Transfer and toxicity of silver nanoparticles in the food chain

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Environmental Significance Statement

Silver nanoparticles (AgNPs) are among the largest groups of manufactured nanoparticles present in the environment, but can pose a risk to the environment and human health. Besides direct impacts from their release, assessing the unintentional impacts on non-target organisms is crucial. This review provides a comprehensive understanding of AgNP trophic transfer and its toxicological consequences, with particular emphasis on identifying ways to decrease uncertainness related to the fate and effects of trophic available AgNPs. We suggest that biodynamic approaches, *in vivo* fate of AgNPs and the molecular features using new tools emerging from methodological advances will capture the complex ecological interactions of AgNPs with non-target organisms compared to conventional approaches. These findings are critical for the application of AgNPs in their sustainable development and use to minimize unintended consequences on environmental and human health.

Transfer and toxicity of silver nanoparticles in the food chain

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Abstract: Despite the tremendous interest in silver nanoparticles (AgNPs) based on their wide range of applications, several key questions remain unanswered, especially regarding the trophic transfer and toxicological consequences of AgNPs along the food chain. A detailed understanding of the mechanisms that drive AgNP trophic transfer is currently limited by the lack of information regarding the steady-state accumulation of AgNPs and their *in vivo* fate in the food chain. This results in variable patterns of AgNP trophic transfer among various food chains. However, biodynamic approaches in combination with the new tools emerging from methodological advances may provide unique perspectives on the accumulation of AgNPs, their *in vivo* fate and the molecular features driving toxicity in the food chain. The successful commercialization and use of AgNPs in sustainable development and the avoidance of unintended consequences for the environment and human health will also require a determination of the biogeochemical factors that influence AgNP trophic transfer. This review focuses on the current state of knowledge regarding (i) the trophic availability of AgNPs in the food chain, evaluated using conventional and biodynamic approaches, (ii) the processes that control AgNP trophic transfer, and (iii) the toxicological consequences of AgNP trophic transfer.

Keywords: Nanoparticle, Food chain, Dietary toxicity, Biodynamics, *In vivo* fate

Introduction

Silver nanoparticles (AgNPs) are used in a broad spectrum of consumer and industrial products, especially as antimicrobial agents, and are also of interest in nano-enabled agriculture. Consequently, AgNPs are one of the largest groups of manufactured NPs present in the environment,[1] which in turn has led to their accumulation in food webs.[2-5] The potential for unintended and indirect side-effects resulting from the high-trophic-level transfer of AgNPs, including to humans, has been pointed out.[6] Indeed, emerging evidence suggests that the trophic transfer of NPs is an important, if not the predominant, uptake pathway in high-trophic-level predators.[2, 7] However, in contrast to the extensive research on direct exposure, little is known about the consequences of AgNPs that enter the food chain, the relationship between exposure scenarios and the toxicological consequences along the food chain, or how an ecosystem might respond to AgNP exposure.[8] Given this lack of knowledge and the interest in environmentally friendly applications of AgNPs, there is an urgent need for studies that capture the complex ecological interactions of these particles with non-target organisms.

A review of published studies and thus of the evolution of AgNP research can provide a larger picture of the trophic transfer (trophic availability) of AgNPs, the factors that influence the underlying processes thereof, and the toxicological consequences of AgNPs along the food chain. A bibliometric analysis was performed based on the database from Web of Science (WOS) between 1991 and 2020. Generally, the silver research from 1991 to 2020 could be grouped into three subject categories, i.e., “Metals and nanoparticles”, “Trophic transfer and bioaccumulation”, and “Toxicity” (Figure 1). The co-word analysis from 1991–2000, 2001–2011, and 2011–2020 is demonstrated in Figure 2. Between 1991 and 2000, much of the studies was focused on the direct exposure of dissolved silver and the associated toxicity. From 2001–2010, in addition to the concerns on the bioavailability and trophic transfer in the aquatic environments, research interest in silver nanoparticles was sparked, which was probably stimulated by the application of manufactured silver nanoparticles. From 2011–2020, silver nanoparticles were of great concern, and their environmental behaviors (e.g., aggregation) and characteristics (e.g., size) were examined. Also during this period, many studies have focused on better understanding AgNP trophic transfer and toxicity. Despite these advances, insufficient knowledge still limits our understanding on AgNP trophic transfer and their transformation during the transfer.

This review begins with an assessment of the trophic availability of AgNPs in various food chains, as evaluated using conventional and biodynamic approaches. Due to the paucity of research on AgNPs, research on the impacts of other metal-based NPs and on dissolved Ag in aquatic food chains is also considered as the findings of those studies may be informative. The factors influencing AgNP trophic transfer are then discussed with respect to risk assessments and a risk-prevention-based paradigm. The molecular mechanisms that mediate the trophic transfer of AgNPs and their relationship to the toxicological consequences of the particles are examined as well. The review concludes with a discussion of the remaining uncertainties and the studies that are needed to obtain a comprehensive understanding of how ecosystems respond to AgNP exposure. Their findings will have important implications for the successful commercialization and application of AgNPs in sustainable development and the avoidance of unintended consequences on environmental and human health.

