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Antagonistic effect of increasing dietary zinc on the efficiency of microbial phytase on calcium, phosphorus, and zinc digestibility and status in pigs: a meta-analysis

J. Labarre [a,b], P. Schmidely [b], P. Schlegel [c], C. Loncke [b], M.P Létourneau-Montminy [a,*]

[a] Département des sciences animales, Université Laval, Québec, QC G1V 0A6, Canada
[b] UMR Modélisation Systémique appliqué aux Ruminants, INRAe, AgroParisTech, Université Paris-Saclay, 91120 Palaiseau, France
[c] Swine Research Group, Agroscope, 1725 Posieux, Switzerland

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ABSTRACT

Dietary zinc (**Zn**), phytate, calcium (**Ca**), and microbial phytase (**PhytM**) interact in the gastrointestinal tract of pigs, which determines the utilization of phosphorus (**P**), Ca, and Zn. Previous studies have assessed the impact of Zn and PhytM on Zn status by measuring apparent total tract digestibility (**ATTD**) of Zn and plasma Zn concentration in pigs, and some of these studies also measured P and Ca ATTD. The objectives of this meta-analysis were to quantify the effect of Zn, PhytM and their interactions on (1) digestible P and Ca content (g/kg diet) and (2) digestible Zn and Zn ATTD (%) and plasma Zn status. To investigate these objectives, an exhaustive literature search was made to create two sub-databases: (1) Ca-P database containing 52 treatments, from postweaning pigs and using pharmacological Zn doses (> 1 000 mg Zn/kg), and (2) Zn database of studies from postweaning and grower pigs with dietary Zn concentration < 250 mg/kg, containing 71 treatments on Zn ATTD and 50 treatments on plasma Zn concentration. Using the Ca-P database, mixed-effects models showed that increasing dietary Zn concentration decreased digestible P ($P < 0.001$) and tended to increase digestible Ca ($P = 0.083$) concentrations. It also reduced the positive effect of PhytM on digestible P (Zn × PhytM interaction, $P < 0.01$) and digestible Ca (Zn × PhytM interaction, $P < 0.01$). Studies within the Zn database showed that increasing dietary Zn content increased digestible Zn with a linear positive ($P < 0.001$) and quadratic negative component ($P = 0.08$) but increasing dietary Zn concentration decreased the positive effect of PhytM on digestible Zn (Interaction Zn × PhytM; $P < 0.001$). Dietary Zn ($P < 0.001$) and PhytM ($P < 0.001$) improved plasma Zn concentration; however, the response to PhytM was dependent on the dietary Zn level (Interaction Zn × PhytM; $P < 0.001$), highlighting the homeostatic regulation response of the animal. In conclusion, pharmacological dietary Zn supply (> 1 000 mg Zn/kg) to postweaning pigs decreased the ATTD of P and Ca. Moreover, the positive effect of PhytM on the digestible content of Zn, P, and Ca as well as on plasma Zn, was dependent on dietary Zn concentration.

Implications

A better understanding of the interactions between minerals, phytate, and phytase is required to improve mineral utilization by pigs. This meta-analysis showed that pharmacological levels of dietary zinc (> 1 000 mg zinc/kg) reduced phosphorus and calcium digestibility likely by impairing phytate hydrolysis in the pig's digestive tract. In contrast, microbial phytase increased digestible and plasma zinc concentrations, particularly at low dietary zinc levels. Mapping the fate of minerals in the digestive tract of pigs can help to fine-tune the dietary levels of these minerals.

Introduction

As a non-renewable resource, phosphorus (**P**) limits our capacity to produce food (Cordell and White, 2013). Phosphorus is essential to support livestock growth and bone mineralization (Suttle, 2010) and is also required for crop growth. Therefore, the sustainability of agriculture depends on the judicious use of P. Additionally, P output into the environment is a major concern for animal production in regions of high animal density (Dourmad et al., 2020). Cereal grains and oilseeds meals provide P; however,

* Corresponding author.
E-mail address: marie-pierre.letourneau-montminy.1@ulaval.ca (M.P Létourneau-Montminy).

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approximately 50 to 80% of the P stored in these crops is in the form of phytic acid or phytate (i.e., phytic P (**PP**); Sauvant et al., 2004), which has a low ileal digestibility in pigs without prior hydrolysis by phytase to liberate the phosphate bound. Pigs are known to have low intestinal mucosal alkaline phosphatase activity (Ushasree et al., 2017), resulting in a limited precaecal PP hydrolysis. Rosenfelder-Kuon et al., (2020) reported an ileal PP digestibility of 18%. There are three other sources of phytase (Lautrou et al., 2021): (1) phytase produced by microorganisms in the large intestine; (2) vegetable-based phytase (**PhytV**) contained in cereals such as wheat, barley, and rye and their co-products (Sauvant et al., 2004); and (3) exogenous microbial phytase (**PhytM**) added to the feed. Absorption of P occurs in the upper gastrointestinal tract (Partridge, 1978; Liu et al., 2000). Therefore, PP degradation by microorganisms in the large intestine does not contribute to overall P absorption. The PhytV is considered as a source of P-releasing enzymes in feed (Sauvant et al., 2004). However, this enzyme is mostly inactivated during high–temperature treatments (> 70 °C) such as those used during diet pelleting (Jongbloed and Kemme, 1990). The PhytM, in contrast, has been developed since the 1990s to have high thermostability (Ushasree et al., 2017) and higher PP degradation activity before the main absorption site. Therefore, PhytM can release P from PP in feed (Selle and Ravindran, 2008), but its efficiency can be modulated by dietary factors, intrinsic factors such as gut pH and the interactions between dietary and intrinsic factors.

Phytic acid can chelate cations such as Fe, Zn, Mg, and Ca (Maenz et al., 1999) at intestinal pH, forming insoluble complexes and leading to impaired absorption (Humer et al., 2015). The degradation of PP in the stomach of the pig will prevent the formation of PP complexes in the small intestine (Schlegel et al., 2010; 2013). Previous meta-analysis demonstrated the positive effect of PhytM on Zn apparent total tract digestibility (**ATTD**), Zn plasma content, and Zn bone content (Bikker et al., 2012; Schlegel et al., 2013). The addition of 500 FTU PhytM/kg diet can replace 27–32 mg Zn/kg diet from $ZnSO_4$ (Jondreville et al., 2005; Schlegel, 2010; Bikker et al., 2012) based on plasma Zn concentration. Bikker et al. (2012) performed a meta-analysis based on data from pigs fed with Zn concentrations below 90 mg/kg to remain within the necessary dose–response effect of the considered criteria. This level needed to be quite low when considering the Zn requirement of 50–80 mg/kg diet for 11–75 kg BW pigs (NRC, 2012).

It is worth noting that the Zn ATTD coefficient is inversely proportional to Zn intake (Revy et al., 2003), explained by the homeostatic regulation of Zn through endogenous Zn excretion into the gastrointestinal tract and Zn absorption efficiency (Brugger and Windisch, 2019). In studies using diets supplemented with 1 200–1 500 FTU/kg of PhytM, the ATTD of Zn increased by 72% in a diet containing 52 mg Zn/kg (Revy et al., 2004), but only by 19% in a diet containing 150 mg Zn/kg (Arredondo et al., 2019). It can therefore be hypothesized that the Zn equivalency of PhytM decreases with increasing dietary Zn and may be overestimated when dietary Zn concentration is higher than the Zn requirement of the animal. The Zn equivalency of PhytM may also be affected by the antagonism between Cu and Zn absorption through the intestinal epithelium (Bueno Dalto et al., 2019; Ren et al., 2021). This antagonistic effect of Cu is likely due to the fact that metallothionein serves as an intracellular binding agent for both Zn and Cu, but preferentially binds Cu, which may reduce Zn uptake and enhance Cu uptake.

