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Experimental studies on safety and efficacy of the dietary use of a clinoptilolite-rich tuff in sows: a review of recent research in Greece

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Abstract

Evidence is available for improved growth and reproductive performance of farm animals fed zeolite-supplemented diets. Zeolite-enriched diets may also have value in reducing the detrimental toxic effects of ingested mycotoxins. To assess this, the safety and efficacy of the long-term dietary use of a clinoptilolite-rich tuff (Cp) in sows were investigated in two experimental designs, in terms of potential undesirable effects on the animals' health and the blood concentration of certain nutrients, as well as of any beneficial effect on their performance. In both studies the participating animals were assigned in two experimental groups (Cp-group and N-group), depending on the presence of Cp, at the inclusion rate of 2%, or not in their feed. The experimental diets were administered for a complete reproductive cycle. No adverse or side effects attributable to the use of Cp were noticed during the critical periods of pregnancy and lactation. Furthermore, no significant alteration in the serum concentration of certain vitamins (vitamins E and A) and mineral elements (inorganic P, K, Cu, Zn) was observed. The consumption of the Cp-enriched diet also proved to exert a promoting effect on sow's reproductive performance, since it resulted in larger litter sizes and piglets' body weights at both birth and weaning, additionally implying a protective role in ameliorating the toxic effects of the zearalenone which was found in considerable levels in pregnancy feed samples throughout the observation period. The overall results established the safety and efficacy criteria for the dietary use of Cp in sows. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The wide range of applications of zeolites are based on their physicochemical properties. In particular, the basis of interest in the biological

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effects of zeolites concerns characteristics such as ion exchange capacity, adsorption and related molecular sieve properties. Research data reported in the published literature provide evidence of a growth promoting effect when zeolites are used as additives in animal nutrition. Improved weight gain rates have been obtained in fattening pigs [1–4] and lambs [5], while a better feed efficiency and egg productivity has been achieved in laying hens [6,7] by the dietary use of zeolites. The extent of these beneficial effects seems to be related to the species and the geographical source of the involved zeolite, its purity and physicochemical properties, as well as the supplemental level used in the diets [1,8]. Furthermore, the dietary and environmental conditions under which consistent positive responses to zeolite administration are expected, should also be considered [9]. Clinoptilolite, a zeolite of the heulandite group, is the most abundant zeolite in nature and also the most widely used natural zeolite in studies involving animals. However, it has to be mentioned that, in general, literature data dealing with the overall effects of the dietary use of zeolite-rich tuffs on the performance of animals do not always provide accurate information about important characteristics, i.e. the net content of zeolitic material, thus leading to an incomparability of the interpretation of the results of the field trials. The latter has also been clearly documented by Sheppard [10].

Dietary use of zeolites has also been shown to sequester mycotoxins and reduce their absorption from the gastrointestinal tract, thus preventing the toxic effects on livestock and their carryover into animal products. Available data primarily focus on aflatoxins [11–14], whereas much less information is available about other mycotoxins. It has been proposed that the beneficial effects of zeolites on aflatoxicosis can be attributed to the conspicuous molecular adsorption process into the zeolitic matrix [15]. It was also demonstrated that feeding zearalenone to rats receiving dietary synthetic zeolite resulted in a positive correlation between zeolite and fecal excretion of zearalenone and a negative correlation with the urinary excretion of zearalenone, establishing the hypothesis that zeolite binds zearalenone to prevent intestinal absorption [16].

