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SILVER AND ZINC NANOPARTICLES IN ANIMAL NUTRITION – A REVIEW

Maciej Bąkowski, Bożena Kiczorowska♦, Wioletta Samolińska, Renata Klebaniuk, Antoni Lipiec

Institute of Animal Nutrition and Bromatology, Faculty of Biology, Animal Sciences and Bioeconomy, University of Life Sciences, Lublin, Poland
♦Corresponding author: bozena.kiczorowska@up.lublin.pl

Abstract

The use of metal nanoparticles as supplements of animal diets does not always bring unambiguous results. There are many reports in the literature about the multifaceted effects of this type of supplementation on the animal organism. Therefore, the aim of the paper is to present the current knowledge of the possible application of nanometal forms in animal nutrition and its potential benefits and threats. The positive effect of nanoparticles used as feed additives has most frequently been reflected in an increase in body weight, higher average daily gain, or improvement of the FCR value. In some cases, however, the effect of nanoparticle addition to diets was indiscernible. The potent antibacterial activity of nanoparticles, especially against Gram-negative bacteria and Gram-positive bacteria, is regarded as a positive effect. In turn, the probability of their toxicity is a potential risk in application thereof. Supplementation of diets with nanometals has been accompanied by pathological changes in animal tissues, primarily in the pancreas, kidney, liver, rumen, abomasum, small intestine, adrenal glands, and brain. Additionally, at the the cellular level, nanoparticles were found to induce toxicity, inflammatory excitation, and cell death. Oral administration of nanoparticles induced a risk of malfunction of the nervous system and even impairment of cognitive processes in animals. The increasing knowledge of the possible toxic effects of nanoparticles on the animal organism suggests caution in their use in animal production and necessitates further precise investigations in this area.

Key words: metal nanoparticles, nutrition, animal production, bactericidal properties, toxicity

Innovations in the agri-food industry have a multifaceted character. They involve implementation of progressive technologies designed to increase the efficiency of animal production by enhancement of the animal health status and improvement of the physico-chemical-nutritional properties of nutritional products (Kiczorowska et al., 2017; Lipińska, 2015). Biological progress is especially important in farming. It is achieved by introduction of new animal breeds and new production technologies. An important role in the development of the animal production technology is played by the nutrition regime and type of feed and additives used (Grela et al., 2017;

Kiczorowska et al., 2015 b, 2016 a; Wawrzynowicz et al., 2012). Currently, animal production is assisted by a number of modern methods, e.g. bioengineering, genetic engineering, or nanotechnology.

Nanotechnology offers new solutions for transformation of biosystems and provides wide potential for improvement of animal production systems. Its applications in biotechnology, biomedicine, and agriculture include surface-focused nanobiotechnological techniques targeted at manipulation with molecules within the cell, use of bioselective surfaces, and control of biocontaminants and cell cultures. In animal nutrition and husbandry, nanotechnology is employed for "intelligent" nutrient supply, bioseparation, signal processing, and protection of animal health (Curtis and Wilkinson, 2001). The literature reports a viewpoint that nanotechnology has the potential to revolutionise agriculture and food industry by providing new tools in molecular and cell biology for separation, identification, and quantification of single molecules that could be used e.g. for increasing the efficiency of animal production (Sawosz et al., 2009). Concurrently, there are investigations that indicate potential threats of nanotechnology related to the toxicity of nanoparticles (Boudreau et al., 2016; Buzea et al., 2007; Sabella et al., 2014; Sirelkhatim et al., 2015). These reports recommend utmost research caution preceded by thorough, comprehensive scientific observations prior to implementation of the technology on an industrial scale, especially in livestock production. The aim of the review is to present the available knowledge of the possibility of using metals in the nano-form in animal nutrition and the resulting potential benefits and threats. The review is based on studies published in 2007–2017, with particular emphasis on the last 5 years, and available in e.g. the Web of Science, Scopus, PubMed, and Polish Scientific Journals Database.

Nanoparticles

Nanoparticles occur in nature (Kumar, 2010). However, only the development of science and technology has created the possibility of exploration of their unique properties and application in many fields of science. The EU Commission defines nanoparticles as a natural or produced material containing at least 50% of particles with a size in the range of 1 nm-100 nm. In special cases of concerns about their negative impact on the environment, health, or safety, the 50% size distribution threshold can be lowered (EU Recommendation, 2011). Nanomaterials are a highly diverse group; therefore, the definition proposed by the EU Commission is mainly recommended for identification thereof. Clear and unambiguous criteria for identification of nanomaterials facilitate assessment of potential risk and threats. Nanoparticles of any compound have different shapes and sizes. They can be organised as aggregates, agglomerates, or composites, which combine at least two components with different physical and chemical properties. Most usually, these are metal oxides, metals, silicon compounds, various types of carbon, semiconductors, and organic or biological particles (Auffan et al., 2009; Chook et al., 2012; Martinez-Castanon et al., 2008).