Dietary Zn contents of 1 000–2 500 mg Zn/kg are commonly called "pharmacological doses" and are widely used around the world to promote piglet growth during the postweaning period (Luise et al., 2024). The Zn cation has a high complexing power (Champagne and Fisher, 1990) and has been shown to reduce P ATTD in postweaning piglets fed diets with pharmacological dietary Zn supplementation (2 500 mg Zn/kg) compared with nutritional levels (100 mg Zn/kg) in the presence of plant and microbial phytase (Blavi et al., 2017). Additionally, Maenz et al. (1999) demonstrated an inhibitory effect of Zn on P release from sodium phytate by PhytM *in vitro*. However, quantification of the range of dietary Zn concentration that reduce the ATTD of P and PP degradation is needed.

Furthermore, zinc oxide (**ZnO**) and limestone possess buffering capacity, enabling them to neutralize acidic chyme and thereby limit the postprandial reduction in gastrointestinal pH (Lawlor et al., 2005). During the early life of a pig, the digestive tract is still in development (Pluske, 2016) and the secretion of hydrochloric acid (**HCl**) is insufficient to efficiently lower the pH. This insufficient acidity in the pig stomach could last until 7 weeks of age (Heo et al., 2013). Gastric pH is an important factor modulating PP solubilization (Pontoppidan et al., 2007) and PhytM efficiency (Menezes-Blackburn et al., 2015). Acid-binding capacity (**ABC**) values of main feed ingredients have been published (Lawlor et al., 2005; Stas et al., 2022) and can be used to evaluate the buffering capacity of a pig's diet.

To better understand Zn, PP, and PhytM interrelationships and maximize the use of dietary P and Zn, a meta-analysis was performed with two objectives: (1) to assess the effect of dietary Zn, ranging from nutritional to pharmacological levels, on the degradation of PP by PhytM through studies of P and Ca ATTD responses and (2) to quantify the impact of dietary Zn concentration and PhytM on Zn ATTD and plasma concentration, and their interactions.

Material and methods

Data collection and database construction

A database was created using information from published experiments in peer-reviewed journals and from abstracts of congress presentations retrieved from public databases (Web of Science, PubMed, and CAB Abstracts). We only considered *in vivo* studies performed in postweaning and growing pigs, where PhytM supplementation and/or Zn content were the major dietary factors of variation. The inclusion criteria in the database were as follows: (1) experiments reported at least one of the following response criteria: ATTD of P, ATTD of Zn, or plasma Zn concentration; (2) publications contained detailed information about the experimental design; and (3) experimental diet composition was provided or could be obtained from the authors. The criterion for exclusion into the database was the use of treatments containing feed additives (e.g., acidifiers). Following graphical examination of the available data, we excluded studies that used treatments containing > 5 000 FTU PhytM/kg diet. Most studies reported values of 500–750 FTU/kg, and the studies reporting > 5 000 FTU/kg were limited. With these criteria, 38 articles describing a total of 77 experiments, published between 1994 and 2021, were retained (Fig. 1; Supplementary Table S1).

Calculation

The nutrient composition of each diet was retrieved if it was analyzed in the study; otherwise, it was recalculated using the diet composition provided by the authors and nutritional values from the feedstuffs table values (Sauvant et al., 2004). The ABC value of each diet was also calculated from published values (Lawlor et al., 2005; Stas et al., 2022) under the hypothesis that ABC values of each feedstuff were additive. We used ABC-4, defined as the ABC value determined to reach pH 4, which is representative of the pig's stomach pH (Narcy et al., 2012). When PhytV was present,

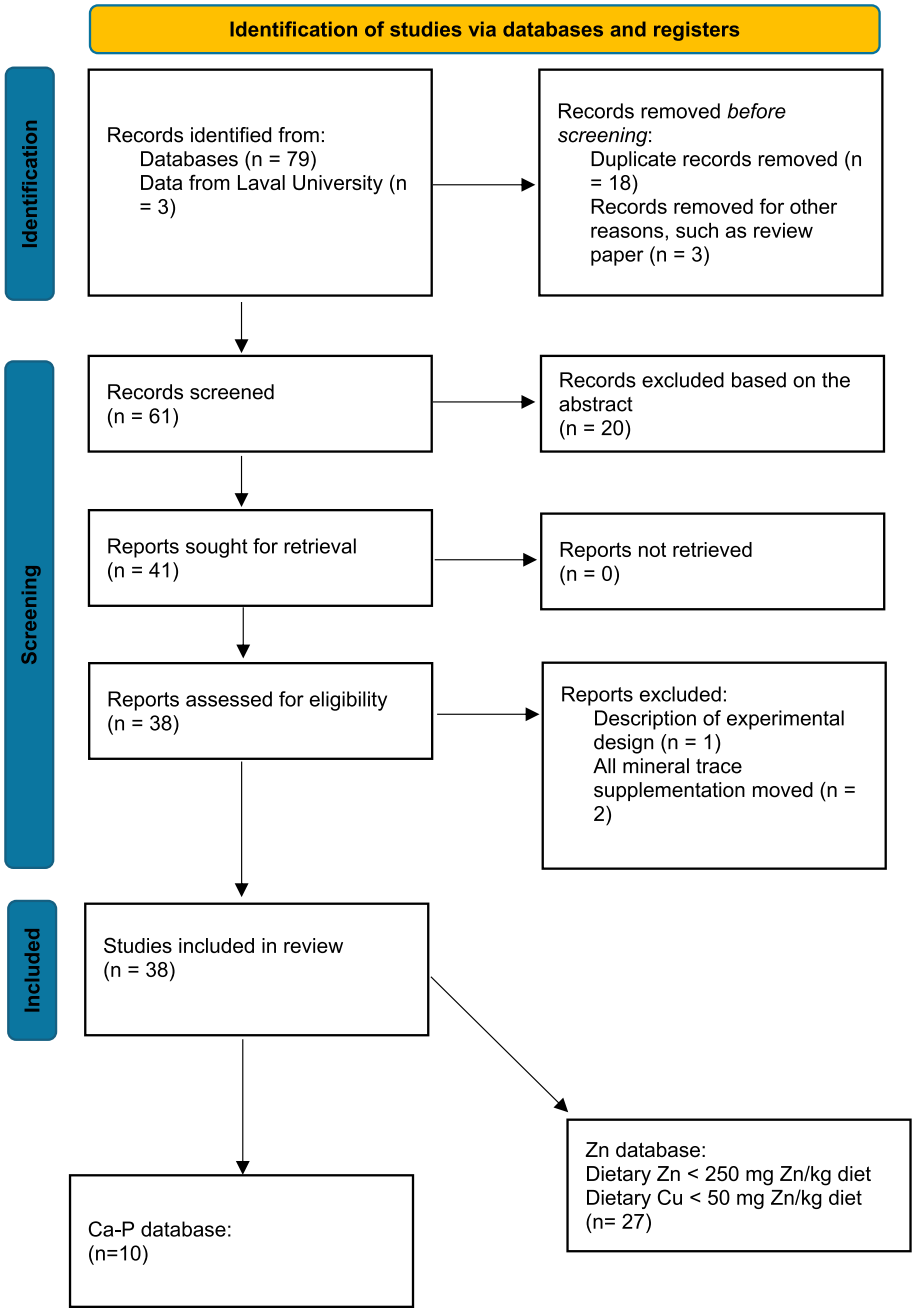

Fig. 1. PRISMA flow diagram of the selection procedure for pig studies included in the meta-analysis.

the phytase activity of the control diet was subtracted from all the other treatments supplemented with PhytM to obtain the PhytM activity. One phytase unit (FTU) is the amount of enzyme liberating 1 µmol of inorganic P from 5.1 mmol/l of sodium phytate per min at pH 5.5 at 37 °C (Engelen et al., 1994). The amounts of digestible nutrients (g/kg diet or mg/kg diet) were calculated as the product of their ATTD coefficient reported in the publications and their dietary concentration (g/kg diet or mg/kg diet). Digestible nutrients refer to apparent total tract digestible Ca, P, and Zn, and can be defined as the net disappearance of ingested Ca, P, and Zn (Stein et al., 2007).