1. AgNP trophic availability in the food chain

1.1 Trophic transfer factors of AgNPs

The trophic availability of NPs is often expressed as the trophic transfer factors (TTFs), described mathematically as the ratio of the metal concentration in a predator organism to that in its prey. However, the TTFs is based on the assumption that the bioaccumulation of NPs reaches a steady state and that the particles (and thus the total amount of Ag in NP form) that bioaccumulate in biological samples can be clearly distinguished from bioaccumulated metal ions. As this is not always the case, there are both many uncertainties associated with a reliance on TTFs and large discrepancies in their values, depending on the food chain, the characteristics of the NPs, and the geochemical conditions of the ecosystem under study (Table 1).

In a study of an earthworm-collembola (*Eisenia andrei-Lobella sokamensis*) food chain, the TTFs was 0.57;[3] in an *Escherichia coli-Caenorhabditis elegans* test system and in food chains from a paddy microcosm it was < 1.[9] These and other similar results led to the conclusion that AgNP transfer in terrestrial food chains occurs without biomagnification (i.e., the absence of the progressive accumulation of Ag with increasing trophic level). Earlier studies in aquatic environments showed that the concentrations in predators of Ag sourced from Ag ions generally decrease with increasing trophic level.[10] By contrast, AgNP biomagnification was demonstrated in an estuarine microcosm contaminated with nanosilver from consumer products, with TTFs ranging from 7 to 420,[11] and in a natural fish food chain in Taihu Lake, where the trophic magnification factor (the slope of the log concentration vs. the trophic level of the organism along the food chain) was 1.21.[12] Our group investigated AgNP biomagnification in snails that consumed lettuce plants exposed to AgNPs via their roots (TTFs: 2.0–5.9) or leaves (TTFs: 0.49–0.57) (unpublished data). Together, these studies show that trophic transfer within food chains is highly variable.

Wide-ranging TTFs have also been determined for other metal-based NPs (Table 1). The respective studies showed that biomagnification is an important route of NP exposure. Different studies reported a 5-fold biomagnification of CdSe quantum dots from the bacterium (*Pseudomonas aeruginosa*) to the protozoan (*Tetrahymena thermophile*),[13] a TTF of nearly 1.0 for quantum dots transferred from thale cress (*Arabidopsis thaliana*) to the herbivore moth (*Trichoplusia ni*),[14] a 6.2- to 11.6-fold biomagnification of AuNPs from tobacco (*Nicotiana tabacum*) to the tobacco hornworm caterpillar (*Manduca sexta*),[15] and a 1.62- to 6.7-fold biomagnification of CeO_2 NPs from kidney bean (*Phaseolus vulgaris* var. red hawk) plants to adult Mexican bean beetles (*Epilachna varivestis*) and further to spined soldier bugs (*Podisus maculiventris*).[16] By contrast, other studies have reported the trophic transfer of NPs but found no evidence of biomagnification, indicating that food chains can also serve as a "trophic filter".[7, 17-20] A study of AuNP levels in contaminated soil showed a decrease by an average of two-order of magnitude during transfer of the particles from earthworms (*Eisenia fetida*) to bullfrog juveniles (*Rana catesbeina*).[7] Decreases in the concentration of TiO_2 NPs along a variety of food chains have also been determined.[17, 21] For CeO_2 NPs, Hawthorne *et al.*,[20] found a more than an order of magnitude decrease in the Ce concentration from zucchini (*Cucurbita pepo* L.) to crickets (*Acheta domesticus*) and wolf spiders (*Lycosiae*), while in the study of the mean TTF of these particles through a food chain consisting of lettuce and land snail was 0.037 ± 0.007.[18] Biomagnification was also not observed in the transfer of La_2O_3 NPs from lettuce (*Lactuca sativa*) to primary (crickets [*A. domesticus*], darkling beetles [Tenebrionoidea]) and secondary (Chinese and African mantises) consumers.[19]

While much of the focus in the past decade has been on TTFs, their high variability reflects the poor understanding of the basic principles driving the trophic transfer of NPs. Because NPs are in thermodynamically unstable forms and difficult to be in equilibrium between two compartments,[22] TTFs is invalid. Further, trophic availability is the product of both the uptake and the elimination of NPs by simultaneously occurring processes mediated by multiple factors.[23] Given the complex and highly dynamic nature of these processes, they are not quantitatively represented by TTFs. Instead, as demonstrated in a wealth of existing research,[2, 24, 25] biodynamic approaches are likely to provide a path forward in obtaining in-depth knowledge of AgNP trophic transfer, with no assumption of equilibrium.[26, 27]