2. Dietary use of zeolites in sows

Although there is a lot of evidence about the use of zeolites in weaned, growing and fattening pigs, the research data dealing with the use of zeolites in sow's nutrition is limited, and their safety and efficacy issues have not been stressed out. The dietary use of zeolites in sows was tested at the Ichikawa Livestock Experiment Station in Japan, where pregnant Yorkshire sows were fed 400 g clinoptilolite/day throughout pregnancy and lactation periods. It was shown that the piglets' birth weight was slightly improved by 13%, and their growth rate was substantially increased, since they weighed 63% more than the control ones at weaning [17]. In another study, the addition of 5% clinoptilolite-rich tuff (Cp) (from the San-King Mine, Taipei Prefecture, Taiwan) to the rations of pregnant Landrace sows during 20–90 days post-mating gave rise to increased litter size at birth by an average of 1.78 piglets [18]. On the contrary, some years later, the same author reported that feeding crossbred sows with diets enriched with the same Cp at the inclusion rates of 2.5% and 5% from 2 to 3 weeks before mating, resulted in a decreased ovulation rate, while the embryo-survival rate was unaffected [19]. However, other researchers concluded that the dietary use of a zeolite-rich tuff (containing approximately 65% clinoptilolite) at the inclusion rate of 4–7% led to increased litter size at both birth and weaning by 6% and 13.7%, respectively [20].

The objective of the present paper was to review the results of a recent research in Greece, which aimed at the evaluation of the safety and efficacy criteria of the use of a Cp in sow's nutrition, during the critical periods of pregnancy and lactation. The experimental studies were conducted under "Good Clinical Practice for the Conduct of Clinical Trials for Veterinary Medicine Products (GCPV)" guidelines [21], on a farrow-to-finish pig farm with a capacity of 450 sows under production.

3. Experimental

3.1. Zeolitic material

The natural zeolite used in both studies reported in this review was clinoptilolite mined from the Pentalofos Paleogene zeolite-rich tuffs of Evros County (Thrace), northeastern Greece. The Cp extrusive rock was won and prepared by the company Silver & Baryte Ores Mining Co. (Athens, Greece). The final product was distributed in the Greek market by the company New Vet S.A. (Athens, Greece). Recently, it has been registered in accordance with Directive 70/524/EEC as additive, no. 3, in feeding stuffs under the conditions laid down in Annex II to this Regulation (Commission Regulation No. 1245/1999 of 16 June 1999). One batch of this product was used and, according to the supplier, the material's NH_4^+ cation exchange capacity (determined by the ammonium acetate method) was 1.50 meq/g, while the mineralogical and chemical composition is shown in Table 1.

Table 1
Mineralogical composition of the Cp used as an additive in sow's diet and chemical composition of the clinoptilolite

Mineralogical composition (wt.%)[a]			
Clinoptilolite	Feldspar	Micas and clays	Quartz
77.3 ± 13.3	12.8 ± 6.6	7.7 ± 5.9	2.2 ± 3.9
Oxides (wt.%)[a]			
SiO_2	67.13 ± 1.24	MgO	1.05 ± 0.2
TiO_2	0.03 ± 0.04	CaO	4.34 ± 0.40
Al_2O_3	12.30 ± 0.30	Na_2O	0.26 ± 0.17
Fe_2O_3	0.08 ± 0.08	K_2O	0.94 ± 0.71
MnO	0.03 ± 0.04		
Trace elements (ppm)[b]			
Ag	2.6	Ni	13
Ba	260	Nb	18
Bi	5.9	Pb	62
Co	<20	Rb	110
Cr	10	Sn	3.6
Ce	52	Sr	1400
Cs	4.7	Ta	19
Cu	7.3	V	22
Ga	16	W	25
Ge	2.9	Y	21
La	32	Zn	41

[a] Data obtained by Profs. A. Yannakopoulos and A. Kassoli-Fournaraki (EU funded research under Brite-Euram project no. BRE2-CT94-0954: "Development of industrial and environmental uses of European natural zeolites") and embodied in the material's registration file by Silver & Baryte Ores Mining Co. Mineralogical composition was determined by means of X-ray powder diffraction analysis using a Philips diffractometer, Ni filtered CuKα radiation. Major oxides were determined from polished thin sections using a Jeol JSM-840 scanning electron microscope equipped with a LINK-An 10000 microanalyzer.

[b] Data obtained by Silver & Baryte Ores Mining Co. Trace element content of a representative sample of the material used in the studies, determined by means of atomic absorption spectroscopy.

