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Metal particles as trace-element sources: current state and future prospects

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Birds have evolved in direct contact with natural nanoparticles (NPs) that are identical to artificial trace-element NPs. This relationship, the high action potential and their ability to reduce environmental pollution make NPs a promising component of bird diets. However, from available published studies there is no unity in justifying the applied dosages of NPs and their calculations. NPs are used in the studies in various doses, for example: Cu 0.5-50 mg/kg, Ag 10-1000 mg/kg, Se 0.2-5 mg/kg, Cr 500-1500 ppb. Therefore, universal approaches and criteria of NP investigations are necessary for the establishment of their use in feed.

The mechanisms of action of the trace elements in artificial NPs in birds vary from the those of ionic forms of trace elements, which determine the differences in the productive effect. According to data from different authors, chickens receiving NPs in feed have higher chickens body weight by 13-24%. Such benefits have increased interest in sources of trace-element NPs significantly over the past two decades. The design of trace-element NPs has led to promising developments in the safe use of NPs for poultry nutrition, such as coating NPs with inert substances and adjusting their size. However, constraining circumstances determined by the difficulty of predicting the toxic properties of nanostructures exist, even though artificial trace-element NPs are a relatively safe class of nanostructures due to their production requirements, and metal NPs are already used in human food and medicine. The following review discusses the benefits and potential hazardous effects of NPs and the possibility of using them as feed supplements for poultry.

Keywords: nanoparticles; trace elements; biological availability; safety; fodders; poultry nutrition

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Introduction

According to some estimates, nanotechnology developments have the potential to create industries that will employ approximately six million people and have a US$3 trillion market by 2020 (Roco, 2011). Currently, more than one hundred thousand tons of NPs are produced each year (Makarov, 2014). The term 'nanomaterial' refers to a natural, incidental or manufactured material containing 50% or more of unbound, aggregated or agglomerated NPs with one or more external dimensions in the size range of 1-100 nm (European Commission, 2013). NPs are increasingly used in biology and medicine as contrast agents in magnetic resonance imaging (Weinstein *et al.*, 2010), as bactericidal agents (Ahrari *et al.*, 2015), for targeted drug delivery and in various disease treatments (Wahajuddin and Arora, 2012). NPs are used to examine the tomography of neoplasms and thrombi (Liu *et al.*, 2014; Pan *et al.*, 2011). The number of works with the keyword 'nanoparticle' has increased more than 6-fold over the last 10 years and has exceeded 143,000 references (www.hcbi.nlm.nih/gov).

The unique applications for NPs are largely determined by their extraordinary biological properties. Their small size, ability to penetrate tissues and organs and high surface area (Barbu *et al.*, 2009; Dominguez *et al.*, 2014) result in previously unknown biological effects, and these characteristics allow fundamentally new and unparalleled technologies to be developed.

Understanding the properties of NPs has resulted in special interest in using NPs for livestock breeding. They could potentially be used as sources of trace elements (Miroshnikov *et al.*, 2015), feeding *in ovo* (Sawosz *et al.*, 2012), to optimise the intestinal microflora of animals (Fondevila *et al.*, 2009), as immunostimulants (Wang *et al.*, 2011), growth stimulants (Yausheva *et al.*, 2015) to improve feed efficiency (Wang *et al.*, 2004; 2012; 2014), reproductive ability (Safa *et al.*, 2016) and reduce the harmful effects of mycotoxins in poultry (Kim *et al.*, 2012).

One increasing area of NP use is veterinary medicine. NPs are expected to be widely used as antibiotics in the future (Wang *et al.*, 2017) as they have a wide range of antibacterial properties against Gram-positive and Gram-negative bacteria. For example, gold (Au) NPs suppress *Staphylococcus spp.* colonisation, and silver (Ag) NPs have antimicrobial activity against *E. coli* and *Pseudomonas aeruginosa* (Pineda *et al.*, 2012a; Ramalingam *et al.*, 2016). Other developments include using silica NPs to improve vaccine protection (Cheng *et al.*, 2017), polyrhodanine NPs to fight against Newcastle disease in poultry (Nazaktabar *et al.*, 2017) and AuNPs to diagnose influenza in birds (Emami *et al.*, 2012). It is thought that the use of NPs will allow livestock products to be produced more efficiently (Verma *et al.*, 2012).