1.2 Trophic transfer of AgNPs using the biodynamic approach

Studies conducted over the last 20 years have used biodynamic models to examine the trophic transfer of dissolved metals in aquatic environments [23] and have provided mechanistic insights into AgNP trophic transfer in complex environmental systems (Table 2). The TTFs of metals in various food webs under equilibrium have been biodynamically modeled using Eqs. 1 and 2.

$$\frac{d\left[NPs\right]_{predator}}{dt} = AE \times IR \times \left[NP\right]_{prey} - k_e \times \left[NP\right]_{predator} - k_g \times \left[NP\right]_{predator} \tag{1}$$

$$TTF_S = \frac{AE \times IR \times \left[NP\right]_{prey}}{k_e + k_g} \tag{2}$$

where $[NP]_{predator}$ and $[NP]_{prey}$ are the AgNP concentrations (μg g^{-1}) in predator and prey, respectively, AE is a first-order dynamic parameter quantifying the efficiency of NP assimilation from a given food (%) and thus the bioavailable fraction of ingested NPs, IR is the food ingestion rate (g g^{-1} d^{-1}), k_e is the elimination rate constant (d^{-1}), and k_g is the growth rate of the predator (d^{-1}), which is typically negligible during short-term exposure experiments.

The AEs of AgNPs and $AgNO_3$ in organisms exposed via their diet has been examined in terrestrial, freshwater, and marine organisms (Table 2). A study in the freshwater snail (*Lymnaea stagnalis*) found that AgNPs were assimilated less efficiently than $AgNO_3$ (49–58% vs. 73%).[28] Comparable AEs for AgNPs and $AgNO_3$ were found in the land snail (*Achatina fulica*) and marine medaka (*Oryzias melastigma*), but the AE of AgNPs is much higher in freshwater/land snails than in marine medaka (64–88% vs. $<$ 6%).[2, 24] Other studies have reported the species-specific AEs of dissolved Ag: the AE of Ag in the marine snail (*Thais clavigera*) was 80%,[29] and in the oyster (*Crassostrea gigas*) was 54–67%,[30] but only 0.3–3% in turbot,[31] 4.2 ± 2.8% in the European plaice (*Pleuronectes platessa*),[32] and 4–16% in the American plaice (*Hippoglossoides platessolides*).[33]

Another important consideration is the IR, especially for predators with intense feeding activity, such as earthworms, which have an IR of 490–4,190 mg dry weight (dw) g^{-1} wet weight (ww) d^{-1}, and deposit-feeders, which ingest roughly twice their body weight per day in order to meet their nutritional requirements.[34, 35] Determinations of the daily dose of dietary metals, calculated as the mathematical product of the IR and dietary NP concentration (see Eq. 1[36]) provide a more appropriate comparison of exposure than the dietary NP concentration alone. For instance, prey organisms that are heavily contaminated with NPs but consumed only occasionally may not be toxic to their predators.[37]

The physiological unidirectional efflux of accumulated Ag in the absence of any influx is represented by the k_e value. In freshwater snails, a much higher k_e resulted from dietary exposure to citrate-coated and humic acid-coated AgNPs (0.058 ± 0.019 d^{-1} and 0.051 ± 0.020 d^{-1}) than from dietary exposure to $AgNO_3$ (0.004 ± 0.013 d^{-1})[28] whereas the k_e values following AgNPs and $AgNO_3$ exposure were comparable in land snails (0.0093 ± 0.0037 d^{-1} vs. 0.019 ± 0.0077 d^{-1}) and in land isopods feeding on Ag-spiked alder leaves (0.004–0.018 d^{-1}) or Ag-spiked soil (0.01–0.26 d^{-1}).[2, 38] The storage and biogenic transformation of NPs in invertebrates were further included in the modelling frameworks,[26] demonstrating the power of biodynamic approach in modeling NP bioaccumulation. Overall, these results are a first step towards the development of a biodynamic modeling approach to assess the trophic transfer of AgNPs in various food chains.

2. Factors affecting AgNP trophic availability

The factors that impact biodynamic parameters (i.e., AE, IR, and k_e) will alter the trophic transfer potential of AgNPs (Eq. 2). The physiological and molecular processes by which this occurs can be investigated by focusing on the characteristics of the particles, the physiological dependence of the predator on its prey, and the exposure route.