3.2. First experimental study

A total of 240 crossbred gilts and sows up to parity 6 (Large White × Landrace) participated in the study, divided equally into two experimental groups, depending on the inclusion or not of Cp in their feed (Cp-group and N-group, respectively). The actual parity distribution among the experimental groups was equal. Cp was incorporated in the basal feed offered to the animals of the Cp-group at the inclusion rate of 2% (20 kg/ton, replacing an equal quantity of corn and barley). The experimental feed was prepared in the feed mill on site. Two types of feed were used for feeding the sows/gilts: a pregnancy feed (PF) and a lactation feed (LF). Both of them were supplemented with commercial vitamin and mineral premixes at the recommended inclusion rates (Vetervit Super Sow 503 and Vetermin 504, Veterin S.A., Aspropyrgos, Attiki, Greece). A proximate analysis and an energy determination of adequate feed samples was conducted in order to ensure feed composition throughout the study period. The basic specifications of the feed (mean values of the analyses throughout the study) were as follows: (a) PF: digestible energy 12.97 MJ/kg, crude protein 16.2%, lysine 0.72%, calcium 0.90%, total phosphorus 0.73%, vitamin A 28 920 IU/kg, vitamin E 65.7 mg/kg, copper 27.2 mg/kg, zinc 159 mg/kg; (b) LF: digestible energy 13.22 MJ/kg, crude protein 16.7%, lysine 0.81%, calcium 0.92%, total phosphorus 0.78%, vitamin A 28 630 IU/kg, vitamin E 60.7 mg/kg, copper 28.3 mg/kg, zinc 144 mg/kg.

The sows/gilts of each experimental group were offered the experimental diets starting from weaning (or since the age of six months for the gilts), during service, pregnancy and lactation and up to the date of service of the next reproductive cycle. Their litters were assigned in the corresponding group of sows/gilts, receiving creep feed (without Cp or any antimicrobial) from the 7th day of age until the 25th ± 3 day of age (i.e. day of weaning).

In the disease history of the farm in which the study was conducted, cases of impaired reproductive efficiency problems were reported, associated with mould contamination of the feed. For this reason, and after following an adequate sampling procedure, representative feed samples were obtained on a monthly basis, throughout the study period, and forwarded for mycotoxicological analysis.

All sows/gilts and their litters were monitored daily. Special attention was paid to adverse or side effects noticed in the Cp-group due to the use of clinoptilolite. Furthermore, parameters that define the health status of sows/gilts were taken into consideration, along with the indexes, which determine their performance and reflect the degree of productivity of a pig farm.

3.3. Second experimental study

Twenty-four crossbred sows in parity 4 (Large White × Landrace) participated in the study, divided equally into two experimental groups, depending on the inclusion or not of Cp in their feed (Cp-group and N-group, respectively). Feed composition and feeding scheme were the same as those described in the first experimental study. Cp was incorporated in the basal feed offered to the sows of the Cp-group at the inclusion rate of 2% (20 kg/ton), replacing an equal quantity of cereals (corn/barley). Sows were kept on study for a complete reproductive cycle, i.e. from the day of weaning up to the day of weaning of the next reproductive cycle (second weaning on study).

Blood samples from each participating sow were collected on the day of the study commencement, on the 30th day and 90th day of pregnancy, at parturition and at weaning (i.e. end of study period, 25th ± 3 day post-farrowing), by puncturing the cranial (anterior) vena cava. The estimated parameters included vitamin E, vitamin A, inorganic phosphorus (P), potassium (K), copper (Cu) and zinc (Zn) blood concentrations. Vitamin E concentration was determined fluorometrically [22], vitamin A and P were determined colorimetrically [23,24] and K by means of flame atomic emission spectrophotometry. Finally, Cu and Zn determination was carried out by means of flame atomic absorption spectrophotometry [25].