In terms of their structure, nanoobjects are divided into three morphological groups: nanoparticles, nanofibres, and nanodusts. In the case of nanoparticles, it was assumed that the ratio between the minimum and maximum dimension of a nanoobject does not exceed the value of 3. Nanoparticles can have different shapes –

flakes, spheres, cylinders, platelets, or dendritic forms. They can have an amorphous (unordered) or crystalline (ordered) structure (Świderska-Środa et al., 2016). Diverging from the classic definition of nanomaterials, fullerenes, graphene flakes, and single-wall carbon nanotubes with one or more external dimensions below 1 nm are regarded as nanomaterials as well (EU Recommendation, 2011).

Engineered nanoparticles with their special properties are used in biology, medicine, and animal production. In addition to their small sizes, they are characterised by low mass, which allows the so-called quantum effect. It is associated with modification of their physical, chemical, and biological characteristics, e.g. increased reactivity, adsorption, and absorption, better mechanical resistance, lower melting point, or a tendency for rapid aggregation. These properties are employed in strong bacteriostatic and bactericidal agents, labelling of biological structures and cells, targeted delivery of drug particles to diseased tissues, or precise mineral nutrition in animals (Li et al., 2016). Silver and zinc nanoparticles arouse especially high hopes e.g. in view of animal production (Choi and Hu, 2008; Elkloub et al., 2015; Fondevila et al., 2009; Uniyal et al., 2017).

Efficiency in animal production

Animal health is largely determined by appropriate nutrition and the living environment. Optimisation of these factors increases the rearing efficiency and can positively determine the quality of food of animal origin (Al-Yasiry et al., 2017; Kiczorowska et al., 2015 a; Smith et al., 2013). As reported by the literature, nanotechnology has the potential to exert a significant effect on animal health and thus on their production performance (Chmielowiec-Korzeniowska, 2015; Kumar, 2010; Li et al., 2016; Milani et al., 2017; Ognik et al., 2016).

Nanoparticles are considered for use as a supplement of animal diets. However, their nutritional application has not always yielded positive effects. Supplementation of diets with nanoparticles was sometimes noted to have a positive impact on animal production or health parameters, although the effect was indiscernible or even negative in some cases (Table 1). Positive effects of such supplementation were reported by Fondevila et al. (2009). They observed a numerical increase in pigs' daily growth when different colloidal silver (60–100 nm) doses were added, compared with the control. Similar beneficial production effects have been reported by Ahmadi (2009) and Elkloub et al. (2015) in chicken experiments. However, the authors do not provide the exact chemical and physical characterisation of the nanosilver applied, which makes verification of their results somewhat difficult (Table 1). The increase in the production effects may also be associated with the potent antibacterial, antifungal, antiprotozoal, and even antiviral activity of silver nanoparticles. As the productive responses to an additive that improves the sanitary status of animals are in general inversely proportional to the environmental quality of the productive site, it is likely that under the stress conditions of commercial farms the concentration of pathogenic bacteria increases and thus the effect of silver will be more manifested. Clearly less optimistic information on the improvement of body weight, feed intake, FCR index, and chicken mortality has been reported by Hassanabadi et al. (2012), Ahmadi et al. (2013), Felehgari et al. (2013), or Ognik et al. (2016). As shown by

their data, despite the differences in the doses administered, the silver particles used by the authors were smaller, e.g. 40 nm (Felehgari et al., 2013) or 22 nm (Ognik et al., 2016) (Table 1). Changes in the size of nanoparticles can significantly affect their physicochemical properties or biological activity. This has been confirmed in animal studies, mainly on poultry, where even smaller silver nanoparticles ranging from 2 to 14 nm were administered to the animals (Ahmadi and Branch, 2012; Chmielowiec-Korzeniowska et al., 2015; Pineda et al., 2012) (Table 1). The authors observed not only a significant decline in the breeding performance expressed in such parameters as body weight, feed intake, or FCR, but also deterioration of some health indicators, e.g. alanine and aspartate transaminase enzymes, bilirubin, and albumin.

Table 1. Effect of silver and zinc nanoparticles on animal productive performance and blood parameters