2.1 AgNP characteristics

The uptake of AgNPs in the food chain, and thus their trophic transfer, is facilitated by the reactivity of the particles, which is a product of their physicochemical properties, including their size and surface chemistry. However, when considering the trophic transfer of AgNPs through various food chains, comparisons must be made to their bulk or dissolved counterparts, as the results will have important ecological implications from both a regulatory and an exposure/risk perspective. Unfortunately, such investigations are rare. Recent studies have demonstrated the particle-size-dependent trophic transfer of AgNPs and CeO_2 NPs and that smaller particles are more bioavailable and toxic to consumers than larger particles.[4, 20, 39] Nano-specific effects on biodynamic parameters (AE and k_e) have also been reported.[2, 28] In other studies, either particle size did not play a role in the trophic transfer of NPs or the results differed according to the duration of the study.[16, 19] For instance, in the trophic transfer of La_2O_3 NPs of increasing size a significant difference was noted over a 48-h but not over a 7-day depuration period.[19] However, a shorter depuration time may introduce an artifact, due to the presence of plant material in the gut, that may account for the conflicting results.

The surface coating of pristine AgNPs may also influence their trophic transfer. This was the case in freshwater snails, in which the AEs of PVP-AgNPs, citrate-AgNPs, and humic acid-AgNPs were 67–100%, 49 ± 7%, and 58 ± 8%, respectively.[28, 40]

Similarly, the TTFs of PVP-AgNPs and citrate-AgNPs differed significantly in a biofilm-water celery (*Oenanthe javanica DC*)-Chinese muddy loach (*Misgurnus mizolenis*) food chain.[9] The retention of trophically transferred AgNPs that originated from citrate-AgNP exposed algae (*C. reinhardtii*) was greater than that of aggregation-induced emission fluorogen (AIEgen)-coated AgNPs in *Daphnia magna*.[41] Different surface coatings may result in different surface affinities to prey and thus in different propensities of the AgNPs to enter the food chain.[42] However, the accumulation of curcumin-coated vs. tyrosine-coated AgNPs in daphnids via trophic transfer was not significantly different, although the average concentration of the latter NPs in daphnids was 2.6 times higher.[43]

2.2 Physiological dependence

2.2.1 Prey dependence

The uptake of AgNPs by prey is a key step in their trophic transfer along the food chain. While the concentration of AgNPs in prey generally decreases with the increasing IR in predators, it does not have a large effect on the AE.[2, 5, 24, 40] However, as noted above, prey quality/quantity can affect AgNP assimilation by the predator. The frustule of the diatom (*Cyclotella meneghiana*) is less digestible than the cell wall of the green algae (*Scenedesmus obliquus*), such that diatoms have a shorter residence time in the daphnid gut and the trophic availability of dissolved Ag is accordingly lower.[43]

How NPs are processed by prey determines their AE, as the different subcellular fractions of accumulated NPs vary in their trophic availability to consumers.[44] For instance, the assimilation of dissolved Ag in two marine predators was shown to be directly related to the metal's fraction in the cytoplasm of their algal prey[45, 46] and thus to its biological fate as prey food. To date, similar relationships have not been validated for NPs. A few studies have reported that in organisms at the bottom of the food chain the distribution of AgNPs differs fundamentally from that of dissolved Ag. In *Nereis diversicolor* fed AgNP-spiked sediment, Ag accumulated predominantly within inorganic granules, organelles, and heat-denatured proteins in the polychaete's gut, whereas exposure to dissolved Ag led to the metal's accumulation in the metallothionein fraction.[47] In phytoplankton (*Thalassiosira weissflogii*) most of the Ag from AgNPs was distributed in the cell wall whereas exposure to dissolved Ag led to deposition in organelles and the endoplasmic reticulum.[48] The biological fates of Ag delivered in NPs vs. in dissolved forms differ and may provide cues to the trophic transfer of AgNPs.[49] It should be noted that most studies on the biological fates of AgNPs at the subcellular level in prey refer to bulk, not particulate Ag. Thus, the subcellular fate of NPs *in vivo* and its effect on trophic transfer remain to be determined.

2.2.2 Predator dependence

The trophic transfer of AgNPs varies widely among food chains, often reflecting basic differences in predator biology, e.g., digestive physiology, feeding strategy, and growth stage. Upon exposure to AgNPs in soils, isopods accumulate greater Ag than springtails, probably because the differences in feeding strategy (isopods mainly ingest contaminated soil particles while springtails are mainly exposed to metals in the porewater) and the lower pH in isopod's guts.[25] Generally, the AE of Ag is lower in teleost fish than in freshwater/land snails, irrespective of whether the Ag is present as ions or in NPs.[2, 10, 24, 48] The difference can be attributed to differences in digestive physiology and feeding strategy, which affect the desorption and assimilation of Ag. While the digestive tract of invertebrates such as snails has a relatively neutral pH, the stomach of fish has a pH of < 2.[50] In fish, the low pH of the stomach as well as the redox conditions of the digestive tract and the composition of the digestive fluid were shown to facilitate the transformation of Ag in the intestine into particulate Ag,[51] which is less available for internalization. In addition, the mucus in the fish intestine may serve as a barrier for Ag internalization.[52, 53] The positive relationship between the gut passage time and AE of Ag suggests that a longer retention time of the metal in the digestive tract will result in its increased internalization.[45] Furthermore, predators can regulate their IR in response to Ag exposure,[2, 5, 18, 28, 40] which in turn will affect the trophic transfer of AgNPs. Differences in the trophic transfer of CeO_2 NPs as a function of the predator's growth stage have also been described: Despite Ce transferred from primary to secondary consumers, biomagnification occurred only until the adult stage of secondary consumers.[16] Collectively, these biological differences result in a variable trophic availability of AgNPs between animal groups that may go undetected when trophic transfer is assessed solely using conventional approaches such as TTFs.