In both studies, data were subjected to one-way analysis of variance using the general linear model procedure of the SAS system (version 8.1 for Windows, 2000; site code: 0084912001/SAS Institute Inc., Cary, NC 27513, USA). The *T*-test was used to compare means and Pearson's χ^2 test to compare frequencies (expressed in results as percentages: actual number of cases in each category × 100/total number of animals examined) among the experimental groups and the significance was attained if the *P*-value was <0.05 [26,27].

4. Results and discussion

4.1. Safety of the dietary use of clinoptilolite

No adverse or side effects were noticed in the sows that were on the Cp-enriched diet throughout the first experimental study. They showed normal oestrus behavior during the breeding period, a considerable percentage of them were mated and operated towards farrowing successfully (92.5% vs. 85.8% in the control group), giving rise to a slightly better farrowing rate in the Cp-group, comparing to the respective of the control one. Furthermore, no teratogenic effects on their offspring were reported, giving further evidence for the safety of the additive when used during pregnancy. These observations are in agreement with previous reports in which the dietary use of zeolites in pregnant rats [28] and sows [19] was not associated with clinically apparent negative effects on the overall health status.

From a clinical point of view, the Cp-enriched diet was also proved to be safe during the lactation period, since the prevalence of animals with obvious symptoms of several pathologic conditions,

Table 2
Sows/gilts health status parameters during the lactation of the first experimental study: percentage (%) of cases in each category per experimental group

	Cp-group	N-group
Reduction of appetite[a]	35.1	40.8
Pyrexia[b]	26.1	29.1
Mastitis[c]	14.4	17.5
Vaginal discharge	8.1	6.8

[a] Consumption of less than the half quantity of the daily offered feed.
[b] Body temperature higher than 39.3 °C.
[c] Confirmed clinically.

including the metritis-mastitis-agalactia complex which has a major impact on sow and litter performance during lactation, did not differ significantly among the experimental groups, as shown in Table 2.

The role of vitamins A and E, as well as the role of minerals such as P, Cu, and Zn in the preservation of the sow's health status and reproductive performance has been well documented [29–32]. It is clearly suggested that meeting nutrient requirements involves an adequate supply via feed and an undisturbed absorption process. Therefore, it is important that zeolites be subjected to in vivo evaluation, both with respect to their efficacy but also, with equal interest to determine whether impaired nutrient utilization occurs, attributable to their inclusion in the sow's diet.

The results of the second experimental study verified the safety of the dietary use of Cp in sows, as far as the availability of certain vitamins and minerals via feed was investigated. The estimated blood serum levels of the examined vitamins were not significantly different among the two experimental groups, as presented in Fig. 1. Additionally, their assessment revealed an adequate status in both groups throughout the reproductive cycle, although the respective level of vitamin E was slightly lower in the Cp-group. As also demonstrated in our study, the concentration of K in serum was not altered by the dietary use of zeolite (Fig. 2), observation which was also found to be in agreement with the results of other researchers' experiments using growing lambs and hens as animal models [33,34]. As far as the concentration of inorganic P in serum is concerned, our results

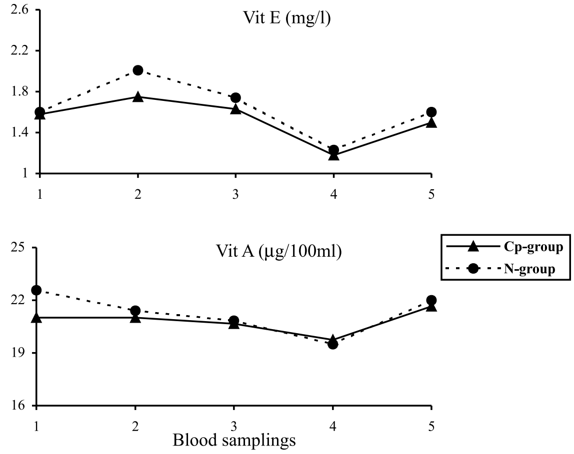
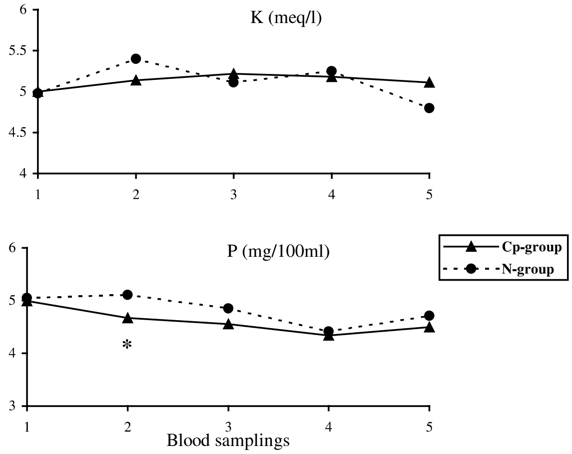


