabovec – PP Zeolite tuff, Final Report, 1985
[4] Ionenaustausch an Naturzeolithen bei Wasserbehandlungsprozessen, Eva Horváthová-Chmielewská

ZEOCEM, a.s., 094 34 Bystré 282, Slovak Republic
tel.: +421 57 4492643 • fax: +421 57 4452679
e-mail: zeocem@zeocem.sk • www.zeocem.com

Appendix 2.3

Appendix 2.3. **Effect of clinoptilolite on the flowability of different feedingstuffs**

Type of feed	Feed particle size[a] (X50, mm)	Clinoptilolite (%)	Storage time (Solidification)[b]	Flow factor[c]
Piglet	0.39	0	–	6.4
		1	–	9.7
		2	–	11.5
		0	+	2.2
		1	+	2.9
		2	+	2.8
Piglet	0.46	0	–	4.5
		2	–	4.8
		0	+	1.9
		2	+	2.6
Sow	0.70	0	–	14.0
		2	–	10.7
		0	+	1.7
		2	+	2.1
Cattle	0.58	0	–	36.7
		1	–	14.5
		2	–	50.9
		0	+	2.1
		1	+	2.2
		2	+	2.4
Layer	1.34	0	–	13.0
		2	–	26.8
		0	+	2.3
		2	+	4.0
Dog	0.23	0	–	3.0
		2	–	4.0
Cat	0.19	0	–	4.2
		2	–	5.1
		0	+	2.5
		2	+	2.8

[a] Expressed as the median diameter of 50 % of the particles.
[b] Storage time of one day in a translation shear cell with 1.5 kg load at ambient conditions (18 °C; 60 % relative humidity).
[c] According to Jenike (1967).
Adapted from EFSA (2013).

Appendix 2.4

BEST COPY AVAILABLE

(b) (4)

[redacted]

Appendix 2.5

Appendix 2.5 Internal and external process controls

(b) (4)

[redacted]

Table 2.5.1 Plan of control system in own laboratory – ZEOCEM (continued)

(b) (4)

Table 2.5.2 Plan of external control - ZeoFeed

(b) (4)

Appendix 2.6a

(b) (4)

(b) (4)

Appendix 2.6b

(b) (4)

[redacted]

Counts

(b) (4)

[redacted]

(b) (4)

[redacted]

Appendix 2.7a

(b) (4)

[redacted]

(b) (4)

[redacted]

Appendix 2.7b

(b) (4)

(b) (4)

Appendix 2.8a

(b) (4)

(b) (4)

[redacted]

Appendix 2.8b

(b) (4)

(b) (4)

Appendix 2.9

(b) (4)

Appendix 2.10a

(b) (4)

Appendix 2.10a

Appendix 2.10b

(b) (4)

Appendix 2.10b

Appendix 2.10c

(b) (4)

Appendix 2.10c

Appendix 2.10d

(b) (4)

Appendix 2.10d

Appendix 2.11

Certificate NL16/818844200
FAMI-QS Registration Number: FAM-0377

The Feed Safety Management System including Good Manufacturing Practice (GMP) of

Zeocem a.s.

Bystré 282
094 34 Bystré
Slovakia

has been assessed and certified as meeting the requirements of

FAMI-QS Code

(Version 5.1, 14 February 2014)

For :

Technological additives
- binders, anti-caking agents

This certificate is valid from 09/04/2016 until 08/04/2019 and remains valid subject to satisfactory surveillance audits.
Issue 4. Certified since 10/04/2007.
For the validity of this certificate please check www.fami-qs.org

Authorised by

D.J. Verweij
Certification Manager
SGS Product & Process Certification

SGS Nederland B.V.
SGS Product & Process Certification
PO Box 200,
3200 AE Spijkenisse, The Netherlands
t +31(0)181-693297 – f +31(0)181-693572 - www.sgs.com

Appendix 2.12

The Central Controlling and Testing Institute in Agriculture in Bratislava
833 16 Bratislava, Matúškova 21
Department of Feeds and Animal Nutrition
Phone no.: 02/59 880 222, Fax: 02/59 880 381, E-mail: krmiva@uksup.sk, www.uksup.sk

T.no.: **KVZ/718/2013**

In Bratislava, **02/09/2013**

CERTIFICATE

The Central Controlling and Testing Institute in Agriculture in Bratislava (further on „controlling institute") – Department of Feeds and Animal Nutrition, as the competent authority to act on Art. 9 Act (SR) No 271/2005 Coll. on manufacturing, marketing and using feedingstuffs („the feed law") and acting on Act No 71/1967 Coll. on administrative proceedings (administrative code) as amended, issues in accordance with Regulation (EC) No 183/2005 laying down requirements for feed hygiene, **the certificate** of the registration according to the Art. 4 § 2 of the the feed law under the registration number:

SK 100139

Feed bussiness: **ZEOCEM, a.s.** Identification number (IČO): **36 457 728**
address: **094 34 Bystré 282**
premises: 094 34 Bystré 282

Registered activity:

Code	Description
C2V	Registered manufacturer of feed additives

Products:

Category	Type
Technological feed additives	1g568 (E 568) – Clinoptilolite of sedimentary origin

The certificate is valid: **since 26. 09. 2013 until 26. 09. 2018.**

Warning:
In the meaning of Act *NR SR* No 271/2005 Coll., Art. 4 § 1 the feed bussiness is obligated to notify in writing any changes of the registered data at least 30 days since the day the data were changed.

Justification:
Based on the registration request of the feed bussiness that was delivered to the Controlling Institute, all the demands in the request were examined and it was concluded that all the conditions needed for registration of the feed bussiness were accomplished and the certificate of registration was issued.
Feed bussiness will be deleted from the register in accordance to measures provided for in the Feed law Coll. Art. 4 § 3.

Instruction:
It is possible to appeal against this certificate according to Art. 54 §.2 of Act on the administrative proceedings in 15 days time-limit since its delivery to the Ministry of Agriculture and Rural Development of SR, Dobrovičova 12, 812 66 Bratislava, through the controlling institute which has issued the certificate. This decision may be reviewed by a court only after using a remedy (an appeal).

