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Effects of sodium selenite and L-selenomethionine on feed intake, clinically relevant blood parameters and selenium species in plasma, colostrum and milk from high-yielding sows

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ABSTRACT

A field study in periparturient sows fed different dietary concentrations of either sodium selenite or L-selenomethionine (SeMet) was conducted to evaluate feed intake, haematological and biochemical parameters as well as to describe some key selenium (Se) species, namely selenoprotein P (SelP), selenoalbumin (SeAlb) and selenomethionine (SeMet) as well as total Se in plasma, colostrum and milk.

Thirty-two sows were allotted to four treatments from 30 days (d) prepartum throughout on average a 32 d lactation period. Sodium selenite supplemented diets contained 0.40 and 0.60 mg Se/kg feed, while SeMet supplemented feed contained 0.26 and 0.43 mg Se/kg feed. Concentrations of sodium selenite and SeMet in complete feed exceeded the upper limits for total dietary Se and added organic Se, respectively, according to the European Union legislation. Blood samples were collected at initiation of the study, at farrowing and at weaning. Colostrum samples were collected at farrowing and milk samples at weaning. Se species were subjected to liquid chromatography, and total Se and Se species were determined using inductively coupled plasma mass spectrometry.

The SeMet supplemented diets resulted in higher feed intake and in higher levels of total Se, SelP, SeAlb and SeMet in colostrum compared with sows fed sodium selenite. Similar results were obtained for levels of total Se and SeMet in milk at weaning. The higher dietary sodium selenite concentration in sows' feed did not increase the Se transfer into colostrum or milk when compared with those receiving the lower level of sodium selenite. However, the increase in serum-Zn from initiation until farrowing, observed in sows fed SeMet as well as the higher glutamate dehydrogenase activity in sodium selenite supplemented sows in this period might indicate a higher requirement of antioxidant defence in sodium selenite-supplemented sows.

To our knowledge, the present data on Se species in plasma, colostrum and milk of sows represent the most complete investigation of Se in sows conducted to date. A higher amount of the above-mentioned Se species in the colostrum of sows supplemented with SeMet might strengthen the piglets' antioxidative system and passive immunity as well as improve their average daily weight gain. The higher feed intake in sows fed diets supplemented with SeMet is an interesting finding that warrants further investigation.

1. Background

Sows are exposed to different types of stress as e.g. social stress, heat stress, and oxidative stress during the production cycle [1–4]. Increased systemic oxidative stress in gestation and lactation due to too low levels of compounds with antioxidant function such as selenium (Se) species

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can negatively affect embryonic development, foetal growth and health, the number of stillbirths, litter size as well as postpartum growth of piglets [4–10]. Lower litter size, increased foetal mortality and weak lethargic piglets have been associated with deficiency of Se or vitamin E (vitE) in sows [11]. Supplementation of sows` diets with inorganic or organic Se has been widely discussed [for review see: 12]. According to Finley [13] the physico-chemical forms of Se are generally well transported over the intestinal membrane (70–95 %), but the uptake varies according to the Se source and Se status of the individual. While vitE acts directly, Se exerts its biological functions via selenoproteins that contain selenocysteine (SeCys) in their primary structure, some of which having antioxidant functions [14–18]. Selenoprotein P (SelP) is a selenoprotein, whereas selenoalbumin (SeAlb) contains Se as the selenized amino acid selenomethionine (SeMet), in positions of methionine residues, which is considered to be a “non-specific” form of Se [19]. Adequate feed intake in high yielding sows during lactation can be challenging [20–22]. Optimization of feed composition will improve the sows´ feed intake and thus improve the composition of both colostrum and milk subsequently leading to a better performance of their progeny [23,24]. After birth, the composition of colostrum and milk, also regarding the concentration of Se and selenospecies (Se species) are of remarkable importance to newborns [25–27]. A beneficial antioxidant status in sows could thereby prevent oxidative stress-related effects on the offspring [12,28]. The composition of bioactive molecules in colostrum and milk reflects the nutritional and developmental requirements of mammalian neonates [29].

While there is no limit for vitE, the European Commission (EU) has limited the amount of inorganic Se to a maximum of 0.5 mg total Se/kg feed based on the narrow dose range between Se deficiency and toxicity [30,31]. The addition of organic Se has been confined to 0.2 mg/kg complete feed in the EU to ensure consumer safety [30,32]. Although receiving feed containing Se levels up to 0.5 mg Se/kg feed, nutritional myodegeneration and reproduction related challenges possibly linked to increased oxidative stress due to insufficient Se and/or vitE supply, still occur [33–35]. This raises the question whether actual feeding strategies meet the Se requirements in high-yielding pigs [36,37].

The objectives of the present study were to evaluate effects of different levels of dietary sodium selenite and L-selenomethionine (SeMet) on high-yielding sows´ feed intake and clinically relevant blood parameters as well as on the distribution of selected Se species in plasma, colostrum and milk.

2. Materials and methods

2.1. Study design and animal ethics

This field trial was conducted at a commercial farm and included 32 loose-housed Landrace x Yorkshire sows. The sows were vaccinated against *Erysipelothrix rhusiopathiae*, porcine parvovirus and *Escherichia coli* (Porcilis Ery Parvo vet., MSD Animal health, Netherlands; Neocolipor, Merial, France) according to the manufacturers' recommendations. Until entering the trial, the sows received a diet supplemented with sodium selenite (Retosel®, Se premix 1%, RETORTE Ulrich Scharrer GmbH, Germany) at a level of 0.21 mg Se/kg and selenized yeast (Se yeast; Sel-Plex®, Alltech, USA) at a level of 0.15 mg Se/kg diet. The Se concentration in the unsupplemented baseline diet was 0.04 mg Se/kg feed. The final Se concentration in this diet fed until entering the trial was 0.4 mg Se/kg diet (Format purke soft, Felleskjøpet, Norway).