Fig. 1. Patterns of mean vitamin E and vitamin A serum levels: (1) commencement of the study (weaning), (2) 30th day of pregnancy, (3) 90th day of pregnancy, (4) farrowing, and (5) weaning (second weaning on study).



*P=0.094

Fig. 2. Patterns of mean K and P serum levels: (1) commencement of the study (weaning), (2) 30th day of pregnancy, (3) 90th day of pregnancy, (4) farrowing, and (5) weaning (second weaning on study).

showed no significant effect attributed to the use of zeolite, apart from a tendency ($P = 0.094$) for a reduction in the Cp-group at the 30th day of pregnancy (Fig. 2), and are generally supported by previously conducted studies involving lambs and pigs [33,35]. However, in other studies published, concerning broiler chickens, laying hens and growing pigs which were fed with synthetic zeolite Na-A [6,11,36], a substantial reduction in the concentration of plasma P was observed, related to the partial degradation of the crystalline structure of zeolite Na-A during the process of digestion. According to Flanigen [37], the stability of zeolites in acid solutions is controlled by the Si/Al ratio of the structure. In general, clinoptilolite is considered to be stable in the acid environment of the stomach (Si/Al ratio around 5 in difference with zeolite Na-A with an Si/Al ratio of 1 [37]) and, for this reason, its structural aluminum ions, not being able to be removed from the crystalline matrix, do not interfere with P to form insoluble phosphates, none the less affect P availability to result in a deficiency [38]. Zeolite Na-A was also found to result in increased liver and bone Zn content in growing pigs [36], while clinoptilolite was proved to exert no alteration response in growing lambs [33]. In our experimental study no significant alteration on Zn concentration was observed in the Cp-group, as depicted in Fig. 3. In the same figure, the results concerning Cu are also presented. Serum Cu level ranged between the physiological limits, although it tended to be lower during the first two thirds of pregnancy in the Cp-group ($P = 0.081$ and $P = 0.094$ at the 30th and 90th day of pregnancy respectively). A reduction in kidney Cu concentration in growing pigs fed a clinoptilolite-enriched diet has also been reported [39]. However, the biological significance of this finding has to be explained by taking also into consideration the pregnant female's adaptations in absorption and retention of dietary Cu [40]. In view of the absence of any obvious consequence to the overall animals' health, it is assumed that the dietary use of Cp is not related to evidence of alterations in mineral element metabolism.

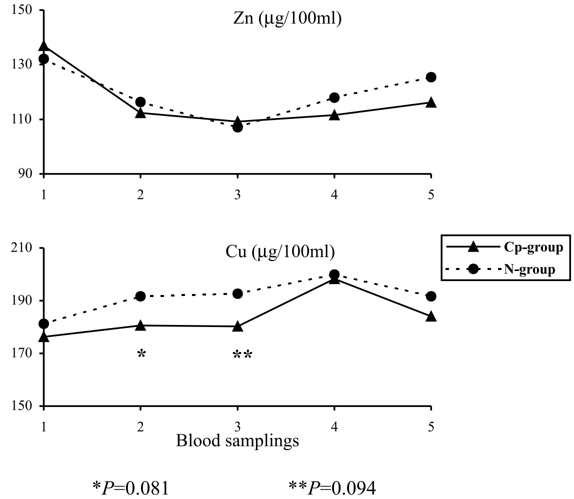


Fig. 3. Patterns of mean Zn and Cu serum levels: (1) commencement of the study (weaning), (2) 30th day of pregnancy, (3) 90th day of pregnancy, (4) farrowing, and (5) weaning (second weaning on study).