Experimental conditions	Nanoparticles dose	NPs characterization	Productive and blood parameters	References
1	2	3	4	5
Silver nanoparticles				
Weaned pigs in period: 28 to 56 days	0, 20, 40 mg/kg	colloidal silver, 60–100 nm	growth (g/day) ↑, feed: growth ratio ↑	Fondevila et al., 2009
Ross 308 broiler chicken in period: 1–56 days	300, 600, 900 ppm	no information	body weight ↑, feed intake ↔ FCR ↓	Ahmadi, 2009
Ross 308 broiler chicken in period: 1–56 days	20, 40, 60 ppm	14±0.8nm	feed intake ↓ FCR ↓, EPEI ↓, ALT, AST ↓, CHOL, albumin ↓	Ahmadi and Branch, 2012
Ross 308 broiler chicken in: Starter diets Grower diets	0.5, 1, 1.5 ppm/kg 1, 2, 3 ppm/kg	no information	feed intake ↔, body weight gain↔, FCR↔, mortality ↔	Hassanabadi et al., 2012
Broiler chicken	0, 10, 20 mg/kg	colloidal silver, 2–35 nm	body weight ↓, feed intake ↓ FCR ↔	Pineda et al., 2012
Ross 308 broiler chicken (male) in period: 1–21 days	4, 8, 12 mg/kg	nano silver powder	body weight ↔, feed intake ↔ FCR ↔ TG, LDL, VCDL ↓, HDL, uric acid↑	Ahmadi et al., 2013
Ross 308 broiler chicken (male) in period: 1–21 days	25 mg/0.2 mg 25 mg/0.2 mg 50 mg/0.2 mg 50 mg/0.2 mg	nano silver powder, 40 nm and inorganic selenium	body weight ↔, FCR↔	Felehgariet et al., 2013
Broiler chicken Hubbard in period: 7–35 days	2, 4, 6, 8, 10 ppm/kg	no information	body weight ↑, feed intake ↔ FCR ↑, EPEI ↑ CHOL, AST ↑,	Elkloub et al., 2015

Table 1 – contd.

1	2	3	4	5
Greenleg Partridge chicken (chickens hatched from nanosilver disinfected eggs)	The eggs were sprayed with colloidal silver at a concentration of 50 ppm	colloidal silver, 10 nm	urea ↓, bilirubin ↓, creatinine ↓, uric acid ↓	Chmielowiec-Korzeniowska et al., 2015
Ross 308 broiler chicken in period 6 weeks	5 mg/kg body weight/day	aqueous solution, lipid-coated, (22 nm) with AgL-nano	body weight ↔, feed intake ↔, FCR ↔, carcass parameters ↔	Ognik et al., 2016
Hens in period 22 day (*in vivo* study)	oral administration	spherical PVP-coated, 20 nm	Ag accumulation in: livers, ↑, yolks ↑, muscles, ↔ kidneys, ↔	Gallocchio et al., 2017
		Zinc nanoparticles		
Cattle (Holstein Friesian) – rumen fermentation pattern	50, 100, 200, 400 mg/kg of diet dry matter	ZnO	ruminal microbial protein synthesis ↑, energy utilization efficiency ↑, volatile fatty acid ↑, microbial crude protein ↑, fermentation of organic matter ↑	Zhisheng, 2011
Cattle (Holstein Friesian)	50, 100 mg/kg diet dry matter	ZnO	somatic cell count in subclinical mastitis ↓, milk production ↑, Zn nano can be used as a preventive and curative agent to control sub-clinical mastitis in cows	Rajendran et al., 2013
Broiler chicken	20, 60, 100 mg/kg	ZnO	body weight gains ↓ (20, 60 mg ZnO) FCR ↑ (20, 60 mg ZnO) body weight gains ↓ (100 mg ZnO) FCR ↓ (100 mg ZnO)	Zhao et al., 2014
Broiler chicken in period: 1–42 days	80 mg/kg	zinc sulphate, zinc methionine	FCR ↔, carcass yield ↓ abdominal fat ↓	Mohammadi et al., 2015
Weanling piglets	120 mg/kg	ZnO, 142±15 nm	Zn digestibility↑ serum growth ↑ carbonic anhydrase activity ↑	Li et al., 2016

Table 1 – contd.

1	2	3	4	5
Guinea pig males in period: 37–42 days	20 ppm/kg	zinc sulphate, Zn methionine	average daily gain ↔, body weight ↔, feed : gain ↔, nutrient digestibility↑ CHOL, AST, ALT, ALP ↔	Uniyal et al., 2017
Weaned pigs in period: 1–35 days	15, 30 or 60 mg	ZnO, 70±38.6 nm	average daily gain ↑, body weight ↑, feed : gain ↓, feed intake ↑ nutrient digestibility↔ AST↓, ALT ↑, HGB ↔,	Milani et al., 2017

NPs, nanoparticles; ADG, average daily gain; BW, body weight; FCR, feed conversion ratio; EPEI, European Production Efficiency Index; ALT, enzyme alanine transaminase; AST, enzyme aspartate transaminase; ALP, alkaline phosphatase enzyme; CHOL, cholesterol; HGB, haemoglobin; DM, dry matter; ↑, increase; ↓, decrease; ↔, no effects.

However, these dosing conditions are considered to have much higher toxic potential than low concentrations of metallic silver given for short periods of time (Wadhera and Fung, 2005). Another important aspect to verify when an additive is promoted to use is to what extent it challenges the health of the potential consumer. Gallocchio et al. (2017) administered 20-nm silver nanoparticles to laying hens in an *in vivo* study and found silver accumulation in birds' kidneys and eggs, which can be a disturbing support for the toxic properties of the metal (Table 1). Studies in animals as models for humans have shown that high silver concentrations in the form of silver salts and given as a chronic dose (for more than 18 weeks) reduce the weight of mice (Wang et al., 2008). In turn, Fondevila (2010), who applied metallic silver nanoparticles (up to 100 nm) in a dose of 20 do 40 ppm as a dietary additive during the growth and finishing phases in pigs (from 20 to 90–100 kg, commercial slaughter weight), did not detect any traces of silver in the muscles, kidneys, or liver of 90 kg pigs receiving the additive up to 20 kg weight. This can prove the detoxifying capacity of the liver to excrete silver. Investigation results indicate that silver nanoparticles are more resistant to inactivation by gastric acids and are characterised by a low level of absorption through the intestinal mucosa, which may reduce the potential risk of their toxicity (Fondevila et al., 2009).