Database splitting according to objectives

To investigate our objectives, two sub-databases (Fig. 1) were extracted from the main database: (1) the Ca-P database (Table 1) and (2) the Zn database (Table 2). Because pharmacological Zn supply was only used in postweaning pigs, only articles using postweaning piglets were included in the Ca-P database. On this basis, the Ca-P database included 10 experiments and 52 treatments. The Zn database contained data from articles with pigs in postweaning or grower phases and dietary Zn levels not exceeding 250 mg/kg diet. This threshold was defined according to the following: postweaning pigs fed with > 1 000 mg Zn/kg diet accumulated plasma Zn status that exceeded the physiological plateau (Schlegel, 2010, Bueno Dalto et al., 2023), thus illustrating that they were deficient in homeostatic regulation. After graphical examination, most of the dietary Zn values were < 250 mg/kg (81%; Supplementary Figure S1); therefore, we only used studies with dietary Zn levels < 250 mg/kg and excluded studies with dietary Zn concentrations > 250 mg Zn/kg. A large range of dietary Cu concentrations was used in the studies, and after graphical examination of

Table 1
Descriptive statistics for the Ca-P database in postweaning pigs (as-fed basis)[1].

Items	Mean	SD	Min	Max
Ca (g/kg)	7.36	2.18	3.16	10.0
P (g/kg)	6.23	1.76	3.00	8.96
PP (g/kg)	2.17	0.36	1.36	2.50
Zn (mg/kg)	928.52	1 317.49	30.00	4 456.00
Cu (mg/kg)	53.82	53.65	15.00	167.10
PhytM (FTU/kg)	685.13	1 019.31	0	3 630.00
ABC-4 (meq/kg)	444.84	70.77	357.38	609.47
Digestible P (g/kg)	3.18	1.21	0.69	5.57
Digestible Ca (g/kg)	4.26	1.39	1.88	7.51
Plasma P (mmol/L)	3.14	1.55	1.20	5.89

Abbreviations: P = dietary phosphorus; Ca = dietary calcium; Zn = dietary zinc; Cu = dietary copper PhytM = microbial phytase; ABC-4 = acid-binding capacity at pH = 4; PP = phytic phosphorus.
[1] Based on 52 experimental treatments from 10 experiments.

Table 2
Descriptive statistics for the Zn database in pigs (as-fed basis).

	Digestible Zn (mg/kg)				Plasma Zn (mg/l)			
Items	Mean	SD	Min	Max	Mean	SD	Min	Max
Ca (g/kg)	7.32	2.06	4.60	12.80	8.64	2.73	4.60	14.00
P (g/kg)	5.20	1.62	3.20	8.32	6.49	2.21	2.90	10.40
PP (g/kg)	2.25	0.43	1.46	3.20	2.34	0.30	1.51	2.91
Zn (mg/kg)	102.31	46.71	26.60	203.00	68.99	50.17	25.0	204.56
Cu (mg/kg)	16.45	9.21	3.96	48.35	15.64	7.99	5.00	27.77
PhytM (FTU/kg)	550.73	580.50	0.00	2 500.00	515.38	540.12	0.00	1 560.00
Digestible Zn (mg/kg)	35.62[1]	31.73	−18.0	109.87	23.48[2]	24.53	−0.49	93.27
ATTD of Zn (%)	31.87[1]	24.96	−38.6	87.97	31.57[2]	16.95	−0.61	71.58
Plasma Zn (mg/L)	0.76[2]	0.29	0.21	1.21	0.73[3]	0.27	0.18	1.21

Abbreviations: P = dietary phosphorus; Ca = dietary calcium; Zn = dietary zinc; Cu = dietary copper PhytM = microbial phytase; PP = phytic phosphorus; ATTD = apparent total tract digestibility.
[1] Based on 71 experimental treatments from 36 experiments.
[2] Based on 21 experimental treatments from 7 experiments.
[3] Based on 50 experimental treatments from 16 experiments.

the dietary Cu distribution (Supplementary Figure S2), most of the studies had a dietary Cu concentration < 50 mg/kg diet; therefore, we only included studies with dietary Cu concentrations up to this threshold. A total of 27 experiments including 71 treatments were used to study the effect of PhytM on the ATTD of Zn, and 18 experiments including 50 treatments were used to assess the effect of PhytM and Zn on plasma Zn concentration. The list of references used for the meta-analysis, and those included in each of the sub-databases, is presented in Supplementary Table S1.

Description of the meta-design

The relationships between independent variables were examined graphically 2 × 2 in each database to understand the within-study and between-study responses and to identify collinearity and outliers. When relevant, Pearson correlations were used to establish the potential relationships between the variables in each database. Physiological stages were tested by one-way ANOVA, and normality of data distribution was tested with a Shapiro test and graphical observation. Secondary factors of variation (Sauvant et al., 2020), such as genetic lines, physiological stages (postweaning vs growing), and measurement methods (grab sampling, metabolism crates), were carefully investigated graphically.

Statistical analysis

In the Ca-P meta-analysis, as proposed by Létourneau-Montminy et al. (2012), digestible P and Ca (g/kg) and plasma P (mmol/l) were the dependent variables. Dietary Zn, ABC-4, PhytM, total P, non-phytate P, total Ca, PP, and PhytV were the independent covariables. In the Zn meta-analysis, the ATTD of Zn (%), digestible Zn (mg/kg), and plasma Zn concentration (mg/L) were the dependent variables. Dietary Zn, PhytM, PP, adaptation period (defined as the time between the pig has accessed to the diet and the sample collection), and Cu were the independent covariables. All statistical analyses were carried out using RStudio (4.5.0), the lme4 (version 1.1-27.1), and lmerTest (version 3.1-3) packages. Accounted studies have similar experimental procedure and were the result of sampling of a large population, and the study effects were considered as random effects as follows:

$$Y_{ij} = \mu + s_i + b_1 PhytM_{ij} + b_2 PhytM_{ij}^2 + b_3 Zn_{ij} + b_5 Zn_{ij}^2 + b_5 PhytM_{ij} Zn_{ij} + e_{ij}$$

where Y_{ij} is the value of the dependent variable Y in experiment i with the treatment j; μ is the overall intercept; s_i is the random effect of the study group j on the intercept μ with the condition that the sum of each s_i is equal to 0; b_1 and b_2, are fixed linear and quadratic coefficients of the relationship, respectively, of the overall response to PhytM; b_3 and b_4 are fixed linear and quadratic coefficients of the relationship, respectively, of the overall response to dietary Zn, b_5 is the coefficient of interaction between the dependent variables; and e_{ij} is the unexplained residual error. All the variables and the interactions between these variables were tested. The normality of residuals was checked, and outliers were identified based on residuals, leverage effect, and Cook's distance. The terms were kept in the model when $P < 0.10$; $P < 0.05$ was considered significant, and $0.05 > P > 0.10$ was considered a tendency.