4.2. Efficacy of the dietary use of clinoptilolite

As demonstrated in Table 3, the results of the first experimental study revealed a clear positive effect of Cp on the animals' reproductive performance, since the treated sows/gilts achieved larger litter sizes and higher mean piglet body weights, at both birth and weaning. In general, suckling piglet's performance depends on its dam's respective lactation performance. In our study, the piglets of Cp-treated sows showed a higher mean body weight gain during lactation than the controls.

Aiming to ascertain the mode of action by which Cp exerted its beneficial effects, we could stand to the conclusions of previous studies conducted with growing pigs, in which the potential

Table 3
Effect of Cp on litter size and litter performance parameters (mean ± SD)

	Cp-group	N-group
Number of piglets born alive	$10.32^{a} \pm 1.40$	$9.60^{b} \pm 1.33$
Number of piglets weaned	$9.49^{a} \pm 1.39$	$8.72^{b} \pm 1.40$
Piglet body weight at birth (kg)	$1.44^{a} \pm 0.07$	$1.34^{b} \pm 0.086$
Piglet body weight at weaning (kg)	$6.28^{a} \pm 0.50$	$6.04^{b} \pm 0.52$
Piglet body weight gain during lactation (kg)	$4.84^{a} \pm 0.50$	$4.70^{b} \pm 0.50$

[a,b]Means in a row with different superscripts differ significantly ($P < 0.05$).

growth promoting action of zeolites had been attributed to the reduction in the uptake of ammonia produced by the deamination of dietary proteins during the digestive processes, via the intestinal wall [1,38]. Indeed, ammonia is considered to act as a cell toxicant in higher animals [41], and the prevention of its buildup to toxic levels in the intestinal tract could lead to a reduction of epithelial turnover, a sparing of energy and a better nutrient utilization. Additionally, clinoptilolite has been proved to efficiently remove toxic agents, such as *p*-cresol from the gastrointestinal tract of pigs [38]. *P*-cresol, a metabolite produced by anaerobic degradation of tyrosine, is responsible for a performance depressing effect, since the energy demand for its detoxification and elimination from the body via urine is considerable [42]. Adversely, ingested zeolite Na-A was proved to be inefficient in binding *p*-cresol, mainly due to its dissociation in the acid environment of pig's stomach (pH around 2) [38].

In general, increased amounts of nutrients during late gestation affect birth weight positively [43] and furthermore, an adequate nutrients supplementation of the lactating sow is strongly correlated to lactation performance and efficiency, which in turn is reflected to an adequate body weight gain and subsequent weaning weight of the suckling piglet [44,45]. It has been reported that in growing pigs which were on a diet enriched with Cp (minimum purity 77%) at the inclusion rate of 2%, serum glucose concentration tended to be higher when compared to the controls [46]. An improvement in the biological value of protein by feeding growing pigs increasing levels of zeolite Na-A has also been reported [38]. Moreover, it was concluded that hens fed a diet with 5% zeolite-rich tuff (80–90% clinoptilolite) showed slightly better rates of lysine and methionine uptakes than the control ones [7], an improvement which was also correlated with the retardation of the passage rate of digesta through the hens' intestines, as revealed in other studies [47]. The same zeolite effect on the transit time of the digesta was also demonstrated in sows [20].

These observations suggest that the overall improvement of the reproductive performance documented in our study, might have been due to a respective improvement of the nutritional efficiency of the feed, giving rise to a sparing effect of energy and nutrients for a better farrowing and lactation performance.