The following review is devoted to assessing the current situation and future prospects of using NPs as sources of important metals in poultry nutrition (*Tables 1, 2 and 3*).

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Table 1 The use of nanoparticles *in ovo* injection and nutrition.

Species	Characteristics of nanoparticles	Delivery type, dose and concentration	Effect and conclusion	References
Chicken embryos	Silver nanoparticles (AgNano)	15 µg/egg; on days 7 and 18 of incubation	Modulation of the post-hatch immune response without affecting the hatchability, growth and other performance parameters in broilers.	Goel *et al.*, 2017
Chicken embryos	Copper nanoparticles (Cu-NP)	50 mg/kg	*In ovo* injection of Cu-NPs might improve broiler performance more efficiently than the injection of $CuSO_4$ or the provision of Cu-NPs and/or $CuSO_4$ in drinking water.	Scott *et al.*, 2018
Chicken embryos	Silver nanoparticles (AgNano)	15 mg	AgNano can act as a metabolic enhancer but not as a growth promoter. AgNano alone or in combination with amino acids administered *in ovo* improved the immune status of embryos and thus can act as a potential agent for the enhancement of innate and adaptive immunity in chickens.	Bhanja *et al.*, 2015
Chicken embryos	Nanoparticles of diamond (ND), l-glutamine (Gln), and the bio-complex of Gln with ND (Gln/ND)	50 mg/l	The bio-complex of glutamine and diamond nanoparticles may accelerate the growth and maturation of muscle cells.	Grodzik *et al.*, 2013
Chicken embryos	Hydrocolloid of nano-Au (50 mg/L) obtained from Nano-Tech (Warsaw, Poland), diameter 5-70 nm	500 µl at a concentration of 50 mg/l	The treatments did not adversely affect the mortality, organ weight, and homeostasis of the embryos. HS stimulated the development and maturation of breast muscle by increasing the number of nuclei, satellite cells, and muscle fibres and affected the expression of basic fibroblast growth factor-2 as well as paired-box transcription factor-7. Furthermore, the nano-Au+HS complex contributed to the increased number of myocytes and nuclei in chicken embryo muscles.	Zielinska *et al.*, 2011
Chicken embryos	copper nanoparticles (NanoCu), Nanotech, Warsaw, Poland, 5 to 70 nm, with an average size of 37 nm	0.3 ml at 50 mg kg^{-1}	Weight gain, high percentage of pectoral muscles and leg muscles, decrease in mortality.	Mroczek-Sosnowska *et al.*, 2016

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Table 1 Continued

Species	Characteristics of nanoparticles	Delivery type, dose and concentration	Effect and conclusion	References
Chicken embryos (Ross 308)	Solutions of silver nanoparticles (Ag), a complex of silver nanoparticles with hydroxyproline (AgHyp)	Water solution of diet	Ag and the AgHyp complex significantly up-regulated the expression of the FGF-2 at the mRNA and protein levels; AgHyp significantly increased blood vessel size, cartilage collagen fibre lattice size and bundle thickness; AgHyp treatment may help to build a stronger and longer lasting form of collagen fibres.	Beck *et al.*, 2015
Broiler and layer embryos	Nanoparticles of silver (AgNano) and gold (AuNano)	Water solution of diet	The metabolic rate of AgNano-injected layer embryos was significantly increased. AgNano could be a potential metabolic modifier for layer embryos.	Pineda *et al.*, 2012b
Broiler chickens and embryos	Nanoparticles of colloidal silver (AgNano)	Water solution in two concentrations (10 and 20 ppm) of diet	AgNano application in poultry feeding influences the expression of FGF2 and VEGFA genes on the mRNA and protein levels in growing chickens.	Hotowy *et al.*, 2012
Broiler chickens and embryos	Nanoparticles of silver (Nano-Ag)	Water solution of diet	Nano-Ag up-regulated the expression of FGF2, VEGF, and ATP1A1 and also up-regulated the expression of myogenic differentiation 1(MyoD1), thus affecting cell differentiation. The results indicate that ATP and Nano-Ag may accelerate the growth and maturation of muscle cells.	Sawosz *et al.*, 2013

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Table 2 The use of nanoparticles in nutrition.