The duration of the study was two months. About 30 days prior to farrowing, the sows were randomly divided into four groups: NaSe-0.40, NaSe-0.60, SeMet-0.26 and SeMet-0.43 according to the diets described in Table 1. In this article, sodium selenite was abbreviated with NaSe for group names, while SeMet was used for the organic Se source and associated group names as well as for the amino acid selenomethionine itself. Each treatment group comprised two gilts and six sows with two or more parities. Prior to farrowing, the six sows in each group were kept in groups of six in pens of 16.5 m^2 (5.44 m^2 was slatted floor) and the two gilts in pens of 10.3 m^2 (3.36 m^2 was slatted floor). One week *ante partum*, the animals were moved into the farrowing unit and allocated to individual farrowing pens. Within these pens of 7.2 m^2, an area of 1.92 m^2 was slatted floor and the piglet creep area was 1.1 m^2. The sows' diets were supplemented with either sodium selenite (Retosel, Selenium premix 1%, RETORTE Ulrich Scharrer Gmbh, Germany) or SeMet (Excential Selenium 4000, Orffa, Netherlands). The Se concentration in the unsupplemented baseline diet was 0.03 mg Se/kg feed. All diets were added 100 mg vitE/kg feed. The composition of the pelleted feed and its nutritional values are listed in Table 1, and details of feed sampling and determination of total Se content are given in the next sections.

Table 1
Dietary components in and chemical composition of the diets.

Ingredients	% of DM
Barley	30.0
Soy bean	11.3
Wheat	20.0
Wheat bran	7.0
Oats	3.0
Horsebeans	5.0
Pea starch	1.7
Beet pellets	4.0
Animal fat	2.2
Feed lime	1.58
Mono-calcium phosphate	0.56
Feed salt	0.34
Microminerals	0.13
Vitamin A	0.07
Vitamin ADKB	0.07
L-Lysine	0.24
DL-Methionine	0.03
L-Threonine	0.08
L-Tryptophan	0.19
Phyzyme XP 5000 TPT	0.014
Chemical composition (Mean (SD))	
Dry matter (%)	87.12 (0.19)
Water (% of DM)*	12.89 (0.19)
Protein (% of DM)*	15.38 (0.36)
Fat (hydrolysis), (% of DM)*	4.64 (0.30)
Ash (% of DM)*	4.84 (0.11)
Fiber (% of DM)*	4.65 (0.17)
Calcium (% of DM)**	0.94 (0.02)
Phosphor (% of DM)*	0.50 (0.01)
Sodium (% of DM)**	0.24 (0.01)
Trial diet	**Se in mg/kg diet** (Mean (SD))***
NaSe-0.40	0.40 (0.03)
NaSe-0.60	0.60 (0.05)
SeMet-0.26	0.26 (0.04)
SeMet-0.43	0.43 (0.08)

Methods:* Dir. 152/2009/EU; ** ISO 6869; ***ICP-MS from 10 samples per diet.

During the gestation period, the sows were fed twice a day (3.5 kg/day). After farrowing, the sows were fed ad libitum up to four times a day, according to their appetite. The experimental feed was provided manually throughout the trial. Water was provided ad libitum. In the farrowing unit, the room temperature (RT) was set to 20 °C and reduced to 18 °C over a period of one week after farrowing. The trial ended at weaning. Piglets were weaned between day 29 and days 34 of lactation.

The Norwegian Food Safety Authority (application ID 7104) approved the performance of this trial, which complies with the current Norwegian Animal Welfare Act (LOV-2009-06-19-97 and LOV-2015-06-19-65, respectively) and the Norwegian regulations on swine husbandry (FOR-2003-02-18-175).

2.2. Sampling

Ten feed samples per diet were collected at initiation and end of the trial to determine the total Se content. Blood samples were drawn at initiation of the trial (*Vena jugularis externa*), at farrowing (*Vena subcutanea abdominis*) and at weaning (*V. jug. ext.*). Nine mL Vacuette® Z serum clot activator and six mL Vacuette® Lithium Heparin tubes (Greiner Bio-One, Austria) along with Venoject needles (20 G x 1½"UTW, USA) were used. For analysis, blood samples were centrifuged at 3.500 x *g* for 15 min (Megafuge 1.0 R, Heraeus SEPATECH, USA). Colostrum and milk samples were isolated from three or more teats and pooled. At weaning, an intramuscular injection of 10 IU oxytocin (Vetocin, Bela-Pharm, Germany) was applied to stimulate milk ejection. Feed, serum, plasma, colostrum, and milk samples were stored at -20 °C until analysis.

2.3. Haematology and clinical chemistry

Blood samples were subjected to a complete blood cell count applying a multi-parametric haematological analysis (ADVIA 120 Haematology System, Siemens Healthcare GmbH) with veterinary software. Clinical biochemistry analysis was conducted by applying the ABX Pentra400 analyser (Horiba, France). The analysed variables included glutamate dehydrogenase (GLDH, Roche diagnostics, Norway), as well as ferritin, bilirubin, iron, creatine kinase (CK), aspartate transaminase (AST) and γ-glutamyltransferase (GGT) applying reagents from ABX, Horiba, France. The concentrations of copper (Cu) and zinc (Zn) in plasma were determined using atomic absorption spectroscopy (AA300, Perkin Elmer, USA) at a wavelength of 324.8 and 213.9 nm, respectively. Ceruloplasmin (Cp) was determined by applying the biochemistry analyser Cobas Mira (Roche) using a modification of the method described by Henry et al. [38]. All analyses were conducted at the Norwegian University of Life Sciences (NMBU), Sandnes.

2.4. Selenium in feed, plasma, colostrum and milk

The total Se concentration in feed, plasma, colostrum and milk samples was determined by inductively coupled plasma mass spectrometry (ICP-MS; Agilent 8800, Japan) after specific sample treatment.

Subsamples, drawn from 10 feed samples per diet, were finely ground and homogenised. An aliquot (~0.25 g) was weighed out directly into Teflon tubes and digested with ultrapure concentrate HNO_3 (5 mL) at 260 °C for 25 min using the UltraClave IV system (Milestone). Digested samples were diluted to 50 mL with ultrapure deionised water and measured directly by ICP-MS. Plasma samples were thawed and treated prior to analysis as described previously by Falk et al. [39], whereas colostrum and milk samples were thawed until reaching room temperature followed by homogenization at 37 °C for 10 min in an ultrasonic bath. Before analysis, subsamples of plasma, colostrum and milk were diluted with a mixture of butanol, EDTA, NH_3 and Triton X-100 (1 + 9 V/V) as described by Liba et al. [40].