Ústredný kontrolný a skúšobný ústav poľnohospodársky v Bratislave - 1 -

v. z.

Ing. Juraj Moško
General director

Doručuje sa: ZEOCEM, a.s., 094 34 Bystré 282

Appendix 2.13

ZEOCEM, a.s. Bystré	Safety Data Sheets
Date of preparation: 16th May 2001	Preparation: Clinoptilolite of sedimentary origin (1g 568) with trade name ZeoFeed
Date of revision: 09.06.2004, 05.12.2005, 29.05.2007,15.08.2010,30.11.2010, 19.01.2012. 16.01.2013,21.07.2013, 21.02.2014, 13.02.2015	Page 1 from 8

1. Identification of the substance/mixture and of the company/undertaking

1.1 **Product identifier** (Trade name of the preparation)	Clinoptilolite of sedimentary origin (1g 568) with trade name ZeoFeed
1.2 **Relevant identified uses of the substance or mixture and uses advised against**	ZeoFeed is registered feed additive from: Category: "Technological additives" Functional group: g, "Binders," i, „anticaking agents " Active substance: Clinoptilolite (hydrated sodium calcium alumino-silicate) of sedimentary origin ≥ 80 % and clay minerals ≤ 20 % (free of fibres and quartz). Based on the selective adsorption effect, it binds harmful substances (ammonia, $NH4^+$, cadmium, lead and mycotoxines) in the digestive tract of animals. It adsorbs unwished substances of the paunch fermentation, and thus contributes to the pH stabilization in the paunch – buffer effect. It binds unbound water in the feed, and thus decreases the risk of fungus creation. The ammonia load from excrements and urine is reduced in the stable.
1.3 **Details of the supplier of the safety data sheet** (Manufacturer, owner of the preparation registration for protection of stored stocks)	ZEOCEM, a.s. 094 34 Bystré 282, Slovak Republic Tel. No.: 00421 / 57 / 4452414 Fax No.: 00421 / 57 / 4452679 E-mail: zeocem@zeocem.sk
1.4 **Emergency telephone number** Toxicological information centre	Slovak Toxicological Information Centre (Národné toxikologické informačné centrum) University Hospital Bratislava (Univerzitná nemocnica Bratislava), workplace Kramáre Industrial Medicine and Toxicology Clinic (Klinika pracovného lekárstva a toxikológie) Limbová 5, 833 05 Bratislava Tel. No.: +421 2 54652307 Mobile: +421 911 166 066 Fax. No.: +421 2 54774605 e-mail: ntic@ntic.sk

2. Hazards identification

2.1 Classification of the substance or mixture	Product ZeoFeed is produced from natural zeolite of clinoptilolite type .Clinoptilolite (hydrated sodium calcium aluminosilicate) of sedimentary origin ≥ 80 % and clay minerals ≤ 20 % (free of fibres and quartz). It is substance which occur in nature. It is substance according to AnnexV Regulation (EC) No 1907/2006 of the European Parliament and of the Council (exemptions from the obligation to register in accordance with article 2(7)(b).

	This substance is not stated in Schedule No. I of Directive No. 67/548/EHS in DSD (Dangerous Substance Directive) and it has not the prescribed classification in compliance with this Directive. This substance is not stated in Table No. 3.1 of Schedule No. VI of Directive ES No. 1272/2008 on classification, labelling and packing of substances and mixtures, and on alteration, amendment and cancellation of Directives No. 67/548/EHS and No. 1999/45/ES and on alteration and amendment of Directive (ES) No. 1907/2006 and it has not any prescribed "harmonized" classification in compliance with this Directive.
2.2 Label elements **according to Directive No. 67/548/EHS DSD**	***ES Classification :*** **This substance has not any prescribed classification according to Directive No. 67/548/EHS DSD** Based on his own decision, the raw material's manufacturer labelled the substance in the following way, as follows: **Warning dangerousness symbol:** it is not given **R-sentences:** it is not given **S-sentences:** S2 Keep it out of range of children. S 36/37 Wear the suitable clothing and gloves.
according to Directive (ES) No. 1272/2008	***GSH classification:*** **This substance has not the prescribed classification according to Directive (ES) No. 1272/2008.** **Based on his own decision, the raw material's manufacturer labelled this substance in the following way, as follows:** **GSH pictograms:** it is not given **Warning word:** it is not given **Warning notice:** it is not given **Safety notice – prevention:** P 102: Keep it out of range of children. P280: Wear the protective gloves / protective clothing / protective glasses. **Safety notice – response:** it is not given **Safety notice – storage:** it is not given **Safety notice – disposal:** it is not given

3. *Composition/information on ingredients*

3.1 **Substances**	*Trade name: ZeoFeed* ***Composition: 100 % natural clinoptilolite/*** ***Clinoptilolite (hydrated sodium calcium aluminosilicate) of sedimentary origin ≥ 80 % and clay minerals ≤ 20 % (free of fibres and quartz).***
3.2	CAS Number 12173-10-3 Molar mass: not specified

4. First aid measures

If any ailments are manifest, or in case of any doubts, a doctor should be informed about it and information, as per this Safety Data sheet, should be provided with him.

Type of hazard	*Acute danger*	*Prevention*	*First aid*
Aspiration	It is not specified.	By means of the technical measures to ensure that the NPEL of dust does not exceed 5 mg / m^3 in the closed rooms (warehouses). Where it is not possible to ensure temporarily these conditions, it is necessary to use, for protection of respiratory track, the anti-dust respirator.	Fresh air, and take medical advice.
Skin	It does not represent any risk after repeated skin applications and it is not absorb by skin in the harmful quantity.	To use the protective gloves and protective clothing.	To wash the affected place with water and soap.
Eyes	It irritates very mildly and short – lasting the conjunctiva mucosa.	To use the protective glasses.	To wash the eyes with huge amount of water during several minutes, and to take medical advise.
Intake	It is not specified.	Do not eat and drink at the workplace. After work completion, to wash your hands.	To drink 0.5 l of drinking water, or lukewarm water with suspension of the activated charcoal. Take medical advice.