Species	Characteristics of nanoparticles	Delivery type, dose and concentration	Effect and conclusion	References
Broiler chickens	Silver nanoparticles (AgNano)	10 and 20 mg/kg drinking water from day 7 to 36 post-hatching	AgNano affects N utilization and the plasma IgG concentration; however, it does not influence the microbial populations in the digestive tract, the energy metabolism and growth performance of chickens.	Pineda *et al.*, 2012c
Broiler chicks (Ross strain)	Commercial nanocompound, Nanocid (Nano Nasb Pars Co., Iran)	2500 ppm in basal diet	Nanocid diminishes the inhibitory effects of aflatoxin.	Gholami-Ahangaran and Zia-Jahromi, 2013
Broiler chickens	Commercial nanocompound, Nanocid (Nano Nasb Pars Co., Iran)	2500 ppm in basal diet	Nanocide reduces the adverse effects of aflatoxin on blood parameters in chickens suffering from aflatoxicosis.	Gholami-Ahangaran and Zia-Jahromi, 2014
Broiler chickens	Copper nanoparticles	0.5, 1.0 or 1.5 mg/kg body weight per day, three 3-day periods (days 8-10, 22-24 and 36-38) or three 7-day periods (days 8-14, 22-28 and 36-42)	It is possible to simultaneously increase the antioxidant and immune defence of chickens by supplementing their diets with copper nanoparticles-up to 12 mg per bird during 6 weeks of feeding, that is to a level no more than 7% over the NRC recommendation for growing broiler chickens.	Ognik *et al.*, 2017
Broilers chickens (Ross 308)	Chromium nanoparticles (nano-Cr)	500, 1000 and 1500 ppb of diet	Improvement in the performance index and antibody titres against AI and IB under heat stress conditions in broiler chickens.	Hajializadeh *et al.*, 2017
Broilers chickens	Copper nanoparticles (NanoCu)	-	Increase in the weight and volume of the femurs, increases their resistance to fracture and cracks.	Mroczek Sosnowska *et al.*, 2017
Broiler chickens	Combination is colloidal silver with nanoside in drinking water	0, 10, 20, 30, 50, and 70 ppm	Negative effects of high dose silver nanoparticles on cardiac structure and function in chickens. In addition, the survey results showed that the most important changes in cardiac parameters can be due to decreased cardiac contractility that probably has occurred due to toxicity with a high dose of nano-silver.	Raieszadeh *et al.*, 2013

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Table 2 Continued

Species	Characteristics of nanoparticles	Delivery type, dose and concentration	Effect and conclusion	References
Broiler chickens	Silver nanoparticles (AgNPs)	1000 mg/kg AgNPs the drinking water	Oxidative stress, significant decrease in the body weights of the broilers.	Song *et al.*, 2017
Broiler chicks	Selenium nanoparticles (Se NPs), spherical in shape with sizes of less than 100 nm	0.6 mg per kg of feed	The activity of the cellular, humoral immune response and enzymatic as well as non-enzymatic antioxidants has been significantly decreased as a result of EFX treatment.	Shirsat *et al.*, 2016
Broiler chicks	Zinc-nano-sulphate, zinc-nano-methionine and zinc-nano-max, nanochelating technology	80 mg/kg of diet	Delivery of zinc in the structure of zinc-nano-methionine and zinc-nano-max at concentrations of 80 mg/kg of diet improves growth performance. However, dietary zinc-nano-sulphate decreased growth performance in broilers.	Mohammadi *et al.*, 2015
Broiler chicks	Selenium nanoparticles (nano-Se)	0.2 mg/kg and 0.5 mg/kg	Se supplementation remarkably improved daily weight gain and survival rate and decreased the feed conversion ratio.	Wang, 2009

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Table 3 The use of nanoparticles in vaccination and treatment.