Standard solutions were prepared from a Se ICP reference solution (1000 mg L^{-1}, Inorganic Ventures) and ^{74}Se (> 99.9% enriched solution) was added as internal standard to all sample and standard solutions before analysis (except for feed samples where it was added before digestion). ICP-MSMS operating parameters are listed in Table A1 in the supplementary material. Blanks and standard solutions were analysed every 10 samples to monitor signal drift during the run. The carbon effect on the Se signal from the samples was negligible due to the presence of 4% butanol and the use of ^{74}Se as internal standard. Total Se concentrations were calculated from the $^{78}Se/^{74}Se$ signal ratio to account for sample loss during preparation and/or physical interferences. Any contribution from natural ^{74}Se (0.89% isotopic abundance) in the samples and standard solutions to the internal standard was subtracted using a mass bias corrected equation. The quantification limit for Se, calculated as 10 times the standard deviation of the method blanks, was 0.02 µg L^{-1} for plasma, colostrum and milk samples and 0.012 mg kg^{-1} for feed samples.

The accuracy of the methods was controlled by preparing and analysing two NIST standard reference materials (1567a wheat flour and 1570a trace elements in spinach, NIST, USA), two Seronorm™ certified reference materials (Trace elements serum L-1 and L-2, SERO, Norway), and two European reference materials (ERM® BD150 and BD151 skimmed milk powder, JRC, Belgium) in the same manner as feed, plasma and milk samples, respectively. Measured concentrations were within the uncertainties of certified values (Table A2, Supplemental material).

2.5. Selenospecies in plasma, colostrum and milk

The concentration of Se species in plasma, colostrum and milk samples was determined by HPLC–ICP-MSMS. Frozen plasma, colostrum and milk samples were allowed to thaw on ice and homogenized. Plasma (0.5 mL) and colostrum and milk (1 mL) subsamples were transferred into 1.5 mL Eppendorf tubes, and the latter were centrifuged for 60 min at 20,000 *g* and 4 °C. Subsequently, using a fine needle (BD Microlance™ 3, 23 G, 0.6 x 30 mm) and a syringe to minimize contact with the upper fat layer, 0.7 mL of aqueous supernatant was carefully removed and centrifuged at 60,000 *g* for 60 min at 4 °C. Defatted colostrum and milk (supernatant) were collected into new vials. As a final step to all sample types, a 0.5 mL aliquot was centrifuged for 60 min at 14,000 *g* and 4 °C using Amicon 0.5 mL centrifugal filters (3 kDa, Merck, USA). The recovered filtrate and retentate were used for the analysis of low (SeMet) and high (SelP, SeAlb) molecular weight Se species, respectively.

All species were separated and quantified using high performance liquid chromatography (HPLC, Agilent HP1260 liquid chromatograph, Agilent Technologies Inc., USA) in tandem with ICP-MSMS (Agilent 8800, Japan) in time-resolved analysis mode (TRA). Three different column set-ups were used under isocratic elution conditions (1-1.5 mL min^{-1}). The free amino acid SeMet in the < 3 kDa filtrate fractions was determined (10 µL injection volume) using an Agilent Poroshell 120 column (SB-C18, 3 x 75 mm, 2.7 µm) with a mobile phase of 5:95 methanol:water with 0.1% (V/V) of heptafluorobutyric acid (HFBA). Both SelP and SeAlb were determined from retentate fractions (50 µL injection volume) using, respectively, 1 mL HiTrap Heparin and HiTrap Blue HP columns (GE Healthcare, Uppsala, Sweden) with 0.05 M and 1.5 M ammonium acetate solutions as mobile phases (named "A" and "B", respectively). The retention-elution strategies were as follows: 100% A from 0 to 2.50 min (HiTrap Heparin) and 0.20 min (HiTrap Blue), and 100% B from 2.51 to 7 min (HiTrap Heparin) and from 0.21 to 10 min (HiTrap Blue). The ICP-MSMS operating parameters to measure ^{78}Se (Table A1) and examples of chromatograms for representative plasma, colostrum and milk samples from pigs of two different diets (Figures A1 and A2) are given in the supplementary material. Although all peaks in the chromatograms were integrated during data treatment, only areas of peaks associated to known Se species, eluting at the correct retention time (t_R; i.e., t_R ~ 6.5 min for SeMet and t_R ~ 4-4.5 min for SelP and SeAlb) were considered for quantification. Since no SelP or SeAlb commercial compounds were available at the time of analysis, seleno-L-methionine (≥ 98% (TLC), Sigma Aldrich) was used to prepare SeMet standard solutions (1–10 and 50–500 µg Se L^{-1} for Agilent and HiTrap column methods, respectively) and to obtain a calibration curve (i.e., peak area vs. Se concentration) under the specific analysis conditions of each method. Even if SeMet is not retained in the HiTrap columns (t_R ~ 1 min) and hence differs in elution time from SelP and SeAlb, isocratic elution conditions (i.e., no changes in mobile phase composition throughout the elution of Se species) enabled the use of SeMet calibration curves for the quantification of the three Se species, i.e., SelP, SeAlb and SeMet. Cross contamination and potential carryover were assessed by running blank samples (vials with mobile phase and washing solutions) every 10 samples, and no ghost or carryover peaks

were detected.

2.6. Statistical analysis

Initially, data from 32 sows were obtained. Two sows were excluded from the trial because of disease (see *Results*). Data from these two sows were removed from the data set. Statistical analyses were performed in RStudio, Version 1.1.383 - © 2009–2017 RStudio, Inc. [42].

To compare the relations between Se and some Se species in colostrum and milk versus that in plasma of all four groups of sows, colostrum-Se/plasma-Se and milk-Se/plasma-Se ratios were calculated. In addition to measurements of various parameters throughout the trial, a Cp/Cu-ratio was calculated. Values obtained by haematology and clinical chemistry, absolute amounts of Se and Se species in plasma, colostrum (farrowing) and milk (weaning) as well as the calculated ratios were modelled using a linear model (R *lm*). The explanatory variable *Diet* was modelled as four different diets.