5. *Firefighting measures*

5.1 Extinguishing media	Material is not inflammable. Shall be necessary to be adapted to the substances stored in their close proximity.
5.2 Special hazards arising from the substance or mixture	It is not specified
5.3 Advice for firefighters	It is not specified
Other information	It is not specified

6. *Accidental release measures*

6.1Personal precautions, protective equipment and emergency procedures	Personal preventive actions (safety measures for protection of persons):

6.2 Environmental precautions	To use the personal protective means, and to not breath in any dust. Environmental precautions: Before its adsorption, the pure Zeolite (without any other mixtures) can be worked into the soil, because Zeolite is the registered soil auxiliary substance. Zeolite does not contaminate even water – it can be also discharged into the sewerage (Zeolite is used as an adsorbent for treatment of drinking water and also for clarification of waste water). Zeolite is not a dangerous waste !
6.3 Methods and material for containment and cleaning up	Mechanically, residues of Zeolite (without any other additives) can be worked into the soil (Zeolite is the certified soil auxiliary substance), or discharged into the sewerage. After its through emptying, the used packs from this preparation should be handed over into the separated collection, or to the approved refuse incinerating plant.

7. *Handling and storage*

7.1 **Precautions for safe handling**	- from the view of safety and health protection in working, the employees must use the personal protective means during manufacturing of this preparation and application thereof, - the working environment, during manufacturing of this preparation and handling with thereof, must be ensured in such a way so that the NPEL of dust has not been exceeded in the air, - the employees must be instructed about product, and they must follow the principles of heath and environment protection.
7.2 **Conditions for safe storage, including any incompatibilities**	This product must be stored in the original and undamaged and closed packs, and in dry, hygienically clean, and in good ventilated and covered warehouses, and separately from foodstuffs. In case of packing for small customers, it should be also stored separately from medicaments and desinfecting agents.

8. *Exposure controls/personal protection*

8.1 Control parameters:
Components

Base	Value	Limiting value	Exposition limiting value
It is not given	It is not given	It is not given	It is not given

8.2 Inspections of exposition – Personal protective means:
In the form of dust (aero-dispersed system) in the working environment, it is necessary to assess Zeolite as a substance with predominantly fibrous effect (respiration limit is 5 μm). NPEL of dust for the working environment is 5 $mg.m^{-3}$. The workplaces shall be dust exhausted, or ventilated, in such a way so that the maximum dust concentration is 5 $mg.m^{-3}$ of air. Where it is not possible to provide temporarily these conditions, the personal protective working means (protective clothing and shoes, respirator with dust separator, protective.

9. Physical and chemical properties

9.1 Information on basic physical and chemical properties	
State at 20 °C	Solid
Colour	Light greyish green

Aroma, malodour	No aroma and malodour
pH	
Boiling temperature	No information is available.
Flash point	Up to 600 °C neg.
Ignition temperature	Settled dust – up to 600 °C neg., raised dust – up to 800 °C neg.
Explosive limits (volume % in the air)	Non-explosive.
Specific weight (kg/m^3)	2200-2440
Oxidation properties	No information is at disposal.
Steam pressure	No information is at disposal.
Solubility	No information is at disposal.
Solubility in water	No information is at disposal.
Distributive coefficient n-octane / water	No information is at disposal.
Viscosity	No information is at disposal.
Vapour density	No information is at disposal.
Evaporation rate	No information is at disposal.
9.2 Other information	
Miscibility	No information is at disposal.
Fat solubility	No information is at disposal.
Conductivity	No information is at disposal.
Melting point	1340 °C
Autoignition temperature	No information is at disposal.

10. Stability and reactivity

10.1 Reactivity	No information is at disposal
10.2**Chemical stability**	No information is at disposal
10.3**Possibility of hazardous reactions**	No information is at disposal
10.4 **Conditions to avoid**	No information is at disposal
10.5**Incompatible materials**	No information is at disposal
10.6 Hazardous decomposition products	No information is at disposal.

11. Toxicological information

Information on toxicological effects	No information is at disposal.
Acute toxicity for substance	
LD_{50}	It was not possible to determine the value of acute oral LD_{50}. After application of dose of 20.000 mg/kg, no animal has died. It is not possible to apply higher doses. It was not possible to determine the value of acute dermal LD_{50}. After application of dose of 5.000 mg/kg on the cut back skin of experimental animals, no animal has died. It is not possible to apply higher doses.
Eye irritability	It irritates very mildly and short-lasting the conjunctiva mucosa. / Apart from the mild congestion after two (2) hours after application of the preparation, which has disappeared within 24 hours, no inflammation changes of conjunctiva mucosa have been observed there /.
Skin irritability	Zeolite does not cause any inflammation changes on the intact

	or damaged skin, as well as any other indications of toxicity, even after multiple applications thereof.
Influence on live organisms	Zeolite can be classified as a substance, which is low toxic up to harmless substance. It does not represent any risk even after repeated skin applications, and it does not absorb by skin in the harmful quantity. It irritates very mildly and short – lasting the conjunctive mucosa.
skin corrosion/irritation	Zeolite does not cause any inflammation changes on the intact or damaged skin, as well as any other indications of toxicity, even after multiple applications thereof.
serious eye damage/irritation	It irritates very mildly and short-lasting the conjunctiva mucosa. / Apart from the mild congestion after two (2) hours after application of the preparation, which has disappeared within 24 hours, no inflammation changes of conjunctiva mucosa have been observed there /.
respiratory or skin sensitisation	No information is at disposal.
germ cell mutagenicity	No information is at disposal.
carcinogenicity	No information is at disposal.
reproductive toxicity	No information is at disposal.
STOT-single exposure	No information is at disposal.
STOT-repeated exposure	No information is at disposal.
aspiration hazard	No information is at disposal.
Other Information:	Even other dangerous properties can not be eliminated. It is necessary to handle with this product with such caution like with chemicals.

12. Ecological information

12.1 Toxicity :

The results obtained by testing of Zeolite of Clinoptilolite type did not enable to define the LC 50 for fish and daphnia, because the tested animals have survived the maximum concentrations exceeding the limits for classification of the preparation into the group of substances "for fish and other animals it is almost non-toxic".
Based on the 96-hour static and acute toxicity tests on fish (Cyprinus carpio L., Poecilia reticulata Peters) and 24-hour acute and immobilization test on daphnia (Daphnia magna Straus), the natural Zeolite was classified as to be a substance almost non-toxic for fish and daphnia (Final Report of research No. 53/NRL/T-102).