Species	Characteristics of nanoparticles	Delivery type, dose and concentration	Effect and conclusion	References
Broiler chickens	NP-EmaxIMP1 (20 nm polystyrene NP+Recombinant EmaxIMP1)	Oral inoculation	Reached deeper tissues within hours of oral inoculation and elicited complete to partial immunity against E. maxima challenge infection.	Jenkins *et al.*, 2018
Male broiler chickens (Ross 308)	Silver nanoparticles (AgNP), Nano-Tech, Warsaw, Poland; size of 3.5 nm, average surface area was 2.827×10^{-13} cm^2	50 ppm, in the drinking water	The application of AgNP reduced broiler growth, impaired immune functions and had no antibacterial effect on different intestinal bacterial groups, which may limit the applicability of AgNP against *C. jejuni* in broiler chickens.	Vadalasetty *et al.*, 2018
Chickens	Lactide-co-glycolidenanoparticle (NP) encapsulated outer membrane proteins (OMP) of C. jejuni.	25, 125, or 250 μg, subcutaneous (s/c) and oral	The s/c route of vaccination with or without NP-encapsulated OMP of *C. jejuni* may serve as a candidate vaccine for control of *C. jejuni* colonization in chickens.	Annamalai *et al.*, 2013
Broiler chickens	Silica nanoparticles adjuvant for vaccine applications comprised of gp85	-	The silica nanoparticles can effectively improve the protection of the gp85 vaccine against ALV-J and present a better performance than Freund's adjuvant.	Cheng *et al.*, 2017
APEC-infected, COBB 500 broiler chicks	Chitosan nanoparticle-encapsulated ΦKAZ14 (C-ΦKAZ14 NPs)	0.2 ml of diet	Decreased mortality from 58.33 to 16.7% with an increase in the protection rate from 42.00 to 83.33% and improved the body weights of the infected chicks. The encapsulation of bacteriophages could enhance bacteriophage therapy and is a valuable approach for controlling APEC infections in poultry.	Kaikabo *et al.*, 2017

Use of trace-element NPs

The preparation of NPs is one method to increase the bioavailability of food components (Rein *et al.*, 2013; Raspopov *et al.*, 2011). The desire to use metal NPs is based on their lower toxicities in comparison with those of traditional trace-element sources. For example, ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Inc., Cambridge, MA, USA), which contains ultra-small superparamagnetic iron oxide (USPIO) NPs, was approved by the US Food and Drug Administration (FDA) (US Department of Health and Human Services, 2011) as an iron-replacement therapy for patients with chronic kidney disease (Kowalczyk *et al.*, 2011) and magnetic resonance imaging is indirectly used for various applications (Weinstein *et al.*, 2010).

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A number of studies have shown the superiority of developed NP preparations over mineral salts and organic forms for feeding poultry. A comparison of selenium NPs with some selenium compounds (sodium selenite, selenomethionine, methylselenocysteine) shows that NPs have significantly lower acute, short-term and sub-chronic toxicities (Zhang *et al.*, 2008b; 2011; Zhang, 2009) and greater efficiency for increasing selenoenzyme generation (Wang *et al.*, 2007). Selenium NPs appear to be more effective than either sodium selenite and selenomethionine for increasing the activity of glutathione S-transferase (GST) (Zhang *et al.*, 2008a), which ultimately determines their use as trace-element sources. The high efficiency of selenium NPs in animal nutrition allows increases in the growth rates and feed conversion rates of chickens (Zhou and Wang, 2011; Jin *et al.*, 2016).