Feed intake was modelled using a mixed effect model where the explanatory variables *Diet* and *Time after farrowing* were included as fixed effects and *Sow* as random effect, allowing each sow to influence the model at an individual level. The continuous variable *Time after farrowing* was modelled as a nonlinear function using spline in a gam model (R library mgcv). Prediction of mean feed intake for each diet with confidence interval (95% CI) was calculated from the final model for each day after farrowing and plotted to visualize differences between diets. The proportion of the variance accounted for by the random effect (sow specific effect) was calculated as the intraclass correlation coefficient (ICC), which is equal to the variance of the random effect divided by variance of the random effect plus variance of the residuals [43]. Based on the average daily feed intake (ADFI), the Se intake/day and sow was calculated. The explanatory variables regarding genetics (sows' genetic/ genetic of father/ genetic of mother) were included.

Plasma-Se concentrations were correlated with colostrum- and milk-Se concentration.

The significance level was set to $P < 0.05$.

3. Results

One week ante partum, one of the sows in group SeMet-0.26 was euthanized due to septic arthritis causing substantial pain and severe lameness. One sow fed NaSe-0.40 was excluded from the experiment the first day after farrowing due to peracute mastitis-metritis-agalactia causing pyrexia, agalactia and anorexia. Piglets originating from this sow were allocated to other sows within the same treatment group. There was no difference in litter size between groups.

3.1. Dietary selenium content and feed intake

Dietary Se levels were determined to be as followed: 0.40 (0.03) mg/kg feed [NaSe-0.40], 0.60 (0.05) mg/kg feed [NaSe-0.60], 0.26 (0.04) mg/kg feed [SeMet-0.26] and 0.43 (0.08) mg/kg feed [SeMet-0.43], respectively.

The mean lactation period lasted 31.5 ± 0.2 days. Over this period, an effect on ADFI was observed (Fig. 1). From day 13 *post partum*, the ADFI became higher in the sows fed SeMet supplemented diets ($P < 0.001$) compared with those supplemented with sodium selenite. Sows fed NaSe-0.40 and NaSe-0.60 reached an ADFI peak at 6.47–6.69 kg feed/day on day 21 and showed subsequent ADFI decrease. However, the ADFI of sows supplemented with SeMet increased almost steadily from day 13 (6.40–6.62 kg feed/day) until the end of lactation (7.47–7.86 kg feed/day).

The mean total amounts of feed consumed in the lactation period (95% CI) in groups fed NaSe-0.40 and NaSe-0.60, and SeMet-0.26 and SeMet-0.43 were 174.1 kg (169.4–178.7 kg), 176.8 kg (172.3–181.3 kg), 195.5 kg (190.8–200.1 kg) and 191.6 kg (187.2–196.1 kg), respectively. On average, ADFI was 0.88 (0.32) kg/day higher in sows given SeMet-0.26 and SeMet-0.43 compared with those receiving NaSe-0.40 and NaSe-0.60. During the whole lactation period, sows fed SeMet-0.26 received significantly less Se than the other groups, whereas sows given NaSe-0.60 were fed the highest amounts of Se ($P < 0.001$, data not shown). Different Se-levels of the same Se source did not influence the ADFI.

3.2. Haematology, clinical biochemistry and microminerals

The haematological and biochemical parameters showing significant differences between groups are summarized in Table 2. Non-significant differences were observed for most studied variables (Tables A3-A6, Supplementary material).

In the period from initiation to farrowing, the GLDH activity increased more in sows provided with NaSe compared with sows fed SeMet-supplemented diets. From farrowing to weaning, the GLDH activity of sows fed SeMet-0.43 increased significantly compared with sows in the other groups. From initiation to farrowing, the enzyme-activity of GGT increased more in sows fed NaSe-0.40 (trend vs. SeMet-0.4: $P = 0.06$) and SeMet-0.26 than in those given NaSe-0.60 and SeMet-0.43. In the same period, the serum Zn-levels tended to increase more in sows fed SeMet-0.43 compared with sows given NaSe-0.40 ($P = 0.05$). Furthermore, the Cp/Cu- ratio decreased more from farrowing to weaning in groups fed sodium selenite versus those fed SeMet.

3.3. Total selenium in plasma, colostrum and milk

Total Se concentrations in plasma, colostrum and milk are shown in Fig. 2. The initial plasma Se concentration was 182 ± 7 μg L^{-1} (mean ± SEM). Total plasma Se increased from farrowing to weaning but there was no significant difference for this parameter between groups during the trial. The total Se concentrations in colostrum and milk tended to increase with the feed concentration of SeMet. The Se concentrations in colostrum and milk from sows fed SeMet were significantly higher than from sows fed NaSe-0.40, and no significant difference was found between the groups fed NaSe-0.40 and NaSe-0.60. This is also shown by the standardised Se concentrations in colostrum and milk towards Se concentrations in plasma (ratio colostrum Se/plasma Se and milk Se/plasma Se; Table 3).

3.4. Selenospecies in plasma, colostrum and milk

Similarly as for total Se, the SelP concentration in plasma showed no dietary effect, but increased in colostrum with SeMet in feed (Fig. 2). However, SelP levels were low in milk without group differences. SeAlb in plasma was found to be influenced by Se type and concentrations in feed, showing low concentrations in sows fed SeMet-0.26 at farrowing and weaning, and in sows given NaSe-0.40 at weaning. In colostrum, SeAlb increased clearly with feed concentration of SeMet, but low concentrations without group differences were found in milk. SeMet was not detectable in plasma but increased with increasing feed SeMet concentration in colostrum and milk. Higher levels of SeMet were observed in milk than in colostrum.