Equally inconclusive results are presented by authors investigating the effect of nano zinc in animal nutrition (Table 1). Its oxide form was used most frequently. Applied in cattle nutrition in doses of 50 up to even 400 mg/kg of dry matter diet, it stimulated ruminal microbial protein synthesis and fermentation of organic matter, thereby not only improving milk production yield but also reducing somatic cell count (Rajendran et al., 2013; Zhisheng, 2011). Nano zinc oxide was also used in poultry production, where the doses of 20 and 60 mg/kg had a beneficial effect on

body weight gains but lowered the FCR index, which had a higher value only in the dose of 100 mg (Zhao et al., 2014) (Table 1). Better animal production results are usually a consequence of improved nutrient utilization from feed. An increase in the digestibility of nutrients and Zn from diets supplemented with zinc nanoparticles has been reported in piglets (Li et al., 2016) and in guinea pigs (Uniyal et al., 2017). A similar effect was also observed by Milani et al. (2017). By increasing the level of nano zinc oxide in diets (15, 30 and 60 mg) of weaned pigs, the authors confirmed the positive linear correlation of the dose with better digestibility of nutrients and energy components in the diet. Additionally, they reported a linear increase in the Zn concentration in pigs' blood plasma (Table 1).

Zinc is used in the form of nanosulphide in animals, e.g. to increase the absorption of this mineral and reduce the level of its supplementation. Such investigations have been carried out on broiler chickens by Mohammadi et al. (2015). Zinc in the form of nano zinc-sulphate and nano zinc-methionine (in a dose of 80 mg/kg in poultry) was found to improve growth performance, but especially zinc-nano-sulphate decreased growth performance in the broilers (Table 1). The disadvantage of the administration of nano zinc-sulphate is the possibility of contamination of the environment, as the element is transferred by sewage, although in smaller quantities than when conventional zinc forms are used (Dhas et al., 2014).

Therefore, nanoparticles are considered as feed additives applied in animal production as growth-enhancing or disease-preventing agents (Li et al., 2016; Milani et al., 2017; Sawosz et al., 2009).

Toxicity of nanoparticles

The literature has addressed the problem of serious interference of metal nanoparticles introduced into the animal organism in physiological and metabolic processes, including the toxicity risk. The results of research conducted in this field are characterised by high variability, from optimistic reports indicating their beneficial effect on e.g. the immune system of animals to disturbing results implying their toxic activity reflected in e.g. accumulation of these compounds in internal organs (Hendrickson et al., 2016; Najafzadeh et al., 2013; Park et al., 2010). The mechanism of the potential danger of toxicity usually associated with high concentrations of nanoparticles has not been fully elucidated yet despite the attempts to clarify this issue. A majority of toxicological studies have been conducted in *in vivo* rodent models due to the similarity of their biochemical and physiological pathways to human metabolism (Houtkooper et al., 2011). Histopathological analyses have revealed dose- and time-dependent cytotoxicity of nanoparticles. Its mechanism is related to oxidative stress, lipid peroxidation, cell membrane damage, and oxidative DNA damage (Lin et al., 2009; Najafzadeh et al., 2013).

In the era of the great interest in the potential of using silver nanoparticles in the animal production sector, mainly as an alternative to antibiotics and chemotherapeutics, the aspect of their toxicity is also increasingly being analysed. There are disturbing reports on the possible Ag accumulation in animal tissues (Table 2). Park et al. (2010) have detected deposition of Ag in the brain, lung, liver, kidney, and testis of mice. The accumulation intensity increased with the decreasing size of the

silver nanoparticles (22–71 nm). This phenomenon was not observed in mice loaded with large-size silver nanoparticles (323 nm). A similar relationship was noted in the elevation of the levels of cytokinins IL-1, IL-6, IL-4, IL-10, IL-12, and TGF-β and enhanced B-lymphocyte distribution and production of lymphocytes and IgE. In rat experiments, Hendrickson et al. (2016) have demonstrated that both single and repeated administration of 12 nm silver nanoparticles resulted in accumulation of silver in the liver, kidneys, spleen, stomach, and small intestine (Table 2). Nevertheless, the silver concentrations detected in the tissues were significantly lower than the administered doses (<99%), which may indicate effective removal of the element from the organism. Authors agree that nanosilver can be absorbed from the gastrointestinal tract into the bloodstream and induce organ toxicity and inflammatory reactions despite the absence of evident pathomorphological abnormalities. An increase in the activity of anti-inflammatory cytokinins in animal defence response to silver nanoparticles has been reported by Chen et al. (2017) and Pineda et al. (2012) (Table 2). In turn, Williams et al. (2015) have demonstrated reduced expression of important immunomodulatory genes, including MUC3, TLR2, TLR4, GPR43, and FOXP3, especially at rat exposure to smaller sizes (10 and 75 nm) and lower doses of silver nanoparticles (9 and 18 mg/kg).