References exist for the use of other trace elements for feeding poultry, including iron (Nikonov *et al.*, 2011), chromium (Zha *et al.*, 2009), zinc (Zhao *et al.*, 2016), copper (Ognik *et al.*, 2016) and antagonist metals (Miroshnikov *et al.*, 2015). High absorption in the intestine and low excretion with faecal matter allows a reduction in the amounts of minerals added to the diet of animals. In China, this has been shown to reduce environmental pollution (Tang *et al.*, 2016).

Use of trace-element NPs *in ovo* feeding

Trace-element NPs are promising for creating a feeding reserve in chicks before they begin eating feed by means of *in ovo* feeding (Uni and Ferket, 2003). Studies have shown that NPs of zinc, copper, and selenium are not harmful to embryos, and can be used to improve the post-natal performance of broilers (Joshua *et al.*, 2016; Wang *et al.*, 2011) and increase hatchability (Bakyaraj *et al.*, 2012).

In ovo injections of Cu-NPs can more efficiently increase broiler chicken productivity than $CuSO_4$ injections (Scott *et al*., 2018) and improve the mechanical strength of bone tissue, preventing weak bones often seen in broiler chickens (Mroczek-Sosnowska *et al.*, 2017), Ag-NPs affect the morphology of the pectoral muscles (Sawosz *et al.*, 2012). Others (Huang *et al.*, 2009) have confirmed the potential of NPs to increase the mineral density of bone tissue.

The more multifaceted action of NP trace elements from mineral salts (Wang, 2009; Sizova *et al.*, 2016b; Hajializadeh *et al.*, 2017) and organic compounds has been demonstrated, which is due to the mechanisms of action in poultry (Mohammadi *et al.*, 2015; Scott *et al.*, 2018).

NP mechanisms of action in poultry

Birds have always been in contact with NPs, and this interaction has been proven by data that show 1 m^3 of atmospheric air contains up to 1 million suspended particles with diameters ranging from 0.001 to 1000 μm. Fresh and salt water contain 5-6 million particles per dm^3, and soil contains the most significantly dispersed systems (Yushkin, 2007; Kravchyshyn, 2010).

Close contact with natural NPs during their long evolution has allowed birds to adapt to these conditions. Natural NPs (nanoclays, organic matter in soil, lipoproteins and exosomes) are often biocompatible and do not affect animals and humans (Stanley, 2014). By introducing synthetic trace-element NPs into feed, the bird's evolutionarily formed response is obtained. Synthetic preparations of NPs affect the physiological and productive features of birds differently compared to mineral salts and organic forms.

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These effects are determined by the absorption mechanisms of trace elements and changes in metabolism caused by intake of NPs. In addition to the absorption of the ionic form of a mineral from metal NPs (Choi and Choy, 2014; Baek *et al.*, 2012), a significant portion enter the body in an unchanged form (Oberdörster *et al.*, 2005; Jain *et al.*, 2008).

Other mechanisms exist for the cellular absorption of metal NPs in comparison with soluble forms (Aslam *et al.*, 2014). Iron in complex aggregates can be absorbed by endocytosis in the cells lining the intestine, *e.g.* ferritin, which comes from plants. Ferritin can contain several thousand ferric atoms (Harrison and Arosio, 1996; Liu and Theil, 2005) and soybean ferritin has ~800 ferric atoms (Ragland *et al.*, 1990). The transport mechanism of metal NPs is similar and is implemented through endocytosis (Aslam *et al.*, 2014). The intensity of the absorption process is lower in comparison with that of ionic forms, but this is an advantage that allows microelemental NPs to be considered as alternatives to mineral salts.

The relatively slow release of iron from NPs and its low availability for intestinal microflora (Pereira *et al.*, 2015) may be an advantage in preventing the generation of iron removal systems, which are observed after the absorption of therapeutic doses of soluble iron (Hurrell, 2011; Lomer *et al.,* 2012) and generally limit the iron intake in the body. This phenomenon is partially due to the lower metal-binding capacity of enterocytes after the introduction of NPs in comparison with that of ions (Pereira *et al.*, 2013).