2.3 Exposure routes

The many different possible exposure routes to AgNPs also contribute to the variability in trophic transfer. Differences in trophic availability between exposure routes reflect differences in the NP concentration, NP transformation in the environment and food chain, and predator physiology. When the deposit-feeding isopod (*Porcellionides pruinosus*) was exposed to AgNPs via soil or surface-contaminated leaves, the amount of Ag that accumulated via soil was 5-fold higher.[5] This could be attributed to the stronger binding of Ag to leaf material and thus to its lower uptake.[38] A study from our group using a stable isotope approach similarly demonstrated the greater trophic availability to the predator snail (*A. fulica*) of Ag_2S NPs that accumulated in lettuce (*Lactuca sativa*) via root uptake than AgNP via foliar exposure.[54] Studies of other metal-based NPs showed that tobacco hornworm caterpillar bioaccumulates more Au after feeding on AuNP-internalized leaves than on AuNP-adsorbed leaves, evidenced by TTFs of 6.2–11.6 vs. 0.16, respectively.[15, 55] The same group found a greater AuNP bioavailability when mediated by trophic transfer than by an equivalent exposure through oral gavage.[7] CeO_2 NPs were more efficiently transferred to the land snail (*A. fulica*) when the particles were internalized within plants (TTFs: 0.037 ± 0.007) than adsorbed on leaf surfaces through foliar exposure (TTFs: 0.0012 ± 0.0004).[18]

2.4 Transformation of AgNPs in the environment and food chain

A limitation common to conventional and biodynamic approaches is the difficulty in determining the transformation of AgNPs in the food chain, both after their environmental transformation, such as by weathering, and after their *in vivo* transformation in prey and predators. Transformed NPs are thus structurally and chemically distinct from their pristine counterparts and their bioavailability may differ accordingly.

Due to the environmental transformation of NPs in real-world environments, prinstine NP characteristics such as coating and size may have an effect on trophic transfer, and the characteristics-specific trophic transfer under simple laboratory conditions was noted. AuNP size and shape controlled the particle number-based biomagnification factors in the algae (*P. subcapitata*)-Daphnia (*Daphnia magna*) - zebrafish (*Danio rerio*) food chain and the distribution of NPs in fish tissues under laboratory conditions.[56] However, AuNPs are not inert in natural environments and can undergo dissolution by freshwater macrophyte (*Egeria densa*) and cyanogenic soil bacterium (*Chromobacterium violaceum*).[57, 58] This is also true for AgNPs, which undergo weathering in real-world conditions.

The weathering of AgNPs results in (a) the dissolution and release of silver ions, (b) sulfidation and the formation of silver sulfide, and (c) aggregation and precipitation.[59-62] Dissolution is a key transformation affecting AgNP fate in the environment and subsequently Ag uptake by plants and invertebrates, the first and key step toward bioaccumulation of NPs in food chain.[25, 63, 64] Sulfidation of AgNPs in soils led to no uptake of Ag in the isopod (*P. Scaber*) and slight uptake in the springtail (*E. candida*),[25] Plants and their seeds showed different responses upon AgNP and Ag_2S NP exposure.[65, 66] However, most organisms in freshwater wetland mesocosms amended with Ag_2S NPs had Ag concentrations that were not significantly different from those in their AgNP counterparts after chronic weekly additions of NPs.[67] A high level of phosphate, a potential weathering ligand and a determinant of phytoplankton productivity, was shown to have a greater effect on Ag trophic transfer from the alga (*Chlamydomonas reinhardtii*) to *D. magna*.[68] Although the weathering of CuO NPs in soils resulted in their reduction and sulfidation, it had no significant effect on Cu transfer from lettuce (*L. sativa*) to crickets (*A. domesticus*) and to the lizard (*Anolis carolinensis*).[69]