Results

Meta-design of the Ca-P database

The dietary P, Ca, PP, ABC-4, and PhytM and digestible P and Ca were normally distributed (tested with the Shapiro test, data not presented). The studies included postweaning pigs with an average initial BW of 9.9 kg (7.3–15.4 kg). The average plant-based dietary Zn concentration was 32 ± 7 mg Zn/kg mg Zn/kg; in 74% of the Zn-supplemented treatments, Zn was provided as ZnO. The detailed Zn supplementation in each diet is shown in Supplementary Table S1. The average PhytM activity was 685 FTU/kg (0–3 630 FTU/kg; Table 1). The correlation between dietary Zn and PhytM (r = 0.05; $P = 0.73$, Fig. 2a) was not significant. However, correlations between dietary P and Ca (r = –0.79; $P < 0.001$, Fig. 2b) and between dietary Zn and ABC-4 (r = 0.78; $P < 0.001$, Fig. 2c) were significant. The within-study variation of PhytM was between 0 and 3 630 FTU/kg diet (Fig. 2a), and the within-study variation of dietary Zn was between 20 and 4 277 mg Zn/kg diet (Fig. 2a).

Meta-design of Zn database

The dietary Zn, digestible Zn, and plasma Zn were normally distributed in the Zn database (tested with the Shapiro test, data not presented). The studies included in the database used pigs with an average initial BW of 15.9 kg (4.9–47.7 kg). The average dietary Zn concentration was 93 ± 52 mg Zn/kg (Table 2). Six treatments included only Zn from plants, 76 treatments were supplemented with $ZnSO_4$, 13 with ZnO, and 5 with organically bound Zn sources. The differences between the Zn sources used in each study are detailed in Supplementary Table S1. The PhytM varied from 0 to 2 500 FTU/kg diet (Table 2). The meta-design analysis showed that only a few studies tested different Zn levels with and without phytase (eight values; Fig. 3a). The within-study variation was mainly PhytM, while dietary Zn levels were mostly a between-study variation. As this database included both postweaning pigs and growing pigs, the impact of the physiological stage was tested by one-way ANOVA on *y* and *x* variables to observe the relevance of including this factor in the model. However, there was no difference in dietary Zn, PhytM, and Cu concentrations. Digestible Zn and Zn ATTD were not different between physiological stages. Plasma Zn concentration was only reported in animals in the postweaning phase. The correlation between *x* variables was tested to identify collinearity: correlations between dietary Zn and PhytM (r = –0.01; $P = 0.91$), between dietary Zn and PP (r = –0.18; $P = 0.07$), or between dietary Zn and Cu (r = –0.13; $P = 0.29$) were not significant. However, a negative correlation was found between the duration of the adaptation period and the Zn ATTD (r = –0.26; $P = 0.02$, Fig. 3c). The within-study variation of PhytM was 418–2 500 FTU/kg diet (Fig. 3a), and the within-study variation of dietary Zn was 0–102 mg Zn/kg diet (Fig. 3a).

Ca-P database: effect of dietary zinc and microbial phytase on phosphorus and calcium apparent total tract digestibility in postweaning pigs

The overall intercept of the digestible P model was not different from 0 ($P = 0.58$; Table 3). We observed a linear within-study relationship between dietary P (g P/kg) and digestible P (g digestible P/kg) ($P < 0.001$). The model indicated that PhytM supplementation increased digestible P with a linear positive ($P < 0.001$) and negative quadratic component ($P < 0.001$), showing a curvilinear overall effect. An increase in dietary Zn content reduced the digestible P ($P < 0.001$) and reduced the positive effect of increasing PhytM on digestible P (interaction PhytM × Zn; $P = 0.01$; Fig. 4).

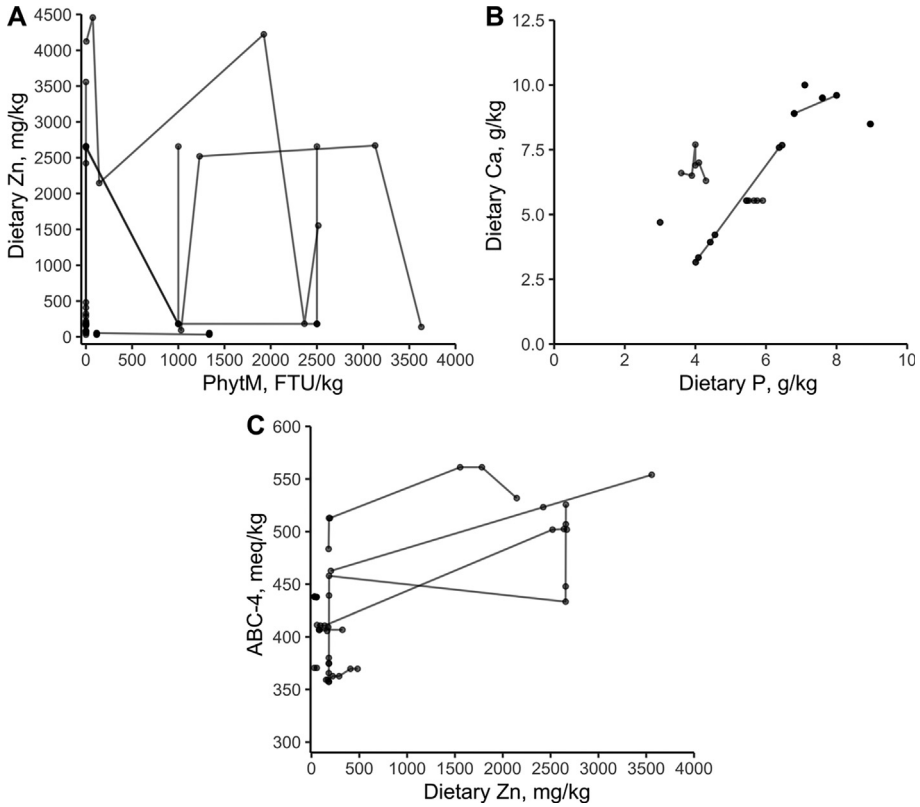

Fig. 2. Meta-design: within-experiment relationships between (a) dietary Zn and microbial phytase (PhytM) concentrations, (b) dietary P and dietary Ca concentrations, and (c) dietary Zn concentration and Acid Binding Capacity at pH 4 (ABC-4) in the Ca-P database in postweaning pigs.