Pursuant to the expert's opinion of the NRL for pesticides UVM Košice No. 265/2004 NRL/P-1219 rekl., the natural Zeolite is "relatively innocuous for domestic animals, livestock and free living animals" (Z4), "for fish and other water animals, it is almost non-toxic" (Vo4), and "for birds, in case of exceeding the prescribed doses or concentrations, it is relatively harmless" (Vt5). "It is not suitable for earthworm population".
Zeolite of Clinoptilolite type is registered as feed additive (1g568).

12.2 Persistence and degradability	No information is at disposal.
12.3 Bioaccumulative potential	No information is at disposal.
12.4 Mobility in soil	No information is at disposal.
12.5 Results of PBT and vPvB assessment	No information is at disposal.

12.6 Other adverse effects	No information is at disposal.

13. *Disposal considerations*

Waste treatment methods :
The method of waste disposal – mechanically. The residues of Zeolite (without any other additives) can be mixed in the soil, because Zeolite is registered as the soil auxiliary substance. Zeolite does not contaminate even water – it can be also washed away into the sewerage. Zeolite is not a dangerous waste!

14. Information about transport

Sea transport (IMDG): UN No.: UN proper shipping name: Transport hazard class(es): Packing group: Environmental hazards: Special precautions for user: Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code :	No information is at disposal.
Land transport (ADR): UN No.: UN proper shipping name: Transport hazard class(es): Packing group: Environmental hazards: Special precautions for user: Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code :	No information is at disposal.
Railway transport (RID): UN No.: UN proper shipping name: Transport hazard class(es): Packing group: Environmental hazards: Special precautions for user: Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code :	No information is at disposal.
Air transport (ICAO/IATA): UN No.: UN proper shipping name: Transport hazard class(es): Packing group: Environmental hazards: Special precautions for user: Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code :	No information is at disposal.

15. Regulatory information

Label elements :	

according to Directive No. 67/548/EHS DSD	***ES Classification :*** **This substance has not any prescribed classification according to Directive No. 67/548/EHS DSD** Based on his own decision, the raw material's manufacturer labelled the substance in the following way, as follows: **Warning dangerousness symbol:** it is not given **R-sentences:** it is not given **S-sentences:** S2 Keep it out of range of children. S 36/37 Wear the suitable clothing and gloves.
according to Directive (ES) No. 1272/2008	***GSH classification:*** **This substance has not the prescribed classification according to Directive (ES) No. 1272/2008.** **Based on his own decision, the raw material's manufacturer labelled this substance in the following way, as follows:** **GSH pictograms:** it is not given **Warning word:** it is not given **Warning notice:** it is not given **Safety notice – prevention:** P 102: Keep it out of range of children. P280: Wear the protective gloves / protective clothing / protective glasses. **Safety notice – response:** it is not given **Safety notice – storage:** it is not given **Safety notice – disposal:** it is not given
Warning designation	Handling with it is in conformity with good operational hygiene, and principles of safety and health protection in working.

16. Other information

The Security Card contains the data necessary for ensuring the safety and health protection in working and environment protection. The given data corresponds to the present state of knowledge and experience, and they are in conformity with the legal regulations. The particular conditions of using this product at the consumer, however, they are outside of the range of our surveillance and control. The customer is responsible himself/herself for observance of the security provisions.

This Security Data Card has been revised and reworked according to the Regulation of the European Parliament and Council (ES) No. 1907/2006 on registration, evaluation, authorization and limitation of chemical substances (REACH).

Appendix 2.14

Information to be included on feed label	
Brand Name	Zeocem
Product Name	ZeoFeed®
Purpose Statement	Anticaking agent for further manufacture of feedstuffs for ruminants, swine, poultry and pets (cats and dogs).
Guaranteed Analysis	Clinoptilolite minimum 80%.
Ingredients Statement	Clinoptilolite of sedimentary origin containing up to 20% clay, free of fibers and quartz.
Directions for Use	Levels of ZeoFeed® must not exceed 40 lbs/ton (20 kg/1000 kg) in complete feed.
Manufactured by	ZEOCEM, a.s., 094 34 Bystré 282, Slovak Republic phone : 00421/57/4452414, fax :00421/57/4452679, e-mail: zeocem@zeocem.sk, www. zeocem.sk
General Information	Lot Number:________
	Date of Manufacture: DDMMYY
	Use within 2 years from date of manufacture. Store in a dry place at ambient temperature.
	For further information contact: G-SCIENCE, Inc. 5500 Highlands Parkway Smyrna, GA, 30082 USA
Net Weight	55.1 lb (25 kg)

Appendix 3.1

(b) (4)

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Appendix 3.2

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Appendix 3.2

Appendix 3.3

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(b) (4)

[redacted]

Appendix 3.4

(b) (4)

[redacted]

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g-pur.com

G-SCIENCE

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By email in advance

Mr. Geoffrey Wong
Dr. Lei Tang
Division of Animal Feeds, HFV-224
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

February 20, 2010

Subject: **GRAS Notice Filing**
Clinoptilolite as an Anticaking Agent/ AGRN #25

Dear Mr. Wong, dear Ms. Tang,

As a follow up to the Memorandum of January 30, 2018 Teleconference (received on Feb 5th, 2018), we respectfully submit the attached addendum in support of the determination that clinoptilolite, a natural crystalline aluminosilicate mineral of sedimentary origin, is Generally Recognized as Safe (GRAS) when used as an anticaking agent in animal feed.

We trust that this addendum satisfies the Agency´s needs and addresses all deficiencies specified in the phone call minutes (Jan 30th, 2018), and will be deemed accepted and complete. Should any questions arise, please contact us, preferably by telephone (+1 678 925 8015) or e-mail (thomas.berger@g-science.com) so that we can promptly reply.

Sincerely yours,

Thomas Berger
Position: Vice President G-Science, Inc.