Table 2. Effect of silver and zinc nanoparticles on the immune system and their accumulation in animals' internal organs

Experimental conditions	Nanoparticle dose	NPs characterization	Effect on the animal organism	References
1	2	3	4	5
Silver nanoparticles				
Mice for 14 days	1 mg/kg body weight	22 nm, 42 nm, 71 nm and 323 nm	Ag accumulation in the brain, lung, liver, kidney, and testis ↑, B cell distribution in lymphocytes ↑ (small-size AgNP), Ag accumulation in tissues (large-size AgNPs) ↔	Park et al., 2010
Mice for 28 days	Repeated-dose toxicity 0.25 mg/kg, 0.50 mg/kg, 1.00 mg/kg body weight	42 nm	cytokines: IL-1, IL-6, IL-4, IL-10, IL-12 ↑, TGF-β ↑ B cell distribution in lymphocyte ↑, IgE ↑	Park et al., 2010
Broiler chicken in period 7–35 days	0, 10 and 20 mg/kg	colloidal silver, 2–35 nm	IgG ↑	Pineda et al., 2012
Sprague-Dawley rats (both male and female) for 13 weeks, administered twice daily.	9, 18 and 36 mg/kg body weight/day, 100, 200 and 400 mg/kg body weight/day silver acetate	10, 75 and 110 nm	expression of immunomodulatory genes: MUC3 ↓, TLR2 ↓, TLR4 ↓, GPR43 ↓, FOXP3 ↓	Williams et al., 2015

Table 2 – contd.

1	2	3	4	5
Rats for 30 days	12 mg/kg of body weight	non-coated silver nanoparticles, 12 nm	silver accumulation in the liver, kidneys, spleen, stomach, and small intestine ↑	Hendrickson et al., 2016
Male CD-1 (ICR) mice in period 7 days	2.5 mg/kg body weight	no information	inflammatory cytokines: IL-1β, ↑ IL-6↑, TNF-α ↑	Chen et al., 2017
		Zinc nanoparticles		
Mice	1, 2, 3, 4, 5 g/kg body weight	20 nm and 120 nm powder of ZnO	Zn accumulation in the bone, kidney, and pancreas ↑; pathological damage in the stomach, liver, heart, and spleen (120 nm ZnO); blood viscosity ↑	Wang et al., 2008
Fishes	no information	no information	superoxide dismutase ↑, metallothionein ↑, heat shock protein ↑	Wong et al., 2010
Fishes (zebrafish)	5 mg/L	ZnO, a bulk ZnO suspension, Zn^{2+}, 30 and 500 nm	Zn accumulation in the stomach and liver ↑ malondialdehyde ↑, gut tissues exhibited oxidative effects after exposure	Xiong et al., 2011
Sheep for 25 days	20 mg/kg body weight	25 nm	Zn accumulation in the liver and kidney ↑ alkaline phosphatase ↓, creatinine ↑, cell swelling, eosinophilic necrosis of hepatocytes, and multifocal interstitial nephritis were also observed	Najafzadeh et al., 2013
Weanling piglets	120 mg/kg	ZnO, 142 ± 15 nm	IgG ↑, γ-globulin ↑	Li et al., 2016

NPs, nanoparticles; ↑, increase; ↓, decrease; ↔, no effects.

The literature provides reports on the neurotoxicity of silver nanoparticles. Skalska et al. (2015) conducted research on the administered silver nanoparticles to rats for two weeks and showed ultrastructural changes in the brain. The authors described blurred synapse structure and strongly enhanced density of synaptic vesicles clustering in the centre of the presynaptic part. Disturbed synaptic membrane leading to liberation of synaptic vesicles into neuropil, which implies strong synaptic degeneration, was a characteristic feature observed under the nanosilver exposure. These observations may indicate malfunction of the nervous system and, in the case of the hippocampus, impairment of cognitive processes.