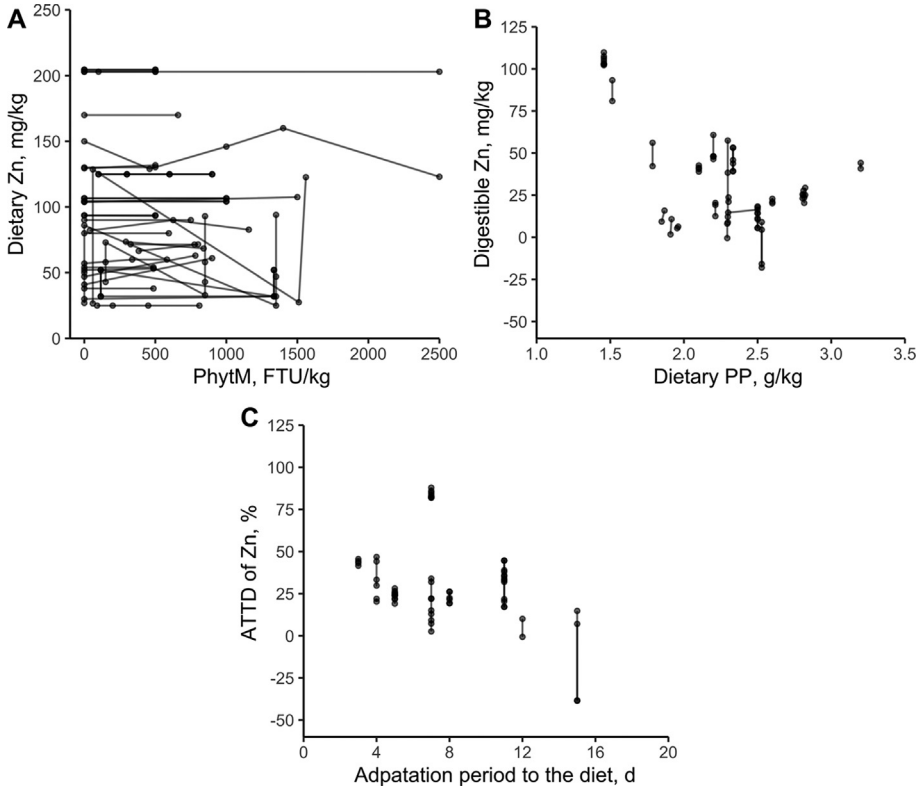

Fig. 3. Meta-design: within-experiment relationship between (a) dietary Zn and microbial phytase (PhytM) concentrations in the diet, (b) dietary phytic P (PP) and apparent digestible Zn concentrations in the diet, and (c) adaptation period to the diet and apparent total tract digestibility (ATTD) of Zn in the Zn database in pigs.

Table 3
Response equations of the digestible P, digestible Ca, and plasma P to Zn supplementation in postweaning pigs.

	Digestible P (g/kg)			Digestible Ca (g/kg)			Plasma P (mmol/L)		
Model parameter	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value
Intercept	−0.300	0.542	0.58	3.993	1.511	0.03	2.975	0.921	0.05
P (g/kg diet)	0.529	0.074	<0.001						0.88
Ca (g/kg diet)				0.522	0.053	<0.001			
PhytM (100 FTU/kg diet)	0.111	0.019	<0.001	0.093	0.018	<0.001			0.26
PhytM × PhytM	−0.002	0.001	<0.001	−0.002	0.001	<0.001			
Zn (mg/kg diet)	−0.00010	0.000	<0.001	0.00003	0.000	0.083	−0.010	0.005	0.05
Zn × PhytM	−0.00001	0.000	0.009	−0.00001	0.000	<0.001			
PP (g/kg diet)				−1.965	0.714	0.006			
Number of experiments	10			8			4.000		
Number of treatments	52			44			31.000		
R^2	0.919			0.952			0.971		
RMSE	0.280			0.245			0.296		

Abbreviations: P = dietary phosphorus; Ca = dietary calcium; PhytM = microbial phytase; Zn = dietary zinc; PP = phytic phosphorus.

The intercept of the digestible Ca model was significant ($P = 0.03$). Digestible Ca was increased by dietary Ca ($P < 0.001$; Table 3) and by PhytM with a linear positive ($P < 0.001$) and negative quadratic component ($P < 0.001$). A negative interaction between Zn and PhytM was observed (Interaction Zn × PhytM; $P = 0.001$) indicating that a diet containing a large amount of dietary Zn reduced the response of digestible Ca to PhytM. Dietary Zn tended to decrease digestible Ca ($P = 0.08$) and the effect of dietary Zn depended on the presence of PhytM. Dietary PP decreased Ca digestibility ($P = 0.03$). An increase of 100 mg Zn/kg diet decreased the plasma P concentration ($P = 0.05$) by 0.01 mmol/L. There was no effect of PhytM ($P = 0.26$) or of P ($P = 0.88$) on plasma P.

In a second model created with the same database (Table 4), the dietary Zn independent variable was replaced by ABC-4 values to evaluate the effects on digestible P. Digestible P was increased by dietary P content ($P < 0.001$) and PhytM with a linear ($P < 0.001$) and quadratic component ($P < 0.001$). This positive effect tended to be negatively modulated by ABC-4 (interaction ABC-4 × PhytM; $P = 0.06$), and increasing ABC-4 linearly decreased the digestible P ($P < 0.001$).

Zn database: impact of microbial phytase and dietary zinc on zinc apparent total tract digestibility and plasma concentration

Supplementation with PhytM increased the ATTD of Zn ($P < 0.001$, Table 5). Dietary Zn did not affect the ATTD of Zn ($P = 0.51$), but a negative interaction was found between PhytM and Zn ($P < 0.001$). No quadratic effect of PhytM was found

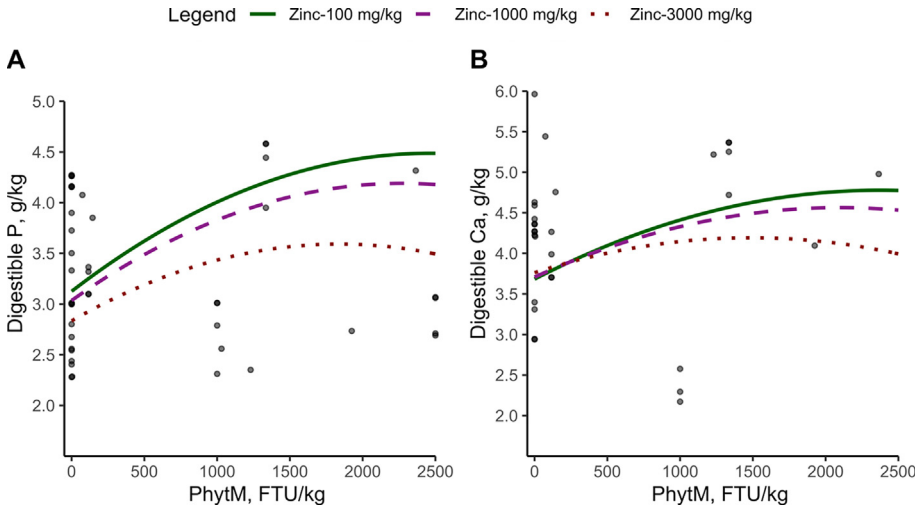

Fig. 4. Response of (A) digestible P (g P/kg diet) and (B) digestible Ca (g Ca/kg diet) to dietary microbial phytase (PhytM; FTU/kg diet) at different dietary Zn concentrations in postweaning pigs (solid curve, 100 mg Zn/kg diet; dashed curve, 1 000 mg Zn/kg diet; dotted curve, 3 000 mg Zn/kg diet). Dietary concentrations: (A) 6.5 g P/kg diet and (B) 7.5 g Ca/kg diet and 2.5 g phytic P (PP) /kg diet. Each point corresponds to an experimental treatment, corrected for study effect.

Table 4
Response equations of the digestible P to ABC-4 value in postweaning pigs.