RECEIVED
FEB 28 2018
By

Enclosures

Generally Recognized as Safe (GRAS) Notice

for

Clinoptilolite
(CAS Reg. No. 12173-10-3)

AGRN#25

Amendment

Submitted to:

Division of Animal Feeds (HFV-220)
Office of Surveillance and Compliance
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place
Rockville, MD 20855

Notifier:

G-Science, Inc.
5500 Highlands Parkway
Smyrna, GA 30082, USA
Phone: 678-306-2505, Fax: 678-306-2500

Reply to issues raised

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INTRODUCTION

In a teleconference dated 30 January 2018 FDA-CVM participants raised several issues identified in G-Science Inc. GRAS notice (AGRN#25) on *Clinoptilolite of sedimentary origin*.

Below we provide additional data as discussed and suggested in the minutes of the teleconference (received on 5th February 2018).

IDENTIFICATION OF THE NOTIFIED CLINOPTILOLITE

The following specifications apply to the product; this revision reflects the analytical data provided in our notice (Appendices 2.1, 2.2, 26a – 2.10) and the applicable legislation for undesirable substances (see footnote 1 on page 5) that is used by the notifier when marketing clinoptilolite in the European Union. The table below replaces Table 2.2. of Part 2.

Table 2.2	**Specification of Zeocem clinoptilolite**
Parameter	Content
Clinoptilolite of sedimentary origin	Not less than 80 %
Clay minerals	Not more than 20 %
Particle size	0.010 - 2.5 mm (d50)
SiO_2	62 - 73%
Al_2O_3	11 - 14%
CaO	2 – 5.5%
Na_2O	0.2 - 1.5%
Fe_2O_3	0.7 – 2.3%
K_2O	2.2 - 3.4%
MgO	0.5 - 1.2%
Pb	Not more than 20 mg/kg
Cd	Not more than 0.1 mg/kg
As	Not more than 2 mg/kg
Hg	Not more than 0.05 mg/kg
Dioxins (such as PCDD/F)	Not more than 0.3 ng WHO - TEQ/kg
Dioxins (such as PCDD/F) + Dioxin-like PCBs	Not more than 0.5 ng WHO - TEQ/kg

With respect to particle size we refer to Reháková et al (2004) which provides granulometric data for clinoptilolite of sedimentary origin described in this notification. This issue is also discussed further in the next section.

UTILITY/TECHNICAL EFFECT AS ANTICAKING AGENT

The Code of Federal Regulation includes in section 582 currently three aluminosilicate compounds that are GRAS when used as anticaking agents in animal feed at a use tolerance level of 2% in accordance with good manufacturing or feeding practice. These are Aluminum calcium silicate (21 CFR 582.2122), Sodium aluminosilicate (21 CFR 582.2727), and Hydrated sodium calcium aluminosilicate (21 CFR 582.2729). The same substances are also listed by CFR as being GRAS when used in human food, 21 CFR 182.2122, 182.2727 and 182.2729.

The use of these GRAS-listed aluminosilicates as anticaking agents in food was reviewed by Peleg & Hollenbach (1994) who provide also some general background on the properties of substances that act as flow conditioners/anticaking agents. Anticaking agents are also known as glidants, antiagglomerants, lubricants or free-flowing agents, they are finely divided solids that are added to a host powder to improve flow and/or reduce its tendency to cake (also Hollenbach et al 1982). They are usually inert materials which do not dissolve in water, but many can adsorb water in large amounts. Typical amounts for their use are up to 2%.

The anticaking activity of conditioners is achieved in several ways. One is coating of host powder particles which reduces their clumping, the lubricant separates physically the host particles and reduces friction caused by cohesion. A second important mechanism is competition for adsorbed water where the host powder stays dry and flowable due to the water adsorption capacity of the anticaking agent (Irani et al 1961). Several other mechanisms may work as e.g. one where the anticaking agent neutralizes electrostatic charges or reduces superficial molecular attractive forces. This mechanism is also important for reducing caking at surfaces of processing equipment. It should be noted that in a given system of a host powder and an anticaking agent these mechanisms may be present jointly and support each other synergistically. This aspect was also emphasized by Adhikari et al (2001) when discussing stickiness of food, and more recently by Zafar et al (2017) in their review on bulk powder caking.

For the described physical separation, a particle size between 1 and 50 µm may be desirable (Irani et al 1959), for fine host powder even very fine conditioner with particle sizes below 0.1 µm may be needed (York 1975). In case of competition for adsorbed water or other mechanisms particles of larger size will work as well.

Aluminosilicates continue to be suitable anticaking agents for powdered food items such as cake and dessert mixes, egg powder, dairy products, sauce, onion and garlic powders, soup powder, sucrose, corn starch, lactose, modified corn starch (MCS), sucrose and MCS matrix (Peleg & Hollenbach, 1994; Adhikari et al, 2001; Zafar et al 2017). Many of these powders are used also as feed ingredients or represent matrices that are found also in feed ingredients.

The suitability of aluminosilicates used as anticaking agents in food applies therefore to their use in animal feed for the same purpose that is to be added to finely powdered or crystalline feed ingredients to prevent caking, lumping, or agglomeration.

Clinoptilolite is member of the group of zeolites which are crystalline, hydrated alkali-aluminum silicates (Merck Index, 14th edition) and therefore chemically closely related to the three GRAS aluminosilicates, and specifically the hydrated sodium calcium aluminosilicate (21 CFR 582.2729).

Clinoptilolite is, like the listed three GRAS aluminosilicates, an inert material which does not dissolve in water, but may adsorb water (Kotova et al 2016). Clinoptilolite from sedimentary origin is available over a broad range of particle diameters (Reháková et al, 2004) and will support any of the described mechanisms of anti-caking. As a fine powder with diameter in the single digit micron range or even lower it will cover host powder particles, more granular forms with diameters larger than 50 µm will still adsorb water and reduce caking of feeds by keeping them dry.