Differences between nano and ionic iron preparations are observed during the systemic transfer of an element within an organism. Thus, along with the ferroportin-mediated transfer (Latunde-Dada *et al.*, 2014), which is similar to that of the ionic forms of iron, some NPs are involved in transformation through macrophages. This is the main distinguishing feature of the mechanism of action of nanoform, trace-element preparations from that of their analogues.

The intake of metal NPs in the body, regardless of the route of administration, is accompanied by an increase in the number of macrophages (Yu *et al.*, 2012; Hamrahi-Michak *et al.*, 2012). The activation of macrophages is accompanied by the synthesis of nitric oxide (NO), and as a consequence, an increase in arginine in the liver. Arginine exchange is closely related to the proliferation of monocytes and lymphocytes through the synthesis of polyamines and protein (Suchner *et al.*, 2002). References in the literature indicate that the activation of arginine metabolism is connected to the development of inflammatory and oxidative stresses (Huang *et al.*, 2008; Mostafavi-Pour *et al.*, 2008).

In addition, the exchange of an entire group of trace elements (Fe, Cu, etc.) is closely related to NO (Weiss *et al.*, 1994). For example, iron affects the expression of inducible NO synthase 2 (Dlaska and Weiss, 1999). NO-induced transcription of Fpn1 reduces the cellular iron content (Nairz *et al.*, 2013) and iron content is reduced by macrophages (Fritsche *et al.*, 2003). In turn, NO is formed due to the oxidation of the terminal guanidine nitrogen atom on L-arginine (L-Arg). This determines the close relationship between the NO production and arginine intake. The formation of physiological levels of NO from arginine may have an indirect positive effect on the productivity of animals (Yausheva *et al.*, 2016), as it is known to have an anti-inflammatory role in the gastrointestinal tract (Li *et al.*, 2007).

As result of a whole complex of biochemical transformations, the introduction of trace-element NPs (Fe, Cu, etc.) into poultry feed is accompanied by an increase in arginine content in the liver (Sizova *et al.*, 2015; Yausheva *et al.*, 2015). This may be a consequence of more broiler growth compared with that achieved with feeding mineral salts (Sizova *et al.*, 2016a).

Arginine is a factor that regulates growth in young animals (Flynn *et al.*, 2002; Wu *et*

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al., 2004). The growth-enhancing effects of L-Arg are associated with a change in the balance of the energy consumed and used for fat burning and a decrease in the production of white fat. L-Arg stimulates mitochondrial biogenesis and the production of brown adipose tissue (McKnight *et al.*, 2010) *et al.*, 2010). Previously, (Fouad *et al.*, 2013) broiler chickens (Cobb 500) showed a decrease in the weight of the abdominal adipose tissue and circulating lipids with dietary L-arginine supplements. The results of studies where the productivity of broiler chickens was increased with additional feeding of arginine NPs (Faddah *et al.*, 2012) confirm the importance of activating the arginine synthesis and may explain the positive effect of trace-element NPs.

However, the use of NPs in feeding is associated with a number of side effects, including the development of oxidative compounds (Møller *et al.*, 2010; Manke *et al.*, 2013; Song *et al.*, 2017) and stimulation of apoptosis (Sizova *et al.*, 2013). For the safe use of NPs in poultry nutrition, new forms are being designed and coated with inert substances, and the size of the NPs is being optimised (Yang *et al.*, 2015) Additional work on the creation of 'green' metal NPs from plants is promising (Kuppusamy *et al.*, 2016; Siddiqi *et al.*, 2016). However, the potential problems with NPs should be considered in detail.