	Digestible P (g/kg)		
Model parameter	Coefficients	SE	*P*-value
Intercept	0.990	0.812	0.230
P (g/kg diet)	0.660	0.079	<0.001
PhytM (100 FTU/kg diet)	0.167	0.043	<0.001
PhytM × PhytM	−0.002	0.0006	<0.001
ABC-4 (meq/kg diet)	−0.0051	0.001406	<0.001
ABC-4 × PhytM	−0.0001	7.24×10^{-5}	0.058
Number of experiments	10		
Number of treatments	52		
R^2	0.95		
RMSE	0.245		

Abbreviations: P = dietary phosphorus; PhytM = microbial phytase; ABC-4 = acid-binding capacity at pH = 4.

(P = 0.19). The Zn ATTD was negatively affected by PP (P < 0.001) and positively affected by Cu (P = 0.02). The diet adaptation period had no effect on the ATTD of Zn (P = 0.98).

The intercept of the digestible Zn model was positive (P = 0.001). Dietary Zn linearly increased the digestible Zn (mg digestible Zn/kg diet) (P < 0.001, Table 5) with a trend towards a negative quadratic effect (P = 0.08). The digestible Zn content was increased by PhytM (P < 0.001); supplementation with 100 FTU PhytM/kg diet resulted in the improvement of 1.099 mg digestible Zn/100 FTU PhytM added to the diet. This positive effect of PhytM decreased with increasing dietary Zn (interaction PhytM × Zn; P < 0.001, Fig. 5b). The dietary PP decreased the digestible Zn content (P < 0.001), and Cu increased the digestible Zn content (P = 0.05). Dietary Zn had a linear positive (P < 0.001) and quadratic negative (P < 0.001) effect on plasma Zn concentration (Fig. 5a, Table 5), and PhytM had a linear positive (P < 0.001) and quadratic negative (P < 0.001) effect on plasma Zn concentration. In addition, PhytM modified the linear component of the response to dietary Zn (interaction PhytM × Zn; P < 0.001).

Discussion

Effect of dietary zinc and microbial phytase on digestible phosphorus and calcium

The purpose of the first part of this meta-analysis was to assess the impact of dietary Zn on PP degradation by PhytM under different Zn supply strategies to postweaning pigs (Table 1) by studying P and Ca digestible content. The current models were developed based on the limited amount of published data available and, therefore, must be used within the data ranges of the predictor

Table 5
Response equations of the apparent total tract digestibility (ATTD) of Zn, digestible Zn, and plasma Zn concentration to Zn supplementation and PhytM in pigs constructed from the Zn database.

	Digestible Zn (mg/kg)			ATTD of Zn (%)			Plasma Zn (mg/L)		
Model parameter	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value
Intercept	64.070	18.1400	0.001	86.080	18.1300	<0.001	−0.044	0.0869	0.616
Zn (mg Zn/kg diet)	0.626	12.3600	<0.001			0.51	0.013	0.0019	<0.001
Zn × Zn	−0.001	6.8090	0.073			0.99	−3.654e-05	8.470e-06	<0.001
PhytM (100 FTU/kg diet)	1.099	0.2292	<0.001	1.486	0.2579	<0.001	0.085	0.0147	<0.001
PhytM × PhytM						0.19	−0.003	0.0010	<0.001
Zn × PhytM	−0.007	0.1868	<0.001	−0.011	0.0020	<0.001	−3.252e-04	8.032e-05	<0.001
Cu (mg/kg diet)	0.707	0.323	0.028	0.719	0.3411	0.035			0.931
PP (g/kg diet)	−41.230	7.984	<0.001	−34.280	8.2440	<0.001			0.140
Number of experiments	27			25			16		
Number of treatment	71			67			50		
R^2	0.976			0.962			0.842		
RMSE	3.438			3.170			0.094		

Abbreviations: Zn = dietary zinc; PhytM = microbial phytase; Cu = Copper; PP = phytic phosphorus.

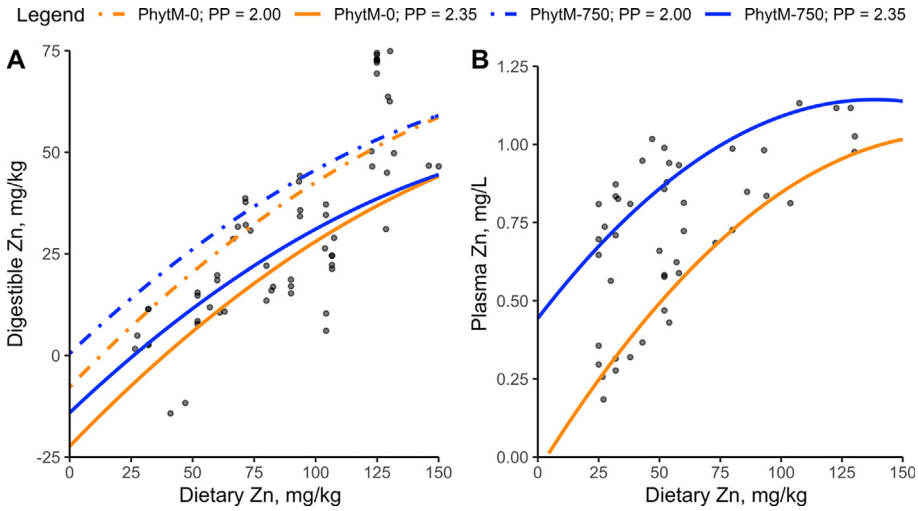

Fig. 5. Response of (A) digestible Zn (mg Zn/kg diet) and (B) plasma Zn (mg Zn/L) to dietary zinc (mg Zn/kg diet) at different microbial phytase concentrations in pigs (PhytM; orange curve, 0 FTU/kg diet; blue curve, 750 FTU/kg diet). Only for digestible Zn, dashed curves represent a dietary phytic P (PP) concentration of 2.00 g/kg and solid curves represent dietary PP concentration of 2.35 g/kg. Each point corresponds to an experimental treatment, corrected for study effect.

variables. To our knowledge, no data are available on the effect of dietary Zn on PP digestibility in pigs and the present study used the P and Ca digestibility to evaluate this effect. Further investigations are needed to quantify the effect of dietary Zn on PP digestibility until the end of the ileum.

Digestible P and Ca are influenced by dietary P and Ca levels, respectively. This effect is linear, with a digestibility of 53 and 52% for dietary P and Ca, respectively, which is consistent with previous results (Stein et al., 2008; Létourneau-Montminy et al., 2012). The addition of 500 and 1 000 FTU PhytM/kg diet resulted in 0.50 and 0.88 g digestible P/kg diet at a concentration of 100 mg Zn/kg diet which corresponds to NRC (2012) requirement of a pig between 7 and 25 kg. These values are in the same range as those reported by Létourneau-Montminy et al. (2012): 0.62 and 0.93 g digestible P/kg diet for 500 and 1 000 FTU/kg diet, respectively. The results are also consistent with values obtained in a recent meta-analysis: 0.57 and 0.82 g digestible P/kg diet for 500 and 1 000 FTU/kg diet, respectively (Rosenfelder-Kuon et al., 2019). The supplementation with PhytM in a diet containing 100 mg Zn/kg increased the digestible Ca/kg diet by 0.41 and 0.73 g for 500 and 1 000 FTU PhytM/kg diet, respectively. Although this observation has been less frequently documented, the values agree with Létourneau-Montminy et al. (2010), who found that the addition of 500 and 1 000 FTU PhytM/kg diet resulted in a digestible Ca concentration of 0.53 and 0.76 g/kg diet, respectively.