TARGET ANIMAL SAFETY (TAS)

Characterization of clinoptilolite used in studies

In Section 6.3 of our notification we discuss safety data obtained from studies with target animals where clinoptilolite from the Nižný Hrabovec mine (as specified in the table on page 3) had been employed. In Section 6.2. we summarized safety data from target animal studies where clinoptilolite from other mines had been used. In Section 6.3.4 and Table 6.2 we discuss the similarities between our clinoptilolite and the other clinoptilolites and conclude that both are closely related and hence all studies available support the safety of our clinoptilolite for target animals.

You suggest that we compare not only the major constituents but also the contaminants (heavy metals and dioxins) present in our clinoptilolite and the other clinoptilolites. Though it is unusual to report such detailed analytical data in trials published in peer-reviewed journals, we offer the following considerations which are based, in the absence of US tolerances, on the maximum limits of the European Union which reflect inter alia international evaluations by JECFA.

For heavy metals, arsenic, and dioxins/dioxin like PCBs maximum limits for complete feed were established in Europe between 1974 and 2007; in addition, for specific types of feeds such as mineral feed or feed ingredients such as feed additives derived from mineral deposits (among them clinoptilolite of sedimentary origin) separate levels were adopted. All these levels reflected and, as they have been reviewed regularly, continue to reflect the state of the art toxicology and good manufacturing practice (which included reported and observed ranges of contamination).

The following maximum limits were applied historically in Europe (many as early as 1974, most of them before 2003) and apply today for complete feed, complimentary feed (mineral feed), and for clinoptilolite. [1] As comparison maximum tolerable levels for heavy metals and arsenic based on animal health as adopted by NRC are given.

	Lead	Cadmium	Mercury	Arsenic	Dioxins	Dioxin and dioxin-like PCBs
	mg/kg				ng WHO - TEQ/kg	
Complete feed	5	1	0.1	2	0.75	1.5
Complementary feed	10	0.5	0.2	4	0.75	1.5
Mineral feed	15	5	0.2	12		
Clinoptilolite	30	2	[0.1]	[2]	0.75	1.5
Maximum Tolerable Levels (NRC 2005)	10 – 100	10	0.2	30	-	-

Note: levels in [ ] are not legally mandatory but respected and applied by the feed chain

The safe/unsafe intake of a contaminant for an animal results from all dietary sources including water for drinking. As long as a single ingredient's content of a contaminant is not higher than what is tolerable for the complete feed or ratio, the resulting net intake by the animal would continue to be safe. Should a higher content be permitted in an ingredient, a dilution in the complete feed to levels below the tolerance for complete feed would assure that intake by the animals is still safe.

Study protocols for animal studies are prepared under applicable regulatory framework including rules for animal welfare and animal feed; they reflect also current feeding practice in the country where the study is run.

We would expect that levels of contaminants in the complete feeds used in the studies we mention in Section 6.2 of our notice are, when performed in Europe, meeting the legal requirements laid down in European Union feed law. This applies specifically to the studies run in Europe which are those reported by Katsoulos et al (2005a, 2005b, 2005c), Karatzia et al (2011), Pourliotis et al (2012), Papaioannou et al (2002), Sardi et al (2002), and Herzig et al (2008). The clinoptilolites used in European studies are therefore similar to our clinoptilolite with respect to their likely contamination with heavy metals, arsenic and dioxins, as they all were products used under applicable European feed law which includes levels for these contaminants. Such studies are done to develop data to be used in the market place which makes only sense if the product comply with regulations and can therefore be marketed.

However, also studies with clinoptilolite run outside of the European Union under a different jurisdiction would support the conclusions on the safety of our clinoptilolite. If results from such studies indicate safety of the applied clinoptilolites at the proposed use level of 2 % or higher, the study material used was at least contaminated at levels that did not results in toxicity. As we are not aware of studies with reported toxicity of clinoptilolite due to presence of contaminants, we consider

[1] DIRECTIVE 2002/32/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 7 May 2002 on undesirable substances in animal feed (as amended subsequently)

that the materials used in these studies were also sufficiently similar with respect to their spectrum and level of contaminants.

In summary, other clinoptilolites used in those studies discussed in Section 6.2 of our notice are similar to our clinoptilolite with respect to their contents in heavy metals, arsenic, and dioxins/dioxin like PCBs.

Use levels for livestock (ruminants, swine and poultry) and pets

You pointed out that the European Commission authorized the use of clinoptilolite as anticaking agent in animal feed for all animal species at 1 % due to safety concerns at higher use levels and you suggested to discuss the studies that EFSA had listed as studies with negative effects.

EFSA reviewed the safety of clinoptilolite of sedimentary origin in 2013 (EFSA 2013). The assessment was based on the publications identified by a structured literature search, performed by the applicant in 2010.

Several studies are discussed in the EFSA opinion as putting into question the safety of 2 % clinoptilolite. EFSA's expert panel agreed that "*considering the adverse, albeit unclear, effect on the mineral status of pigs, chickens and dairy cows and the effects of approximately 15 000 mg clinoptilolite/kg on rumen fermentation*" it seemed "*prudent not to consider 20 000 mg clinoptilolite/kg in complete feed as safe for all animal species*".

Pigs

EFSA's expert panel reviewed six studies in pigs of which two were deemed to show some effects assessed to be negative.

According to EFSA in the study from Pond et al (1988) "*some changes in the mineral concentration of the kidney of pigs were found*". EFSA did not consider the second publication by Pond et al (1989) were the authors assessed further the tissue mineral element content in swine. In this study fattening pigs received diets low and high in calcium with low and high content in iron plus 0 or 2 % clinoptilolite. The authors determined in liver and kidney the levels of sulfur, phosphorus, potassium, sodium, magnesium, iron, aluminium, copper, and zinc. There was no effect of clinoptilolite on liver concentration of any mineral element measured. They noted small shifts in the kidney level of potassium, magnesium and copper, however, those were of no consequence to overall animal health or tissue or cellular integrity, since no pathological lesions or clinical signs of aberrations in mineral element metabolism were evident. Concluded that the addition of 2% clinoptilolite to corn-soybean meal ail-plant diets fed continuously to growing-finishing pigs for 84 days is not associated with adverse effects on tissue mineral element concentrations even when dietary calcium and iron concentrations are altered. The several observed changes in tissue mineral concentrations in response to dietary clinoptilolite do, however, suggest that dietary mineral element composition should receive special attention when clinoptilolite is added to the diet.