More importantly, NPs transform in biota. In the biota gut, AgNPs are subject to a range of biochemical processes that alter their bioavailability and toxicity, including oxidative dissolution, the release of ionic species, thiol- or protein- binding, and *in vivo* transformation to sulfides and selenides.[70-72] Unfortunately, among the available NP trophic transfer studies, only six studies have examined the transformation of NPs using single-particle inductively coupled plasma mass spectrometry (spICP-MS), a fluorogenic ionic Ag sensor, or X-ray absorption near edge structure (XANES) (Tables 1-2). The most notable changes due to the transformation is the size redistribution. In an algae-Daphnia-fish food chain (Table 1), *D. magna* modified the size distribution of AuNPs via the dissolution of larger AuNPs (up to 56% of the NP mass), or via the dissolution followed by re-precipitation and agglomeration of the smaller AuNPs. Finally all AuNPs, irrespective of initial size, had similar sizes in daphnids (original size from 10−100 nm in the environment to 28−38 nm), and the size distribution in the intestine of fish remained almost the same as that in *D. magna*.[56] Our group used spICP-MS to follow the biodissolution of AgNPs within the snail gut after lettuce ingestion, with the results showing a reduction in the original size of the particles from 55−68 nm in the environment to 17−26 nm (unpublished data, Table 1). XANES analysis showed that only metallic Au, rather than ionic Au, was present within the predator exposed to AuNPs.[15] As for snails feeding on lettuce leaves via foliar exposure to CeO_2 NPs, XANES analysis showed that more than 85% of Ce(IV) was reduced to Ce(III) in digestive gland.[18] In *D. magna*, a study using AIEgen-AgNPs showed that ingested AgNPs dissolved in the gut and reached a much higher concentration in the anterior gut.[72] The group further quantified the *in vivo* dissolution kinetics of trophically transferred NPs in daphnids gut, with much higher ionic Ag released from citrate-AgNPs than that from AIE-AgNPs.[41]

Nanoparticles in contact with biomolecules such as proteins also experience changes in surface chemistry and form corona that can impact their bioavailability. For example, vitellogenin and zona pellucida were identified in AgNP coronas in the plasma of female smallmouth bass (*Micropterus dolomieu*), and the corona is assumed to promote AgNP translocation to the ovaries.[73] Protein corona was also identified in *Daphnia magna*: the corona compositions varied with NP type, aging and medium composition, and the bound proteins were associated with metabolic and cytotoxic damage.[74] In addition to NPs alteration, biota including microorganisms, plants and animals can serve as "NP biofactory", i.e., nanoparticulate Ag was formed upon exposure to Ag ions.[64, 75, 76] Hence, discrimination between ions and AgNPs in biological samples[77] and between intact NPs taken up directly from the environment (i.e., pristine NPs) and the secondary NPs that form *in vivo* via the reduction of internalized Ag ions to AgNPs remains challenging.[76] This further impedes a thorough understanding of AgNP trophci transfer.

3. Toxic mechanism of dietary AgNPs

An evaluation of the toxicological consequence of the trophic transfer of AgNPs is essential to obtain a more complete picture of the risk of AgNPs in the environment. However, the literature on dietary toxicity of NPs is limited and most studies have focused on phenotypical end points. For instance, negative effects on mortality, IR, and egestion ratios were determined in the isopod (*P. pruinosus*) feeding on AgNP-contaminated leaves.[5] For the collembolan (*L. sokamensis*) feeding on earthworms (*E. andrei*) in soils containing 500 μg AgNPs g^{-1}, locomotion was suppressed and mortality increased.[3] The toxicity of AgNPs may also be transgenerational, as demonstrated in *C. elegans* feeding on *E. coli*.[4] In that study, the AgNPs increased germ cell death (an indicator of toxicity in gonadal cells) while decreasing both the brood size (reproduction rate) and the lifespan of *C. elegans*. Moreover, germ cell impairment also occurred in subsequent generations, with recovery first observed in the fourth generation in worms exposed to 25 nm AgNPs but in the third generation exposed to 75 nm AgNPs. In addition to the terrestrial food chain, toxicity studies have been performed in aquatic food chains. In rainbow trout with a 58-day dietary exposure to food spiked with 3−3,000 Ag_2S mg kg^{-1}, the IR decreased significantly but neither growth nor survival was affected.[78] Several studies have reported the chronic toxicity induced by the trophic transfer of AgNPs, including a 39% reduction in *D. magna* reproduction relative to controls,[79] disruption of the endogenous microbiota in zebrafish,[80] harmful biochemical alterations in marine medaka,[24] an altered intestinal microbial community structure in the zebrafish (*Danio rerio*),[80] and a decline in the IRs of freshwater snails and *D. magna*.[68] In other studies, Ag nanowires induced immobilization and mortality in *D. magna* in addition to destroying its digestive organs and causing the production of lipid droplets.[39, 81] However, dose-response curves for AgNPs based on the various endpoints of toxicity have yet to be established and difficulties remain in correlating these results to actual environmental exposure levels.[82]