Evidently as demonstrated by the calculated ratios, transfer of SelP and SeAlb, and thus total Se, to colostrum (farrowing) was much higher than to milk at weaning (Table 3, *P < 0.001*). Feeding of diets added SeMet led to proportionally higher ratios of SelP and SeAlb at farrowing. Interestingly, despite an even greater difference in the dietary Se dose, the ratios for SelP and SeAlb at farrowing were similar for the two inorganic Se diets. In the *Discussion* section, detected Se species were divided in low (< 3 kDa, free amino acid SeMet) and high (> 3 kDa, SelP and SeAlb proteins) molecular mass species, with the latter containing Se bound in their amino acid chain.

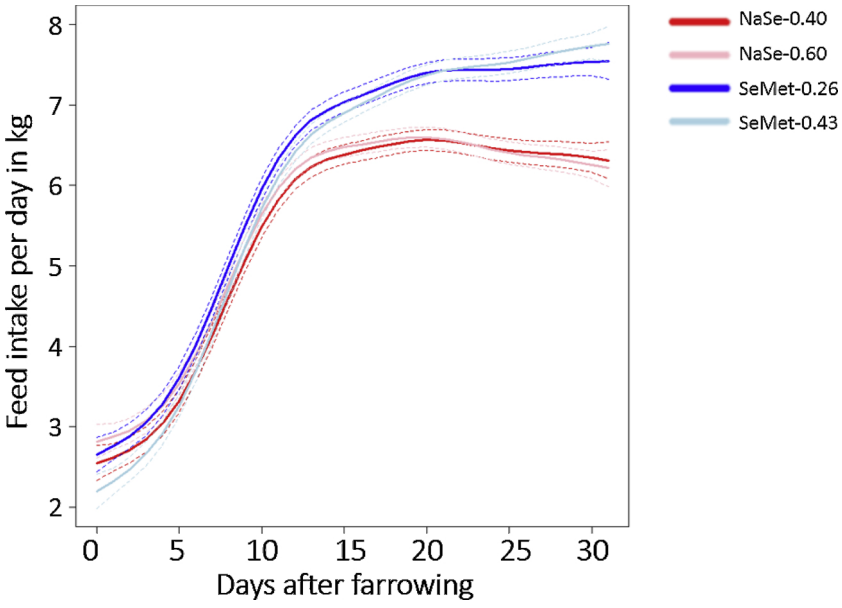


Fig. 1. Effect of time and diet on feed intake (kg/day ± 95% confidence interval).
Feed intake of sows throughout the lactation period. The variance of the residuals in this gamm model was 0.93. ICC = 0.346. During the lactation period, a dietary effect on average daily feed intake (ADFI) was observed. From day 13 post partum until the end of the study, the ADFI was significantly higher in the SeMet supplemented SeMet-0.26 and SeMet-0.43 compared with the sodium selenite supplemented NaSe-0.40 and NaSe-0.60 ($P < 0.001$). Both SeMet-0.26 and SeMet-0.43 showed a continuing increase in ADFI whereas NaSe-0.40 and NaSe-0.60 reached an ADFI peak with subsequent decrease.
NaSe-0.40: sodium selenite 0.40 mg Se/kg diet; NaSe-0.60: sodium selenite 0.60 mg Se/kg diet; SeMet-0.26: L-selenomethionine 0.26 mg Se/kg diet; SeMet-0.43: L-selenomethionine 0.43 mg Se/kg diet.

Table 2
Blood parameters in sows (Mean (SD)).

Parameter	Initiation[1]	Change over time (%)		
		I-F	F-W	I-W
Enzyme activities				
GGT (U/L)				
NaSe-0.40	52.1 (15.0)	−30.5 (10.1)	64.9 (26.9)^{ab}	13.7 (19.1)$^{ab\hat{}\hat{}}$
NaSe-0.60	67.0 (18.7)	−24.4 (9.7)	29.8 (25.3)^{a}	−7.4 (17.7)^{a}
SeMet-0.26	62.4 (18.3)	−28.4 (16.2)	81.8 (66.5)^{b}	23.2 (30.3)^{b}
SeMet-0.43	63.5 (16.7)	−30.9 (7.7)	34.4 (15.3)^{a}	−7.6 (10.8)$^{a\hat{}\hat{}}$
GLDH (U/L)				
NaSe-0.40	1.9 (0.4)	50.0 (76.4)^{bc}	14.3 (24.4)^{a}	64.3 (69.0)
NaSe-0.60	1.0 (0.6)	90.0 (74.2)^{b}	6.3 (80.6)^{a}	80.0 (83.7)
SeMet-0.26	2.1 (0.7)	21.4 (39.3)^{ac}	11.9 (38.1)^{a}	38.1 (77.4)
SeMet-0.43	2.3 (0.5)	−20.8 (23.1)^{a}	93.8 (72.9)^{b}	39.6 (17.7)
Microminerals related results				
Cp/Cu				
NaSe-0.40	3.5 (0.6)	−23.7 (11.8)	−15.0 (19.9)^{ab}	13.0 (26.3)
NaSe-0.60	3.6 (0.5)	−20.4 (4.7)	−21.6 (16.2)^{a}	−1.7 (15.9)
SeMet-0.26	3.4 (0.6)	−30.3 (13.2)	−8.5 (16.8)^{b}	35.1 (33.0)
SeMet-0.43	3.5 (0.5)	−26.8 (5.7)	−4.2 (19.3)^{b}	31.5 (28.1)
Zn (μmol/L)				
NaSe-0.40	10.0 (1.0)	−9.0 (15.5)$^{a\hat{}}$	17.4 (15.1)	17.4 (15.1)
NaSe-0.60	10.3 (1.2)	−1.3 (16.6)^{ab}	18.3 (10.3)	18.3 (10.3)
SeMet-0.26	10.4 (1.5)	4.3 (19.3)^{ab}	33.5 (18.5)	33.5 (18.5)
SeMet-0.43	9.7 (1.5)	15.8 (33.6)$^{b\hat{}}$	31.3 (28.7)	31.3 (28.7)

Only parameters showing significant inter-group differences are presented. [1]Initiation: Measured values. I–F: Change from initiation to farrowing, F − W: Change from farrowing to weaning; I − W: Change from initiation to weaning; GGT - γ-glutamyl transferase, GLDH – glutamate dehydrogenase, Cp/Cu – ceruloplasmin/copper ratio, Zn – zinc; Means within a column without a common superscript differ significantly ($P < 0.05$). $\hat{}P = 0.05$, $\hat{}\hat{}P = 0.06$.
NaSe-0.40: sodium selenite 0.40 mg Se/kg diet; NaSe-0.60: sodium selenite 0.60 mg Se/kg diet; SeMet-0.26: L-selenomethionine 0.26 mg Se/kg diet; SeMet-0.43: L-selenomethionine 0.43 mg Se/kg diet.