The study of Poulsen & Oksbjerg (1995) investigated effects of 0 and 3% clinoptilolite on protein-poor and -rich diet. The feed was not adjusted to the reduced energy content in the clinoptilolite group and, as pigs did not compensate for this effect by increasing feed intake, daily weight gain was slightly reduced. Additionally, the authors state that protein retention was not influenced significantly. The clinoptilolite used in this study contained less clinoptilolite (70%) than our clinoptilolite or the one authorized in the EU. Test material and inclusion rate differ from our notification, and the observations made in this study are explained by the study design. Its results do not affect our GRAS conclusion.

Chicken

EFSA's expert panel reviewed one study in chicken, performed by Scheideler (1993) which investigated the efficacy of four different aluminosilicates (two of them zeolites; all added at 1%) on aflatoxin B1 toxicity. Due to the complicated study design it is not easy to discern results for the aluminosilicates only from those resulting from the interaction with aflatoxin B1. Body weight, feed consumption, and feed conversion were not affected by any of the aluminosilicates, and calcium, phosphorus, sodium, and potassium levels in serum were not affected either. The author concludes that the type of aluminosilicate had no effect on serum calcium, phosphorus, sodium, or potassium, compared with the control diet. A statistically significant reduction of chloride serum levels is reported. However, the control had 102 mEq/L, and for the four treatment groups levels of 97, 98, 100 and 101 were reported (the author notes that the diet had not been adjusted for chloride imbalance due to addition of aluminosilicates). Bone ash was reduced by one synthetic aluminosilicate, but not by the two zeolites used in the study.

EFSA did not review any of the fourteen publications we discuss in Section 6.2.3 where other clinoptilolites had been used in poultry, and the three publications in Section 6.3.3 with our own clinoptilolite. This study was not designed to investigate the safety of clinoptilolites but focussed on interaction with aflatoxin B1, the results do not provide evidence that clinoptilolites are unsafe for chicken.

Dairy cows

EFSA reviewed one study in dairy cows (Karatzia et al 2011) where animals received 200 g of clinoptilolite per day. The test material was offered together with a concentrate (4 kg), corn silage (25 kg) , and molasses (2 kg). The aim of this study was to investigate whether the dietary inclusion of 200 g of clinoptilolite has any effect on the blood serum concentrations of aluminum and inorganic phosphorus as well as on the ruminal pH and the ruminal concentrations of aluminum and of certain volatile fatty acids.

The aluminum concentrations in rumen fluid and blood serum were not affected by clinoptilolite supplementation throughout the experimental period which indicates that clinoptilolite was stable at the acidic pH of the gastrointestinal tract. Concentration of soluble phosphorus in the rumen fluid was not significantly affected by clinoptilolite supplementation. Clinoptilolite significantly increased the pH of the rumen fluid, an increase that was attributed to the buffer effects of clinoptilolite when added to acidic or basic aqueous solutions. The total volatile fatty acid concentration was not significantly affected by clinoptilolite supplementation, but, the molar proportions of the volatile fatty acids evaluated were significantly affected by clinoptilolite. Acetate was increased while propionate and valerate were decreased.

The authors' findings are in contrast to results obtained by other authors (see Section 6.2.1), however, we would question that the observed changes were negative effects. It is generally acknowledged that increase in rumen pH and acetate, and decrease in propionate are beneficial. The levels achieved in this study are those you would expect in healthy animals and hence are not an evidence of clinoptilolite being unsafe for dairy cows (Krause and Oetzel, 2006; Enemark, 2008; Abdela, 2016)[2].

Other species

You ask us to comment on the study performed by Martin-Klainer et al (2001) that had been considered by EFSA. In this study young adult mice were supplied with food containing 12.5%, 25% or 50% clinoptilolite powder. Control animals received the same food without the clinoptilolite. Clinoptilolite ingestion was well tolerated, as judged by comparable body masses of treated and control animals. A 20% increase of the potassium level was detected in mice receiving the zeolite-rich diet, without other changes in serum chemistry. No other parameter showed a deviation despite the high feed inclusion level. Data obtained at levels of 12.5 % or higher serve for hazard identification, as such moderate changes have not been observed at 2% or lower, this finding is not relevant for the risk assessment of our proposed conditions of use.

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[2] Text books that discuss the need of avoiding low rumen pH and low acetate/propionate ratios are among others: "Merck Veterinary Manual", Dukes' Physiology of Domestic Animals", "Veterinary medicine A textbook of the diseases of cattle, sheep, goats, pigs and horses."

You refer further to two studies that are mentioned by EFSA which had been performed by Gerasev et al (2003a, 2003b) who described reduced potassium absorption and increased renal excretion in rats. In these studies, a clinoptilolite (from Siberia) was added at 5% to the diet and fed to male rats for a short period of seven days. This study's design is inadequate to study long term administration of clinoptilolite to rodents. The data presented and discussed in Section 6.4 and specifically 6.4.2 of our notice are more comprehensive and include subchronic and reproductive studies in mice and rats at higher levels and do not confirm this observation.

Conclusions on target animal safety (TAS)

EFSA's expert panel opinion on safety of clinoptilolite was based on a limited number of studies and publications; considering the arguments discussed above for pigs, poultry, and dairy cows, and our much broader review in Part 6 of our notice we continue to conclude that available data for food producing animals, particularly cattle, pigs, and poultry support that our clinoptilolite is safe at 2 % for complete feed in all animal species.

Use levels for dogs and cats

You suggest that data from studies in cats and dogs that we discuss in Section 6.2 do not support a safe use at 2% level in per food. These studies in pets were performed at levels of 1% or lower and they did not report any concern at the highest level tested. Considering the comprehensive data set that support safety of 2% in laboratory and food producing animals it may be justified to conclude for cats and dogs on the same level of 2% of being safe, however, if you require that safety should be established on data obtained in pet animal studies only, we would agree that the safe level is 1%.

Safety of radioactivity and dioxin

You suggest that we describe how the radioactivity and dioxin content of clinoptilolite affect target animal safety.