However, the current models showed that increasing the dietary Zn level reduced the positive impact of PhytM on digestible P and Ca. For example, the impact of adding 1 000 FTU phytase/kg to diets containing either 100 or 2 500 mg Zn/kg resulted in 0.88 and 0.65 g digestible P/kg diet, respectively, while 0.58 and 0.37 g digestible Ca/kg diet were released, respectively. Thus, the digestible P and Ca equivalency of PhytM was reduced by 26 and 38%, respectively. Microbial phytase is a source of P (Selle and Ravindran, 2008) because it releases P from soluble phytate (O'Dell and De Boland, 1976); for optimal phytase action, phytic acid must be hydrolyzed upstream from the sites of absorption of P (*i.e.*, the upper small intestine; Partridge, 1978). Therefore, PhytM has been developed to have maximal activity at the pH level in the stomach (Menezes-Blackburn et al., 2015). After a meal, stomach pH rapidly increases to pH 5, and gut filling activates HCl secretion, which subsequently decreases the pH of the stomach (Kidder and Manners, 1978). Chiang et al. (2008) found that it takes 12 h after a meal to decrease the stomach pH from pH 5 to a stable value of pH 3. Notably, the affinity of phytic acid is greater for some cations than for others, with Zn having the highest affinity (Maenz et al., 1999) and, therefore, forming more stable and insoluble complexes (Maddaiah et al., 1964; Oatway et al., 2001). Complexes of phytic acid with Zn^{2+} are soluble or negligible at pH < 4 (Nolan et al., 1987; Pontoppidan et al., 2007). Assuming that the stomach pH remains above 4 (Narcy et al., 2012), the formation of *de novo* insoluble PP-Zn complexes in the stomach will probably limit the effect of phytase on releasing P in animals fed diets with pharmacological Zn supply.

The model predicting digestible P content from ABC-4 showed that adding 1 000 FTU PhytM/kg to diets containing 450 or 525 meq ABC-4/kg and 6.5 g total P/kg led to a release of 4.09 and 3.44 g digestible P/kg diet, respectively. Limestone and ZnO are the two feed ingredients with the highest ABC-4 values (Lawlor et al., 2005), which can be defined as the amount of HCl in milliequivalents required to lower the pH of 1 kg of feedstuff to pH 4.0 (Van Slyke, 1922). In the database, ZnO was the main contributor to the within-study variation in ABC-4 (Fig. 2c) and limestone was the main contributor to between-study variation (data not shown). After feeding, the stomach gradually empties the bolus into the small intestine, and at the same time, the parietal cells secrete HCl, and the stomach pH drops. However, a diet with a high buffering capacity will reduce the amount of bolus exposed to a pH < 4, and the reduced effect of phytase in animals receiving pharmacological Zn supply could be attributed to the limited decrease in stomach pH that will allow dissociation of Zn from PP. PP-Ca complexes, which are considered soluble at pH < 5 (Wise, 1983; Kaufman and Kleinberg, 1971), do not bind to phytic acid in the stomach, but rather in the intestine (Létourneau-Montminy et al., 2011). Therefore, the phytic acid not hydrolyzed by PhytM in pharmacological Zn diets would transit into the intestine, where it could form *de novo* complexes with Ca, limiting Ca digestibility in the intestine and explaining the reduced effect of PhytM on digestible Ca with increasing Zn. Another possible explanation for the negative effect of Zn on digestible Ca is that Ca^{2+} and Zn^{2+} may compete for a common transport pathway in the intestine of piglets (Bertolo et al., 2001). Our results do not support this hypothesis, no effect of Zn on Ca digestibility was observed in absence of the PhytM. Further research is needed to clarify this hypothesis.

Diets with a fixed amount of 6.5 g dietary P/kg and 100 or 2 500 mg dietary Zn/kg without PhytM resulted in 3.13 and 2.88 g digestible P/kg, respectively. This antagonistic effect confirms results by Blavi et al. (2017) and Walk et al. (2015) and could also be explained by the formation of *de novo* Zn-PP complexes in the small intestine (Pontoppidan et al., 2007). Although pigs have a low ability to hydrolyze PP with mucosal phytase, some studies have estimated 20% PP digestibility without any phytase activity when Zn supplementation is supplied in the nutritional range (Létourneau-Montminy et al., 2012; Rodehutscord et al., 2022). Therefore, the formation of more Zn-PP complexes at pharmacological Zn supply in the small intestine could inhibit the availability of PP for degradation by mucosal phytase. In the digestible Ca model, dietary Zn had a positive effect on digestible Ca, which could be related to the stronger affinity of PP for Zn than for Ca (Maenz et al., 1999), leading to an increase in soluble Ca at pharmacological Zn supply in the small intestine. Nevertheless, increasing PP decreased digestible Ca (Selle et al., 2009; Humer et al., 2015) and explains the positive effect of PhytM on Ca.

Effect of the interaction between dietary zinc and microbial phytase on zinc digestibility and plasma zinc concentration

The second objective of this work was to study the impact of PhytM and dietary Zn on digestible Zn content, Zn ATTD and Zn status using plasma Zn concentration (in diets containing < 250 mg Zn/kg). The intercept of the digestible Zn model, i.e. the value when no Zn is ingested, was surprisingly high; a diet without PhytM or dietary Zn still supplied 64 (± 18) mg digestible Zn/kg. However, a similarly high intercept was already reported by a previous meta-analysis (Schlegel et al., 2013). A model without intercept has thus been tested (Supplementary Table S2) and resulted in a reduction of the PP coefficient (−41 vs −15), whereas coefficients for Zn and PhytM remained unchanged. The PP coefficient suggests that 1 g of PP could chelate either 41 mg or 15 mg of Zn, which corresponds to 0.12 or 0.04 mol of Zn chelated per mole of PP, respectively. In rats, a previous study has reported that 1 mol of PP can chelate approximately 0.01 mol of Zn (Schlegel and Windisch, 2006). A precise estimation of the PP effect is challenging due to the structure of the meta-design, which lacks studies with PP variations. This limitation may have led to an overestimation of the PP effect, which was compensated by an elevated intercept. Another possible explanation for the high intercept may be a scarcity of dietary Zn data near zero (minimum is 25 mg/kg), and the assumption that the slope is the same at those very low concentrations (Fan et al., 2001).

The digestible Zn model and plasma Zn model have a quadratic response to increasing dietary Zn. Zinc homeostasis is known to be maintained by intestinal absorption and endogenous secretion (Revy et al., 2003). The presence of specific transporters at the basal and apical membranes of intestinal mucosal cells are essential for Zn homeostasis (Lichten and Cousins, 2009). Intestinal Zn transporter ZIP4 transports Zn from the intestinal lumen into mucosal cells. Brugger et al. (2021) have shown that increasing dietary Zn concentration from 27 to 57 mg Zn/kg decreased ZIP4 expression in the intestinal cells of pigs. This response is interpreted as reduced Zn absorption, and similar results were previously reported by Martin et al. (2013). This effect could explain part of the quadratic effect observed for Zn intake on Zn digestibility and plasma Zn concentration. Endogenous secretion of Zn occurs when the liver and pancreas uptake a large amount of Zn from the net portal vein (shown in rats; Methfessel and Spencer, 1973) and later secrete it into the upper small intestine through biliary or pancreatic secretions. Mucosal cells sloughed into the gut are another source of endogenous Zn (Krebs, 2000). The amount of Zn in biliary and pancreatic secretions increases with dietary Zn concentration in pigs (Sullivan et al., 1981) and in rats (Weigand and Kirchgessner, 1980) and can explain the quadratic effect of dietary Zn observed.