4. Discussion

The difference in dietary Se levels between 0.43 (group SeMet-0.43) and 0.40 (group NaSe-0.40) is within the uncertainty of the analytical method and considered numerically comparable.

4.1. Feed intake

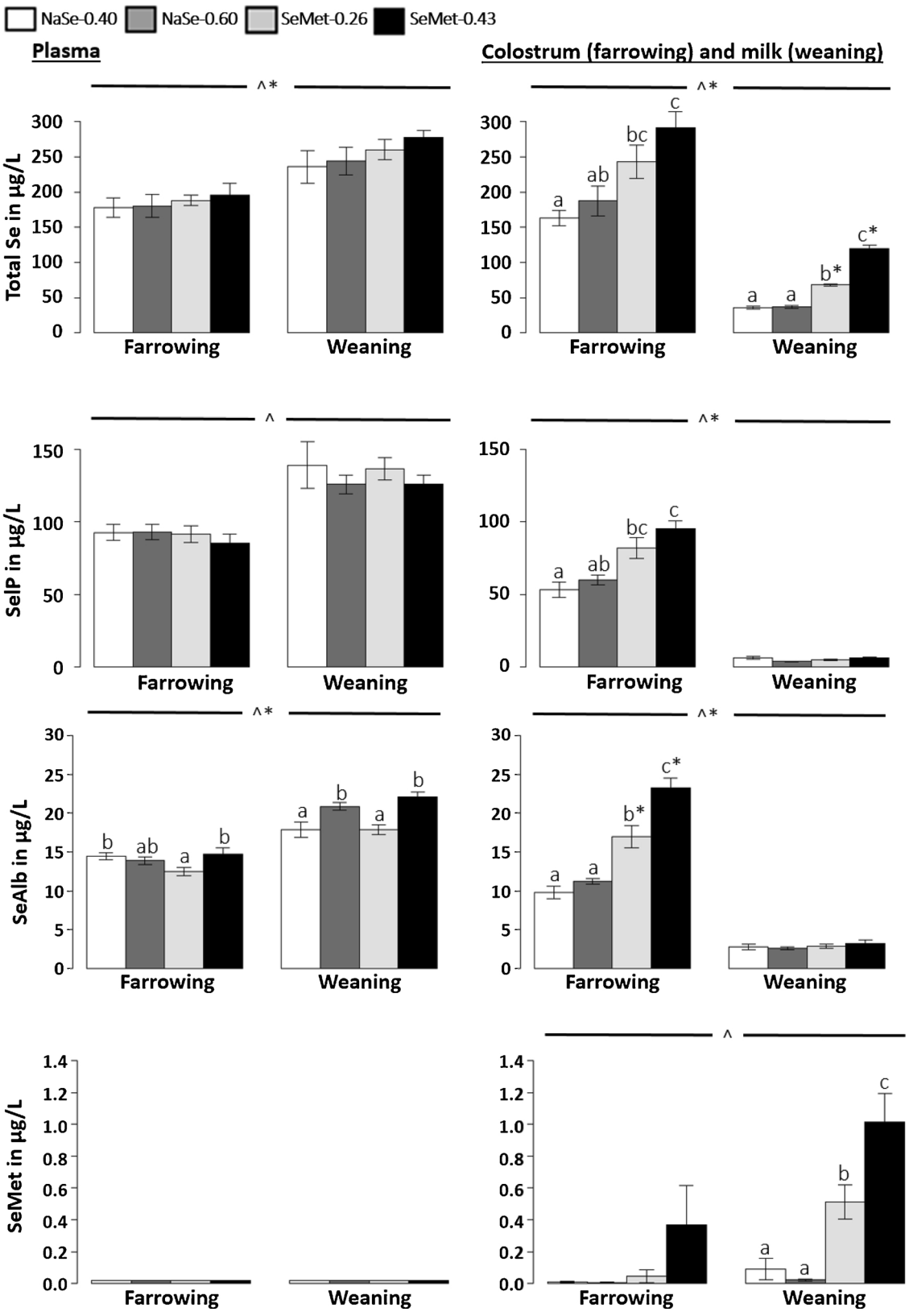
The reason for the higher ADFI observed in SeMet supplemented sows compared with those fed NaSe-0.40 and NaSe0.60 remained uncertain. It could be related to the smell of the feed. The farmer and researchers had a clear perception of different odours of the sodium selenite supplemented diets versus those supplemented with SeMet. The olfactory system of pigs is highly developed with quite large and highly organized structures [44,45]. As smell is an initial attractant to feed, the sows fed SeMet may have consumed more feed due to an appealing smell perception. Jankevicius and Widowski [46] suggested that pigs decide whether to consume offered feed or not according to their olfactory or taste perception. Taheri et al. [47] observed a higher feed intake in goats fed organic Se versus those fed sodium selenite in a 45 days feeding trial conducted after parturition, which is in line with our findings.

The Norwegian Landrace x Yorkshire hybrid used in this study is a very lean and feed efficient sow [48] being more prone to nutritional stress, especially during lactation, compared with sows that have higher levels of body reserves [49]. Maintenance requirements of contemporary modern lean genotypes are higher due to the increased needs for energy to maintain lean muscle tissue compared with adipose tissue [50,51]. Sows fed SeMet-0.26 and SeMet-0.43 consumed more feed over a period of more than 2 weeks, in theory enabling them to maintain or re-establish their body condition for the subsequent reproductive cycle

4.2. Clinical biochemistry

From initiation until farrowing, the increase in serum-Zn observed in sows fed SeMet than in those receiving NaSe-0.40 may relate to its antioxidant function. Zn decreases when oxidative stress levels increase [52]. In the same period, the enzymatic activity of GLDH increased stronger in sodium selenite supplemented sows compared with those fed SeMet. GLDH controls the intracellular levels of fumarate, which binds to and activate glutathione peroxidase 1, thus regulating redox homeostasis [53]. This might indicate a higher requirement of antioxidant defence in sodium selenite-supplemented sows.