Dioxins

In the absence of US regulatory levels for dioxins in food or feed[3] we refer to the levels established by the European Union. For complete feed and clinoptilolite tolerances of 0.75 ng WHO - TEQ/kg (ppt) for dioxins and 1.5 ng WHO - TEQ/kg (ppt) for the sum of dioxin and dioxin-like PCBs are enforced.

Our clinoptilolite contains dioxins and dioxin-like PCBs at levels typically below 0.3 ppt, the average content is 0.15 ppt (Appendix 3.2). At the proposed use level, the contribution to complete feed is 0.003 ppt. This is at least one order of magnitude lower than the lower side of the range of reported levels of contamination in feed ingredients summarized in Table 4-4 of the review performed by the Institute of Medicine (US) Committee on the Implications of Dioxin in the Food Supply [3] in 2003. The intake of dioxins and dioxin-like PCBs by target animals from our clinoptilolite when added to feed is very low. Estimates of intakes by target animals are provided in the attached Table (page 11).

Radioactivity

Our clinoptilolite is regularly monitored for presence of ^{137}Cs (0.6 – 2.3 Bq/kg) and ^{134}Cs (not detected), but we provided also for one batch data on ^{40}K (1179.20 Bq/kg), ^{226}Ra (45.6 Bq/kg), and ^{232}Th (56.4 Bq/kg).

The levels for Cesium are well below the agencies guidance levels for food[4], the levels for the three natural radionuclides will, at the use level of 2%, contribute little to total intake as these

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[3] Dioxins and Dioxin-like Compounds in the Food Supply. Strategies to Decrease Exposure. Institute of Medicine (US) Committee on the Implications of Dioxin in the Food Supply. Washington (DC): National Academies Press (US); 2003. (available at https://www.ncbi.nlm.nih.gov/books/NBK221718/)

[4] https://www.fda.gov/food/foodborneillnesscontaminants/chemicalcontaminants/ucm078331.htm

radionuclides are known to be present in other feed ingredients (Wiechen 1998; ATDSR 1990a; ATDSR 1990b). Estimates of intakes by target animals are provided in the attached Table (page 11).

Conclusion

Target animals' safety is not affected by dioxins and radionuclides present in our clinoptilolite as resulting incremental intakes are insignificant when compared to intakes from other sources and with regulatory tolerance or guidance levels.

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We list below as reference and include copies only those references which have not been included in our original GRAS notice.

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Table		Target animal exposure to clinoptilolite (upper limits)												
Animal category[a]		Daily feed intake[b] (kg)	Daily clinoptilolite intake[c] (g)	Amounts of dioxins and radionuclides contained in respective amounts of clinoptilolite consumed per day[d]										
				Sum of dioxin and dioxin-like PCBs		Potassium (40)		Radium (226)		Thorium 232		Caesium 137	
				ng/d	ng/kg feed	Bq/d	Bq/kg feed	Bq/d	Bq/kg feed	Bq/d	Bq/kg feed	Bq/d	Bq/kg feed
Ruminants	Calves (≤15 months, 300 kg)	7.10	142.00	0.02130	0.003	167	24	6	1	8	1	0.085	0.01
	Dairy cows (≥2 years, 680 kg)	26.90	538.00	0.08070	0.003	634	24	25	1	30	1	0.323	0.01
	Sheep (≥8 months,140 kg)	1.98	39.60	0.00594	0.003	47	24	2	1	2	1	0.024	0.01
	Goats (≥8 months, 90 kg)	1.54	30.80	0.00462	0.003	36	24	1	1	2	1	0.018	0.01
Swine	Piglets (3.5 - 5 kg)	0.25	5.00	0.00075	0.003	6	24	0	1	0	1	0.003	0.01
	Piglets (5.0 - 10 kg)	0.50	10.00	0.00150	0.003	12	24	0	1	1	1	0.006	0.01
	Piglets (10.0 - 20.0 kg)	0.22	4.40	0.00066	0.003	5	24	0	1	0	1	0.003	0.01
	Pigs (20 - 50 kg)	1.86	37.10	0.00557	0.003	44	24	2	1	2	1	0.022	0.01
	Pigs (50 - 80 kg)	2.58	51.50	0.00773	0.003	61	24	2	1	3	1	0.031	0.01
	Pigs (80 - 120 kg)	3.08	61.50	0.00923	0.003	73	24	3	1	3	1	0.037	0.01
	Sows (lactating) (175 kg)	5.25	105.00	0.01575	0.003	124	24	5	1	6	1	0.063	0.01
Poultry	Layers (commercial/breeder)	0.10	2.00	0.00030	0.003	2	24	0	1	0	1	0.001	0.01
	Broilers (starter, 0-3 weeks)	0.07	1.32	0.00020	0.003	2	24	0	1	0	1	0.001	0.01
	Broilers (grower, 4-6 weeks)	0.15	3.06	0.00046	0.003	4	24	0	1	0	1	0.002	0.01
	Broilers (finisher, 7-9 weeks)	0.20	4.04	0.00061	0.003	5	24	0	1	0	1	0.002	0.01
	Turkeys (starter, 0-8 wk)	0.21	4.20	0.00063	0.003	5	24	0	1	0	1	0.003	0.01
	Turkeys (grower, 8-16 wk)	0.49	9.80	0.00147	0.003	12	24	0	1	1	1	0.006	0.01
	Turkeys (finisher, 16-24 wk)	0.75	15.00	0.00225	0.003	18	24	1	1	1	1	0.009	0.01
Pets	Dogs (adult 15 kg)	0.21	4.19	0.00063	0.003	5	24	0	1	0	1	0.003	0.01
	Cats (adult 3.0 kg)	0.04	0.83	0.00013	0.003	1	24	0	1	0	1	0.001	0.01

[a] Animal categories as per age, weight and/or production categories used by the NRC.
[b] See assumptions for animal categories as described in Appendix 3.1.
[c] Use level of 2% of diet by weight.
[d] For dioxins the average content of 0.15 ppt was used, for the radionuclides: ^{40}K: 1179.2 Bq/kg ^{226}Ra: 45.6 Bq/kg ^{232}Th:56.4 Bq/kg ^{137}Cs: 0.6 Bq/kg