Research on the potential toxicity of nanoparticles also includes zinc compounds. A reported by Xia et al. (2008), zinc oxide nanoparticles were found to induce toxicity towards cells leading to production of free radicals and causing oxidative injury,

inflammatory excitation, and cell death. However, the first disturbing signal, as in the case of silver, is the accumulation of Zn in animal tissues and organs. Accumulation of this element in the bone, kidney, and pancreas in mice has been observed by Wang et al. (2008) (Table 2). The 120 nm ZnO nanoparticles used by the authors induced pathological changes in the stomach, liver, heart, and spleen, whereas the 20 nm nanoparticles caused adverse changes in the liver, spleen, and pancreas. The authors have concluded that these organs and bones are the targets at an oral exposure to ZnO nanoparticles. Similar results were obtained in experiments on fish and sheep. In addition to enhanced accumulation of this element in internal organs, doses of zinc nanoparticles with a size not exceeding 30 nm induced oxidative stress in fish gills without oxidative damage and cell swelling, eosinophilic necrosis of hepatocytes, and multifocal interstitial nephritis in sheep (Najafzadeh et al., 2013; Xiong et al., 2011) (Table 2). In response to exposure to doses of 120 mg/kg nano ZnO an average size of 142 nm, piglets' organism triggered body defence reactions by increased secretion of IgG and γ-globulin (Li et al., 2016) (Table 2).

Bactericidal properties

Nanoparticles are characterised by potent bacteriostatic and bactericidal properties (Atiyeh et al., 2007; Arabi et al., 2012; Choi et al., 2008; Diarra et al., 2007; Hwang et al., 2007; Rai et al., 2009). Such features are desirable in the case of feed additives used in animal nutrition. Farm animals kept in large flocks in conditions of intensive livestock production are highly exposed to instability of the gastrointestinal microbiome or bacterial infections, which result in a decline in the production efficiency (Elkloub et al., 2015; Kiczorowska et al., 2016 b; Milani et al., 2017). The bactericidal properties of nanoparticles, compared with large particles, are associated with the greater surface area available for interactions with the bacterial surface (Adams et al., 2006). The antibacterial effects of nanoparticles mainly depend on their size, concentration, accompanying and coating substances, or the substrate (Arabi et al., 2012). However, the actual mechanism of penetration of nanoparticles across the bacterial cell wall is not fully known and the literature proposes various explanations for this issue. As reported by Rajendran et al. (2010), ions released from the nanoform react with the thiol groups of proteins present on the cell surface and involved in nutrient transport. Nanoparticles can inactivate proteins, thereby reducing membrane permeability and finally leading to cell death.

Silver nanoparticles exhibit unique bacteriostatic and bactericidal properties. At the atomic level, silver has the ability to absorb oxygen and acts as an oxidation catalyst. Atomic oxygen absorbed on the silver surface reacts with the thiol groups surrounding the surface of bacteria and viruses and removes hydrogen atoms. The bacterium loses respiration ability by disruption of the so-called respiratory channel, which results in bacterial death (Hartemann et al., 2015). Observations of proteomic changes on the surface and inside bacterial cells were conducted by Lok et al. (2007). They found that short-term exposure of *E. coli* cells to silver nanoparticles (average diameter – 9.3 nm) resulted in an accumulation of envelope protein precursors, indicative of the dissipation of proton motive force. This destabilized the outer cell membrane and reduced its potential and the level of intracellular adenosine triphos-

phate, thus impairing its function. The catalytic properties of silver and the presence of active oxygen contribute to oxidation of the genetic material of bacteria and viruses. The mechanism of nanosilver binding with bacterial DNA is not yet fully understood; however, it is known to prevent DNA chain unfolding without damaging hydrogen bonds, which impedes replication and inhibits bacterial multiplication (Cui et al., 2013; Lara et al., 2009; Li et al., 2011; Padmavathy and Vijayaraghavan, 2008; Yang et al., 2009).

Given their non-specific mode of action towards bacteria, nanoparticles are regarded as antimicrobial agents without the risk of developing bacterial resistance. The total inhibition of bacteria depends on the concentration of nanoparticles, their size, and the number of bacterial cells (Arabi et al., 2012).

Nanosilver exerts bactericidal effects against many species of human bacteria (Kim et al., 2008; Taglietti et al., 2012) and their veterinary counterparts (Sawosz et al., 2010; Smekalova et al., 2016; Soltani et al., 2009), including highly resistant strains, such as methicillin-resistant *Staphylococcus aureus* (Lara et al., 2009). The literature emphasizes that the antimicrobial efficiency of silver nanomaterials depends on the individual characteristics of bacterial strains. In *in vitro* tests of silver nanocomposites, Kędziora et al. (2013) confirmed their potent bactericidal properties against *Staphylococcus aureus, Escherichia coli*, and *Klebsiella pneumonia* and Gram-negative bacteria, and slightly weaker activity against Gram-positive bacteria. Similarly, other researchers observed a broad spectrum of antibacterial activity against Gram-negative bacteria, including *Acinetobacter*, *Escherichia*, *Pseudomonas*, *Salmonella*, and *Vibrio* (Wijnhoven et al., 2009; Varner et al., 2010). Investigations conducted by Shrivastava et al. (2007) confirm the clear bactericidal effect of silver particles (10–15 nm in size) on Gram-positive bacteria, such as *Bacillus*, *Clostridium*, *Enterococcus*, *Listeria*, *Staphylococcus*, and *Streptococcus*. In human medicine, nanosilver has been applied for wound dressing, impregnation of catheters, as implants, and in surgical mesh (Antonelli et al., 2012; Nistico et al., 2015; Nirmala et al., 2010; Wu et al., 2014). Most silver-based products for animals are designed for surface disinfection, but some preparations are used as drops, ointments, sprays, or gels to suppress bacterial infections. The most effective recent disinfectants include aqueous solutions of metallic silver containing 10^{-12}m particles embedded in different silica or polymer carriers. They provide the products with durable antibacterial, fungicidal, and antistatic properties with efficacy up to 99%. 1 cm^3 of a 1 ppm solution contains approximately 600×10^{-12} silver particles (Wzorek and Konopka, 2007).