During lactation, a stronger increase of GGT activity was observed in sows fed NaSe-0.40 and SeMet-0.26 compared with those fed higher levels of sodium selenite and SeMet, respectively. This could be related to the metabolism of glutathione, where GGT catalyses the first step of



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the recycling process. Serum and dietary antioxidant vitamins have been shown by others to have inverse dose response relations to serum GGT level within its normal range [54].

SeMet-supplementation may have allowed maintenance of a stable antioxidative status in sows without the need to compensate by applying alternative antioxidative molecules like Zn-containing enzymes when experiencing elevated systemic oxidative stress levels, e.g. during late gestation and lactation [4]. The stronger increasing Cp/Cu-ratio from farrowing to weaning in groups fed SeMet versus those fed sodium selenite might indicate a smaller pool of free copper ions in the

Fig. 2. Levels of total selenium in plasma, colostrum and milk compared with selenospecies (µg/L ± 95% confidence interval).
Colostrum and milk samples isolated from SeMet-0.26 and SeMet-0.43 showed higher selenium (Se) than NaSe-0.40 and/or NaSe-0.60. Colostrum contained much higher amounts of Se compared with milk. Selenoprotein P- (SelP)- and selenoalbumin- (SeAlb)-levels in plasma were highest in samples isolated at weaning. Milk-levels of SelP and SeAlb, where lower compared with those in colostrum. The concentration of SeAlb in milk seemed to correlate with the dietary Se source.
Selenomethionine (SeMet) was not detected in plasma (graph shows LOD = 0.02 µg/L). In colostrum samples, SeMet was only detected with organic Se diets. In milk samples, the concentration of SeMet was higher in SeMet-0.43 sows than with SeMet-0.26. Milk-SeMet levels appear to correlate with the level of SeMet supplementation.
Bars at one time point without a common superscript differ significantly ($P < 0.05$). The symbol ˆ between time points notifies significant difference ($P < 0.05$); *$P < 0.001$
NaSe-0.40: sodium selenite 0.40 mg Se/kg diet; NaSe-0.60: sodium selenite 0.60 mg Se/kg diet; SeMet-0.26: L-selenomethionine 0.26 mg Se/kg diet; SeMet-0.43: L-selenomethionine 0.43 mg Se/kg diet.

Table 3
Calculated ratios (colostrum/plasma [farrowing] and milk/plasma [weaning]) for total selenium and related species.

Group	Time point	Ratio Total Se	Ratio SelP	Ratio SeAlb
NaSe-0.40	Farrowing	0.93 (0.20)^{a}	0.59 (0.15)^{a}	0.69 (0.17)^{a}
NaSe-0.60	Farrowing	1.26 (0.30)^{ab}	0.66 (0.17)^{a}	0.81 (0.10)^{a}
SeMet-0.26	Farrowing	1.40 (0.27)^{ab}	0.92 (0.28)^{b}	1.36 (0.26)^{bcˆ}
SeMet-0.43	Farrowing	1.59 (0.52)^{b}	1.15 (0.27)^{b}	1.57 (0.32)^{c}
NaSe-0.40	Weaning	0.16 (0.04)^{a}	0.05 (0.02)^{ab}	0.16 (0.06)^{a}
NaSe-0.60	Weaning	0.15 (0.05)^{a}	0.03 (0.00)^{a}	0.13 (0.02)^{a}
SeMet-0.26	Weaning	0.28 (0.04)^{b}	0.03 (0.01)^{ab}	0.14 (0.02)^{a}
SeMet-0.43	Weaning	0.43 (0.02)^{c}	0.05 (0.01)^{b}	0.15 (0.03)^{a}

The table shows the above−mentioned ratios for the concentrations of total selenium (Total Se), selenoprotein P (SelP) and selenoalbumin (SeAlb) as mean (SD). Means within a column and at the same time point denoted with different superscripts differ significantly ($P < 0.05$). ˆ$P = 0.05$.
NaSe-0.40: sodium selenite 0.40 mg Se/kg diet; NaSe-0.60: sodium selenite 0.60 mg Se/kg diet; SeMet-0.26: L-selenomethionine 0.26 mg Se/kg diet; SeMet-0.43: L-selenomethionine 0.43 mg Se/kg diet.

organic Se supplemented sows. In humans, non-Cp copper levels correlate negatively with antioxidants and positively with free radical products, conforming the pro-oxidant role of intracellular free copper [55].

Our results on GGT, GLDH and on the Cp/Cu-ratio could indicate a reaction of the body on the increased level of oxidative stress caused by dietary sodium selenite in addition to the reproduction-induced stress. A study in grower-finisher pigs indicated that supplementing with sodium selenite increases the levels of stress after exposure to LPS compared with pigs supplemented with organic Se sources [39].

4.3. Total Se in plasma, colostrum and milk

The observation of increasing Se levels in sows' plasma from farrowing to weaning is in line with a study by Yoon and McMillan [56], who observed a gradual increase during lactation. During late gestation, the blood volume increases leading to hemodilution [57], possibly improving placental microcirculation to accelerate foetal development [58]. Blood and serum volumes normalize again after farrowing [57], which might explain the observed lower plasma Se levels at farrowing.