Accordingly, the toxicity of AgNP trophic transfer remains unclear, as negative effects of AgNPs at environmental concentrations have been described by some authors[3] but not by others.[2, 82] The inconsistencies may, at least partially, derive from the insensitivity of the traditional endpoints used in those studies, such as mortality and growth, when the response to trace levels of accumulated NPs is the focus (Figure 3). As a result, there is no simple correlation between toxic endpoints and NP exposure scenarios. However, remarkable progress is being made with respect to mechanism-based assessments of direct exposure.[83, 84] A number of studies have investigated the complex molecular networks under direct interactions of NPs with plants (see reviews[16, 85]) or with animals using high-throughput unbiased omics approaches (e.g., transcriptomics, proteomics and metabolomics).[86, 87] For example, a metal-analysis of NP transcriptomic study demonstrated the molecular mechanisms of nanotoxicity common for different species exposed to different NPs, including interference with energy generation, oxidative stress, mitochondria- or DNA-related toxicity and translational repression, which were identified by heterogenous studies, as well as DNA/RNA methylation, protein folding, and interference with neurological functions, which were less-described.[88] However, the majority of investigations concern about the molecular responses upon direct interactions, and few has focused on trophic transfer. Determinations of the toxicity of NP trophic transfer will no doubt benefit from these omics-based tools, which can be expected to provide insights into the mode of action of NPs in the food chain, by identifying hazard-relevant molecular features and their causal connection to biological phenotypes.[89] Li *et al.*, (unpublished) showed that the trophic transfer of AgNPs from lettuce to land snails caused a notable metabolic shift (~27% of global metabolic reprogramming) involving functions related to osmoregulation, phospholipid, energy, and amino acid metabolism. Perhaps more importantly, omics-based approaches can be used to develop biomarkers of NP exposure or its effects for use in routine assays. Advancements in the tools used to investigate the trophic transfer of AgNPs will facilitate ecological risk assessments and thus improve product registration as well as guideline development.

Another key challenge to obtaining a mechanistic understanding of AgNP toxicity along the food chain is the *in vivo* fate of NPs, especially their transformation and subcellular localization within prey and in the predator (Figure 3). Several studies have demonstrated the trapping of AgNPs in the gut and associated impairments in gut function, thus concluding that the gut is the target organ for dietary AgNP toxicity.[28, 90-92] In an another study, fish brain had most profoundly Au-particles transferred from daphnids (45−59%, mean size of 50−61 nm), followed by intestine (18−23%, mean size of 38−47 nm) and liver (17−22%, mean size of 4−61 nm), indicating that brain and liver are also targets of NPs.[56] However, the majority of research has not evaluated the *in vivo* fate of NPs during trophic transfer as noted above (Tables 1-2). Few studies have evaluated the subcellular localization of NPs in the prey using an artificial approach.[47, 48] With appropriate nano-specific considerations, this approach may provide a concept to explore the trophic availability of NPs.[44, 49] An alternative approach is to visualize the exact location of NPs in the prey. The lysosome is visualized to be the most involved organelle in the oyster gill filaments to regulate the cellular process of AgNPs, including AgNP-induced autophagy and lysosome-enhanced AgNP dissolution using high-resolution nanoscale secondary ion mass spectrometry elemental mapping (Nano-SIMS) with SEM imaging.[93]

The importance of *in vivo* investigations of AgNP fate rather than measurements of bulk samples, and of discriminating between pristine and secondary AgNPs, are illustrated as shown previously. Both require powerful analytical tools of high spatial resolution and chemical sensitivity. In addition to analytical methods such as synchrotron-based X-ray spectroscopic and high-resolution microscopy, these include the new and sophisticated tools that have been incorporated into nanosafety research, such as spICP-MS and asymmetric flow field flow fractionation (see the reviews).[77, 94] Such studies have found that the discrimination of particulate and ionic Ag in the food chain reveals differences in the trophic availability of AgNPs, with biomagnification determined for particulate Ag but biodiminution for bulk Ag.[12] Finally, risk assessments must take into account not only short-term, high-dose exposure scenarios but also long-term, low-dose exposures, which are more realistic.

4. Research needs

Despite the increasing number of studies aimed at a better understanding of the trophic transfer of AgNPs and its toxicological consequence, many fundamental questions remain to be answered, including those related to the mechanisms, processes, and factors controlling trophic transfer, the mode of action of AgNPs in the food chain, and the connections between exposure scenarios and toxicological consequences (Figure 3).

Unlike conventional approaches, the results of which are expressed as TTFs, biodynamic approaches not only address the critical processes of AgNP trophic transfer but also capture the biologically driven patterns that differentiate trophic transfer among different food chains. With the use of Ag stable isotopes, uptake and elimination processes during trophic transfer can be tracked. Thus, compared to conventional approaches such as TTFs, biodynamic approaches hold tremendous promise for revealing the mechanisms of AgNP trophic transfer and the relevant factors that drive it in a variety of field settings.

A mechanistic understanding of AgNP trophic transfer and its toxicological consequences will be greatly enhanced by direct investigation of the *in vivo* fate of AgNPs in the food chain, including the discrimination of ions and NPs and of pristine and secondary NPs as well as the localization of NPs at the subcellular level. These investigations depend on the quantification and localization of NPs in biological samples and thus require powerful tools such as synchrotron-based X-ray microscopy and spICP-MS.