Silver nanoparticles are also used as prebiotics in animal nutrition (Fondevila et al., 2009). The authors used a colloidal form of metallic silver as an additive in diets for weaned pigs in a dose of 20 and 40 mg/kg to limit the occurrence of diarrhoea and provide the gastrointestinal microbiome with probiotic reinforcement. The authors observed a linear trend in the reduction of the *E. coli* concentration in the ileum and an unchanged level of lactobacilli. Still, the application of silver nanoparticles is associated with some concerns about its role as an effective antibacterial agent acting selectively on pathogens but not on the beneficial gastrointestinal microflora, a possible toxic effect on animals (and indirectly on the human consumer), and the

risk of environmental pollution (Chen et al., 2013; Dos Santos et al., 2014; Speed et al., 2015).

Zinc oxide in the nano form exhibits strong antibacterial activity towards a broad bacterial spectrum. The antibacterial mechanism of its action has not been fully elucidated, as in the case of silver nanoparticles. One of the mechanisms of the action of zinc oxide may involve photocatalytic production of reactive oxygen species, which lead to cell membrane disorganization and bacterial growth inhibition. Nano zinc oxide releases zinc ions in contact with moisture. Researchers suggest that zinc ion binding by microbial membranes can prolong the lag phase, i.e. stagnation in the microbial growth cycle (Seil and Webster, 2012; Zhang et al., 2007). Moreover, zinc oxide nanoparticles can penetrate the bacterial cell and cause cell damage through interactions with sulphur- and phosphorus-containing compounds, e.g. DNA (Arabi et al., 2012). In their *in vitro* investigations of the effect of zinc oxide nanoparticles (size: 70 nm, dose: 12 mmol l^{-1}) on *E.coli* bacteria, Liu et al. (2009) observed complete inhibition of the growth of these microorganisms. The authors detected damage to the bacterial cell membrane resulting in leakage of intracellular contents and cell death. However, the structures of nucleic acids were not damaged. Yousef and Danial (2012) analysed *in vitro* the impact of zinc oxide nanoparticles on bacterial colonies of *Bacillus subtilus*, *Bacillus megaterium*, *Staphylococcus aureus*, *Sarcina lutea*, *Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella pneumoniae, Proteus vulgaris*, *Candida albicans*, and *Aspergillus niger* and found good bacteriostatic effects but a weak bactericidal effect.

Influence of nanoparticles on the gastrointestinal tract of animals

In animal production, silver and zinc nanoparticles may exert an effect on intestinal microbial populations and improve the health and immunological status of the animals (Table 3). This can provide animals with an opportunity to expend less metabolic effort for immunological control purposes and to use surplus nutrients for other physiological and productive purposes. Furthermore, it is speculated that nanoparticles, as a carrier of available oxygen, could be also a potent modifier of metabolism. Nanoparticles can be deposited at the tissue and cell level via *in ovo* injection and it is possible that the oxygen that accumulates in the octahedral holes of nanoparticles may increase anabolic activity and subsequently stimulate growth and development. Moreover, the *in vivo* method of introducing nanoparticles could be a valuable technique for earlier establishment of animals' immunity and intestinal integrity, which are essential to reach maximum potential for growth and feed efficiency (Ferket, 2011; Pineda et al., 2012).

In ovo studies carried out by Fondevila et al. (2009), in which 20 and 40 ppm of metallic silver nanoparticles were applied in weaned piglets, confirmed reduction in coliform bacteria in ileal contents. Besides, although the concentrations of major bacterial groups in the ileum of pigs were not markedly affected, the concentration of the pathogen *Clostridium perfringens/Cl. histolyticum* group was reduced by 20 ppm of silver. Pineda et al. (2012) analysed the influence of *in ovo* injection of silver nanoparticles on the microbial profile in Ross 308 broiler chicken (Table 3). The authors observed strong antimicrobial activity of silver nanoparticles *in vitro*.

However, the results of *in vivo* investigations demonstrated reduced antibacterial activity of nanosilver against some bacterial species, e.g. lactic acid bacteria and lactose-negative enterobacteria. The differences in the *in vivo* and *in vitro* activity of silver nanoparticles were explained by the large variation and number of intestinal microbiome species. The authors confirmed the hypothesis that silver nanoparticles can exhibit higher antimicrobial activity in poultry reared in stressful conditions, e.g. at a high level of pathogenic bacteria.