Potential threats of using NPs in poultry nutrition

Further developments of nanotechnology for animal husbandry are aimed at improving the livestock feeding efficiency (Hill and Li, 2017), minimising losses from animal diseases and converting animal by-products into high-value-added products (Sekhon, 2014). However, the prospects of using nanotechnology in livestock are constrained by the difficulty in predicting their nanotoxicology (Bondarenko *et al.*, 2013; Scott *et al.*, 2018). A decrease in growth intensity and immunosuppression in the presence of Ag-NPs (Ahmadi and Kurdestany, 2010; Vadalasetty *et al.*, 2018) as well as a decrease in myocardial contractility and increase in the internal diameter of the left ventricle (Raieszadeh *et al.*, 2013) have been observed in chickens. Most likely, Ag-NPs increase ROS (reactive oxygen species) production and interrupt ATP synthesis, leading to DNA damage and cell cycle arrest at the G2/M phase (Asharani *et al.*, 2008), thus inducing apoptosis (Park *et al.*, 2010; Song *et al.*, 2017). Feeding Mo-NPs and MoO_3-NPs induced an increase in serum aminotransferase activity, oxidative stress, anaemia, and capillary-trophic insufficiency in rats (Sizova *et al.*, 2016b). Pro-oxidant signs, such as increases in the activities of the antioxidant enzymes glutathione reductase and catalase, were seen in *Eisenia fetida* when Mo-NPs were introduced into the soil (Lebedev *et al.*, 2016). Penetrating into the cell, Cu-NPs and Zn-NPs can accumulate, contributing to the excessive production of intracellular ROS, damaging lysosomal membranes, activating caspase-3 and caspase-7, and resulting in apoptosis (Sizova *et al.*, 2013; Lu *et al.*, 2015). ZnO-NPs, in doses customarily added to animal feed, changed the indices of haematology and blood chemistry, altered the expression and activity of hepatic CYP enzymes, and induced pathological changes in liver and kidney tissues of rats (Tang *et al.*, 2016). This is the basis for taking special measures to control NPs. Thus, in the USA, guidelines on the use of NPs in feeds have been adopted (https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf). The European Food Safety Authority (EFSA) has produced a guidance document explaining the data that must be provided for the NPs to be included in feed (Antunović *et al.*, 2011). Products containing NPs should be labelled accordingly (Linsinger *et al.*, 2013). Concerns about nanoscale structures in food and feedstuffs have resulted in the implementation of a number of international research

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projects on the issue, including the NanoRelease Food Additive (NRFA; Szakal *et al.*, 2014a). Further research is needed to define safe NPs that can enter the market (FAO and IFIF, 2010; Belluco *et al.*, 2016.).

Further developments in the synthesis and use of NP feed additives are impossible without detailed studies on toxicity. Artificial trace-element NPs produced according to certain requirements can be viewed as a relatively safe. The basis for this statement is the current practice of including metal NPs in foods (Johnston *et al.*, 2008; Chaudhry *et al.*, 2008; Augustin and Hemar, 2009) and medicine and maximum permitted doses. In particular, for internal use, iron NPs in a bolus dose of 0.16 mmol of Fe/kg of body weight can be used (Neubert *et al.*, 2015).

Controlling the turnover of metal NPs as feed additives is not simple. The evaluation of NPs in feed are complex and multifaceted (Szakal *et al.*, 2014a; 2014b). This has been shown by studies conducted by ten laboratories from countries in the European Union, USA and Canada when the size and concentration of NPs (polyvinylpyrrolidone-stabilised AgNPs) in the homogenates of chicken meat were determined (Weigel *et al.*, 2017).

Conclusions and future prospects

The mechanisms of action of artificial trace-element NPs in birds differ from those of those in their ionic forms, and these mechanisms determine the differences on the positive effect and influence of NP preparations on immunity and other important characteristics in breeding birds. Therefore, interest in NP sources of trace elements has increased significantly over the last two decades. Initially, NP preparations were created for humans and further work was then carried out to create preparations of NP antagonist metals for combined feeding of NPs with amino acids. Regarding the design of trace-element NPs, the development of safe uses for NPs in poultry nutrition seems promising and can be achieved by coating NPs with inert substances, optimising their size, and creating 'green' versions from plants.

However, the potential use of nanotechnology in livestock is constrained by the difficulty of predicting the toxic properties of NPs. Thus, special measures must be taken to control NPs for use in livestock. Meanwhile, only NPs that are synthesised the controlled physical and chemical characteristics (size, surface modification and concentration) can be used to achieve maximum productive results without toxic effects.

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