4.3. Amelioration of zearalenone toxicity

The results of the mycotoxicological assays of PF samples throughout the first experimental study revealed a high contamination level with zearalenone and a medium one with trichothecenes (Table 4). It has to be pointed out that the mean monthly concentration of zearalenone in June and July far exceeded the upper advisory limit of 250 ppb [48]. Moreover, the synergistic role of the prementioned mycotoxins should also be considered, and although there is no clear evidence of any additive net effect of zearalenone and trichothecenes, the potential action of zearalenone might have been enforced further by the co-occurring trichothecenes.

Zearalenone's impact on sow's reproductive efficiency has been established by many researchers [49–51]. In our study, although the results of the mycotoxicological analysis showed a substantial variation over time, it was clearly demonstrated that the Cp-enriched diet affected positively some parameters, which are correlated with zearalenone ingestion by the sows (Table 5), maintaining health status and reproductive performance at a satisfactory level. It is worth noticing that the female offspring showing vulvovaginitis are considered

Table 4
Mycotoxicological analysis of PF samples throughout the first experimental study[a]

Month of sampling (1998)	Zearalenone (μg/kg)	Trichothecenes (μg/kg)
February	200	140
March	278	166
April	263	152
May	285	143
June	1550	310
July	1042	258
August	622	244
September	158	217

[a] Analyses were performed at BIOMIN Laboratories (BIOMIN Gesunde Tiernahrung International GmbH, Herzongenburg, Austria) by means of HPLC.

Table 5
Affected parameters that could be attributed to the reduced impact of zearalenone-contaminated diets during the first experimental study: percentage (%) of cases in each category per experimental group

	Cp-group	N-group
Anoestrus[a]	7.3^{c}	15.8^{d}
Returns to oestrus[b]	7.8^{c}	17.6^{d}
Prevalence of farrowed litters with splay-leg piglets	9.9^{*}	17.5^{*}
Prevalence of litters with female piglets showing vulvovaginitis	4.5^{c}	14.5^{d}

Percentages in a row with different superscripts (c and d) differ significantly ($P < 0.05$), $^{*}P = 0.106$.
[a] Percentage of sows failed to come back into heat within a 30 day interval post second weaning on study.
[b] Percentage of served sows which (after the second weaning on study) were re-served within a 44 day interval.

as a reliable indicator of zearalenone toxicosis in pregnant sows [52,53]. Moreover, the farrowing of litters with larger size and higher weight in the Cp-group (Table 3) could also be attributed to the reduction of continuing zearalenone exposure of the Cp-treated gestating sows/gilts [54].

5. Conclusions

The reviewed results of a recent research in Greece indicated that the dietary use of Cp 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 vitamins and mineral elements. Furthermore, it was proved to exert a beneficial effect on the productivity of the pig farm, since it promoted sow and piglet performance parameters, additionally implying a potential protective role against the detrimental consequences of zearalenone toxicosis.

6. Suggestions for future research

Previously reported research data indicate a beneficial effect of zeolites on cow's milk quantity and quality. Milk production was increased by 6.6% when Holstein cows were on a zeolite enriched diet [55]. In addition, the incorporation of synthetic zeolite Na-A in the feed of Holstein cows at the inclusion rates of 1 and 1.5% increased milk fat percent and milk protein level [56]. It is also demonstrated that several antimicrobials used in sow nutrition exert their growth promoting properties in litter performance by improving milk quality [57,58]. Therefore, the potential for a better lactation efficiency due to the dietary use of Cp in sows should be examined through similar research efforts.

With respect to Cp efficacy in reducing the toxic effects of zearalenone, the encouraging results obtained from our research need further in vivo studies in order to be confirmed and established by conclusions that will verify the actual biochemical mechanisms of Cp's action on zearalenone. It is proposed that in such studies, the experimental diets are to be contaminated at a steady concentration, which will ensure a measurable toxic response, along with respect to the exclusion of the possibility that other individual mycotoxins co-occur, since the extent of any resulting interaction on animal health and performance remains unclear yet.

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