Table 3. Effect of nutritional supplementation with nanoparticle metals on animal intestinal microbiome

Experimental conditions	Nanoparticle dose	NPs characterization	Bacterial groups	Reference
Silver nanoparticles				
Japanese quail in period 12 days	0, 5, 15, and 25 mg/kg added to drinking water	no information	*Lactobacillus* spp. ↑, *Leuconostociactis* ↑, *Antinomycesnaeslundii* ↑ at the dose 25 mg/kg	Sawosz et al., 2007
Broilers chicken in ileum, and cecum	0, 10, 20 mg/kg	colloidal silver, 2–35 nm	anaerobic bacteria ↔, lactic acid bacteria ↓, lactose-negative bacteria ↔, coliform bacteria ↔, *Enterococcus* ↑, *Clostridium perfringens*↔,	Pineda et al., 2012
Hubbard broiler chicken for 7–35 days	2, 4, 6, 8, 10 ppm/kg	no information	*E.coli* ↓, *Lactobacillus* ↔,	Elkloub et al., 2015
Sprague-Dawley rats (both male and female) for 13 weeks, administered twice daily	9, 18 and 36 mg/kg body weight/day, 100, 200 and 400 mg/kg body weight/day of silver acetate	10, 75 and 110 nm	Gram-negative bacteria↑, *Firmicutes* ↑, *Lactobacillus*↓	Williams et al., 2015
Mice for 28 days	10 mg/kg body weight/day	PVP and Citrate coatings, 20, 110 nm	gut microbiome ↔	Wilding et al., 2016
Male CD-1 (ICR) mice in period 7 days	2.5 mg/kg body weight	DSS, Ag TiO_2 and SiO_2, 12.2±3.0, 10.8±1.7, 16.8±1.8 nm	*Alistipes*, ↑ *Bacteroides*↑, *Prevotella*↑ *Lactobacillus* ↓	Chen et al., 2017
Zinc nanoparticles				
Cattle (Holstein Friesian) – rumen fermentation pattern	50, 100, 200, 400 mg/kg of dry matter	no information	ruminal microorganisms ↑	Zhisheng, 2011

Table 3 – contd.

1	2	3	4	5
Weaned pigs in period 1–35 days	15, 30, 60 mg/kg	ZnO, 70±38.6 nm	in jejunum: *Enterococcus* spp. ↔, *Escherichia coli*↔, *Lactobacillus* spp. ↔, in cecum: *Enterococcus* spp. ↔, *Escherichia coli*↔, *Lactobacillus* spp. ↑ (30 mg/kg)	Milani et al., 2017

NPs, nanoparticles; ↑, increase; ↓, decrease; ↔, no effects.

There are literature reports in this research area about a neutral or even unfavourable effect of supplementation with metal nanoparticles on the animal microbiome. In investigations of broiler chickens supplemented with nanosilver doses, Pineda et al. (2012) reported reduction of the abundance of lactic acid bacteria and a nearly neutral effect on the other species of microorganisms analysed. In turn, a study on rats conducted by Williams et al. (2015) showed that the addition of silver nanoparticles to the feed caused changes in the microbial population in the ileum. There was a clear induced shift in the intestinal microflora towards greater abundance of Gram-negative bacteria (Table 3). Concurrently, the expression of important immunomodulatory intestinal genes was reduced. The authors confirmed that oral exposure to nanosilver changes the mucous membrane microbiome and modulates the intestinal immune response and the overall intestinal homeostasis.

The literature in this field provides many reports on the impact of zinc nanoparticles on animal microbiome. In investigations of the effect of nano zinc oxide administered in doses of 15, 30, and 60 mg (70 ± 38.6 nm) on weaned pigs, Milani et al. (2017) observed stabilisation of the intestinal microbiome and limitation of diarrhoea (Table 3).

Summary

The use of nanoparticles as supplements of animal diets has not always yielded unambiguous results. The beneficial effect of nanoparticles used in animal production was most frequently observed in such parameters as weight gain, average daily gain, or improvement of the FCR value. In some cases, the effect of nanoparticle addition to diets was indiscernible in terms of measurable animal production parameters and health status indices. Metal nanoparticles had higher antibacterial activity than their larger forms, especially against Gram-negative bacteria, including *Acinetobacter*, *Escherichia*, *Pseudomonas*, *Salmonella*, and *Vibrio* and Gram-positive bacteria, such as *Bacillus*, *Clostridium*, *Enterococcus*, *Listeria*, *Staphylococcus*, and *Streptococcus.* Furthermore, metal nanoparticles were found to be more resistant to inactivation by gastric acids. However, pathological changes have been observed in animals, mainly in the pancreas, kidneys, liver, rumen, abomasum, small intestine, adrenal glands, and brain. At the cellular level, nanoparticles were found to induce

toxicity via free radical production, inflammatory excitation, and cell death. Oral administration of nanoparticles was associated with the risk of malfunction of the nervous system and impairment of cognitive processes. The increasing knowledge of their possible toxic effects on the animal organism suggests caution in the use of nanoparticles in animal production and shows the need for further precise research in this area.

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