The described mechanisms of Zn homeostasis take time to be implemented. In rats, true absorption of Zn adapted to dietary Zn concentration within 4 days, while endogenous Zn excretion required 12 days to reach a plateau in response to Zn deficiency (Windisch, 2003). In this meta-analysis, we showed a negative correlation between the adaptation period to the diet and ATTD of Zn. However, the adaptation period to the diet, which represented the time between the animal receiving the dietary treatment and the sample collection, was tested as a covariable in the digestible model and the ATTD of Zn model, and no significant effect was found; however, it could be an interfering factor. The digestible Zn and ATTD of Zn models also presented a positive effect of dietary Cu on Zn absorption (Table 5). Zinc homeostasis within enterocytes is primarily regulated by metallothionein, which serves as the main intracellular reservoir for this mineral (Davis and Cousins, 2000). However, metallothionein preferentially binds with Cu over Zn within enterocytes (Oestreicher and Cousins, 1985), which could reduce Zn sequestration in the enterocyte and enhance Zn absorption.

In a previous meta-analysis, which distinguished between the effects of dietary Zn sources (native, organic, and inorganic), Schlegel et al. (2013) showed a linear and quadratic response of plasma Zn concentration to dietary Zn supplementation. In the current meta-analysis, the main source of Zn supplementation was inorganic ($ZnSO_4$), and the linear effect of dietary Zn was the same as that found in the meta-analysis of Schlegel et al. (2013; linear coefficient: 0.015). Plasma Zn concentration reached a physiological plateau in response to dietary Zn which is described by the negative quadratic effect of dietary Zn. However, the quadratic coefficients were quite different between the two meta-analyses (quadratic coefficient: −0.000113). To reach the physiological plateau of 1 mg/L of plasma Zn concentration without PhytM, a dietary Zn concentration of 141 mg/kg is needed using our equation, whereas a dietary Zn concentration of 94 mg/kg is needed using the equation of Schlegel et al. (2013). The difference in response observed between the two meta-analyses can be explained by data selection related to the different objectives of each meta-analysis. In summary, Zn homeostasis through absorption and endogenous secretion explains the quadratic response to dietary Zn observed in the different models and confirms the response previously published by Schlegel et al. (2013).

The positive response of plasma Zn concentration to PhytM also showed a quadratic response; for example, the addition of 500 and 1 000 FTU PhytM/kg diet resulted in plasma Zn concentration of 0.73 and 0.90 mg/L at a concentration of 45 mg Zn/kg diet. The results are consistent with a previous meta-analysis using a log model (Bikker et al., 2012) where 500 FTU PhytM/kg diet increased the plasma Zn by 0.34 mg/L, compared with an increase of 0.29 mg/L found with the current model for a fixed amount of 45 mg Zn/kg diet. The quadratic effect of PhytM on plasma Zn concentration could be also explained by the homeostatic regulation described for dietary Zn, where microbial phytase acts as a source of Zn. The amount of digestible Zn increased by 5.5 mg/kg diet when 500 FTU PhytM/kg diet was added, which was comparable with the increase of 3.4 mg Zn/kg diet found by Bikker et al. (2012). In contrast to plasma Zn concentration, the effect of PhytM on digestible Zn was exclusively linear. The digestible Zn model is based on ATTD of Zn and, by definition, cannot distinguish between dietary and endogenous Zn, which may explain a missing quadratic effect. Alternatively, the expected quadratic effect of PhytM on digestible Zn could be represented by the negative interaction between dietary Zn and PhytM.

There are two mechanisms that can explain the positive effect of PhytM on plasma Zn concentration, digestible and ATTD of Zn. First, the PP hydrolysis in the stomach by PhytM limits the interaction between Zn-PP in the small intestine and increases the amount of Zn^{2+} ions available for absorption. Second, the PP hydrolysis by PhytM in the stomach may have prevented an interaction between phytic acid and endogenously secreted Zn in the small intestine, as a part of this, Zn may form complexes with phytic acid thus limiting the endogenous Zn reabsorption. Endogenous Zn reabsorption is relevant as it represents 35% of the endogenous Zn secreted by rats (Davies and Nightingale, 1975). Therefore, the apparent digestibility used in the studies does not allow to quantify the amount of endogenous Zn that was reabsorbed. Based on a study using diets labelled by Zn^{67} in pigs, the apparent Zn absorption was not different between the pigs fed a diet (90 mg Zn/kg) with or without PhytM. However, true Zn absorption and endogenous secretion were increased by 44 and 199%, respectively, when PhytM was added to the diet (Chu et al., 2009). Thus, results showed that there was a relative change in Zn fluxes in the small intestine that cannot be quantified by ATTD.

In a diet containing 40 and 150 mg Zn/kg, the supplementation of 500 FTU PhytM/kg increased plasma Zn concentration by respectively 0.29 mg/L and 0.12 mg/L compared to a diet without PhytM. This meta-analysis found a negative interaction between dietary Zn and PhytM, which was not observed by Bikker et al. (2012). The negative interaction was also reported on digestible Zn and ATTD of Zn. The fitted model clearly illustrates the dependency between the two variables. Both dietary Zn and PhytM will increase the amount of Zn available for absorption, and the animal then regulates absorption and endogenous secretion to maintain Zn homeostasis. Although phytase equivalencies are proposed in the literature, it would be misleading to estimate an equivalency from our equations since the response to PhytM depends on both dietary Zn concentrations and the non-linear response to dietary Zn. As shown by the interaction between the dietary Zn and PhytM, there will not be any additional effect when adding PhytM in diet already meeting the Zn requirement of the animal.

Conclusion

The results from the two meta-analyses show that: (1) pharmacological Zn supply decreased the amount of digestible P and digestible Ca by likely impairing PP degradation by PhytM and (2) PhytM increased the amount of digestible Zn and plasma Zn concentration. However, the response to PhytM is dependent on the dietary Zn level, illustrating Zn homeostasis. PhytM is commonly used to improve P and Ca utilization and thus establish response equations to dietary Zn and PhytM providing an important way to improve Zn utilization in growing pigs and decrease the environmental impact of pig production in terms of Zn. Further investigations of the response of PP digestibility until the end of the small intestine according to dietary Zn levels will help to better understand and quantify the effect of Zn on PP degradation. Mapping the fate of minerals in the digestive tract of pigs can help us better understand the digestive and metabolic fate of minerals; indeed, this knowledge is valuable for enhancing PP degradation and optimize the use of natural mineral resources.

Supplementary material

Supplementary Material for this article (https://doi.org/10.1016/j.animal.2025.101604) can be found at the foot of the online page, in the Appendix section.

Ethics approval

Not applicable.

Data and model availability statement

The script of the model is deposited on the repository Zenodo and is publicly available via the following link: https://doi.org/10.5281/zenodo.15720208. The data that support the study findings are public and have been published; see Supplementary Material.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) did not use any AI and AI-assisted technologies.

Author ORCIDs

J. Labarre: https://orcid.org/0009-0009-2883-0333.
P. Schmidely: https://orcid.org/0000-0002-7566-7868.
P. Schlegel: https://orcid.org/0000-0001-5095-0889.
C. Loncke: https://orcid.org/0000-0001-5551-8542.
M.P. Létourneau-Montminy: https://orcid.org/0000-0001-5364-2662.

CRediT authorship contribution statement

J. Labarre: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **P. Schmidely:** Writing – review & editing, Supervision, Conceptualization. **P. Schlegel:** Writing – review & editing, Supervision, Conceptualization. **C. Loncke:** Writing – review & editing, Supervision, Conceptualization. **M.P Létourneau-Montminy:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of interest

None.

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