Higher protein levels in colostrum versus milk [59–61] explain the higher Se concentrations in colostrum compared with milk obtained at weaning. In line with previous studies [62–66] we observed higher total Se levels in colostrum and milk from sows fed SeMet enriched diets compared with sows fed sodium selenite. Consistent with results from previous studies in sows [62,63] and cows [65], diet showed a dose-response effect on milk Se in sows given SeMet. Some of this increase in milk-Se in SeMet-fed sows versus sodium selenite-fed sows could have been associated with the higher ADFI, but colostrum- and milk- Se levels did not reflect the total Se-intake per day and sow during the lactation period. The daily total Se-intake was lowest in sows fed SeMet-0.26, and highest in those provided with NaSe0.60 of all groups (data not shown). Milk from sows in the groups fed NaSe-0.40 and NaSe-0.60 showed similar Se levels, despite different dietary sodium selenite-levels. Our results correlate well with previous studies indicating higher bioavailability and higher ability of organic Se versus inorganic Se to increase Se in colostrum and milk [62–68]. Mahan [62] calculated that, with an assumed daily milk production in sows of 10 kg/d, approximately 30% of the inorganic and 80% of the organic dietary Se would be excreted with the milk. However, Mahan and Kim [63] could not find any influence of neither Se-source nor dietary Se levels on Se in colostrum. In that study, however, Se yeast was used as organic Se-source, and recent literature has shown that there may be a large batch-to-batch and product-to-product variability of the SeMet content in Se yeast [69].

Higher Se concentrations in colostrum have shown to increase the passive absorption of immunoglobulin G in calves [70]. Kielland et al. [71] suggested that improved levels of IgG in piglets potentially increase the survival of piglets. Based on the significant higher milk/plasma-ratio for Se in sows fed SeMet one could suggest that they received a Se-source and dietary level covering their demands, and simultaneously allowing a higher transfer of Se to the mammary gland. In contrast to sodium selenite, SeMet can be stored in the body´s protein pool and is continuously available by protein turnover enabling a Se homeostasis.

4.4. High molecular mass Se species in plasma, colostrum and milk

Overall, the concentrations of SelP, the major Se transport protein to the mammary gland secretions [72], and SeAlb showed a similar trend compared with the total Se levels in both plasma and colostrum. SelP [72] and SeAlb [73,74] are transferred from extramammary tissue to colostrum and milk. Olson et al. [75] showed a receptor –mediated uptake for SelP via the megalin receptor in kidney cells. Rowling et al. [76] showed that megalin was expressed by human mammary derived cells. An active, receptor-mediated transport mechanism could explain our results on SelP-levels in colostrum and milk versus plasma. Colostrum- /plasma- and a milk- /plasma- ratios were calculated for SelP and SeAlb, implying that the transfer of SelP and SeAlb, and thus that of Se in total, is higher to colostrum than to milk. Thus, in opposite to de la Flor et al. [77], who examined human colostrum and milk during the first month after delivery, the distribution patterns in the sows´ mammary gland secretions changed throughout lactation.

In line with observations made by Fantuz et al. [78] in donkeys, our results indicate that the mammary gland actively regulates the transport of Se. Milk levels of SelP and SeAlb and thus the total Se concentration in milk decreased as lactation progressed possibly by active reduction of their transport. However, Lönnerdal [79] suggested that human milk Se levels are closely correlated with circulating Se levels, making a regulating mechanism unlikely. Our results cannot support the statement made by Lönnerdal [79], which might reflect the different nutritional and developmental requirements of mammalian neonates [29].

4.5. Low molecular mass (< 3 kDa) Se species in plasma, colostrum and milk

Muñiz-Naveiro et al. [80] detected three Se species in milk from

cows supplemented with Se yeast (SeCys, selenite and SeMet), whereas only SeCys and selenite in milk from cows supplemented with sodium selenite. Milk levels of SeMet detected in our trial are comparable to those found in cow milk [81]. Free amino acids in milk have been shown by others to increase throughout lactation in sows [82], which is in line with our observations.

A lack of Se or individual selenoproteins has been shown to result in growth retardation in young mice and human [25]. Thus, the higher level of the selenized amino acid SeMet, in milk compared with colostrum may relate to the high growth rate and the resulting high metabolism of the newborns.

Our calculations showed that SelP, SeAlb and SeMet comprised about 57% (at farrowing) and 62% (at weaning) of total Se in the sows' plasma. As shown by others, Se in plasma is mainly bound to SelP (~50%, [83,84]) and glutathione peroxidase 3 (Gpx3; 4 30%; [84–86]). However, our results on Se speciation comprise only about 34% of total Se in colostrum and 13% in milk at weaning. In the present study, the levels of GPx3 were unfortunately not determined in the sows' plasma, colostrum nor milk due to the lack of methodological requirements.

Fat has been removed from colostrum and milk prior to Se speciation, but was shown to be quite low in Se. Regardless of species (cow, sheep, goat, human) < 3-5% of total Se in milk were associated with the lipid fraction [85,87]. In contrast to plasma Se (< 3%), a large fraction of milk Se, approximately 30%, is present in small-molecule forms of Se not yet characterized [85,88]. In addition, SeMet enters proteins non-specifically and sodium selenite provides Se only for selenoproteins [72], partly explaining the differing fractions of Se from colostrum and milk in our study. Bierla et al. [89] showed that most of the total Se, over 70%, was present in the casein fraction.

Occurrence and concentrations of SelP, SeAlb and SeMet have not been described earlier in plasma, colostrum and milk from sows. Knowledge of the fate of these molecules during gestation and lactation is important in order to understand their significance and contribution to animal health and to provide a basis for further research.

4.6. Conclusion

Organic Se was superior to inorganic Se when comparing sows´ feed intake as well as transfer of total Se and the main Se transport protein SelP from plasma to colostrum and milk. In addition, we suggest that substitution of dietary sodium selenite with SeMet might decrease oxidative stress in highly prolific sows as indicated by serum-Zn, GLDH and GGT. Elevated concentrations of selected Se species as detected in colostrum from sows supplemented with SeMet compared with those fed sodium selenite potentially improve the piglets´ survival and growth due to increased uptake of IgG and probably better antioxidative status. The significant lower levels of total Se, SelP and SeAlb found in milk at weaning versus colostrum may be consistent with an active regulation of the Se transport from extramammary tissue to colostrum and milk. Future research should focus on the influence of different Se sources on blood parameters as well as on the Se transfer in the mammary gland throughout lactation and on subsequent effects on production parameters of the progeny.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jtemb.2018.12.009.

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