The molecular features of accumulated NPs are also poorly understood. However, omics-based approaches are expected to reveal the molecular features not only of isolated empirical end-points but also of the integrated pathways leading to toxicity induced by AgNP trophic transfer. With a more complete understanding of the connections between exposure and the toxicological consequences for the food chain, it will be possible to predict how an ecosystem will respond to AgNP exposure. The resulting comprehensive risk assessments of AgNPs will accelerate developments in nanotechnology involving AgNPs while reducing the risk to wildlife and humans.

Author contributions:

All the authors have contributed to the discussion and the writing of the manuscript.

Conflicts of interest:

There are no conflicts of interest to declare.

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Table1. Summary of NP trophic transfer studies as a function of NP types, capping, particle size, exposure media, NP concentration in the media and food chain types. Trophic transfer factors (TTFs) are listed.

Nanoparticles	**Capping**	**Particle size**	**NP exposure media**	**NP concentration in the media**	**Food chain**	***In vivo* fate**	**TTFs**	**Reference**
AgNP	PVP	<100 nm	Soil	500 μg Ag g^{-1}	Earthworm (*Eisenia andrei*) – Collembola Collembola (*Lobella sokamensis*)	-	0.57	Kwak and An, 2016
AgNP	PVP	25, 75 nm	LB medium	0, 1, 5, 25 μg Ag mL^{-1}	Escherichia coli (*E. coli*) – Caenorhabdits elegans (*C. elegans*)	-	0.012-0.016	Luo et al., 2016
AgNP	PVP, Citrate	-	Paddy microcosm	20, 60 μg Ag L^{-1}	Water dropwort (*Oenanthe javanica DC*) – River snail (*Cipangopaludina chinensis*)	-	<1	Park et al., 2018
AgNP	PVP, Citrate	-	Paddy microcosm	20, 60 μg Ag L^{-1}	Water dropwort (*Oenanthe javanica DC*) – Chinese muddy loach (*Misgurnus mizolepis*)	-	<1	Park et al., 2018
AgNP	AgNP-containing products	-	Seawater	240, 000-300, 000 μg Ag g^{-1} seawater	Biofilm – Eastern mud snails (*Ilyanassa obsoleta*)	-	14-270	Cleveland et al., 2012
AgNP	AgNP-containing products	-	Seawater	240, 000-300, 000 μg Ag g^{-1} seawater	Biofilm – Juvenile hard clams (*Mercenaria mercenaria*)	-	8-140	Cleveland et al., 2012
AgNP	AgNP-containing products	-	Seawater	240, 000-300, 000 μg Ag g^{-1} seawater	Biofilm – Grass shrimp (*Palaemonetes pugio*)	-	7-420	Cleveland et al., 2012
AgNP	Bare	26 nm	Aquatic environments	0.2 ng Ag L^{-1}	Zooplankton – Fishes	Particulate and ionic Ag were distinguished by spICP-MS	1.21	Xiao et al., 2019
AgNP	Bare	100 nm	Soil (root exposure)	500; 1, 000 mg Ag kg^{-1} soil	Lettuce plants – Snail	Particulate and ionic Ag were distinguished by spICP-MS	2.0-5.9	unpublished
AgNP	Bare	100 nm	Soil (foliar exposure)	0, 1, 10 mg Ag L^{-1}	Lettuce plants – Snail	Particulate and ionic Ag were distinguished by spICP-MS	0.49-0.57	unpublished
AgNP	Citrate	57 nm	SM7 medium	1, 000 μg Ag L^{-1}	Algae (*C. reinhardtii*) - Daphnids (*Daphnia magna*)	Ionic Ag was identified using a fluorogenic sensor	8.40 L g^{-1}	Yan and Wang, 2021
AgNP	Fluorogen coated	60 nm	SM7 medium	1, 000 μg Ag L^{-1}	Algae (*C. reinhardtii*) - Daphnids (*Daphnia magna*)	Ionic Ag was identified using a fluorogenic sensor	4.49 L g^{-1}	Yan and Wang, 2021
CdSe	Bare	5 nm	LB medium	75 mg Cd L^{-1}	Bacteria (*Pseudomonas aeruginosa*) – Protozoan (*Tetrahymena thermophile*)		5.1	Werlin et al.,2010
CdSe/CdZnS QDs	Poly(acrylic acid-ethylene glycol) (PAA-EG); Polyethylenimine (PEI); Poly(maleic anhydride-alt-1-octadecene)-poly(ethylene glycol) (PMAO–PEG)	19, 27, 53 nm	Drop of media	10 mg Cd L^{-1}	Arabidopsis thaliana – *Trichoplusia ni*	-	<1	Koo et al., 2015
AuNP	Tannic acid	5, 10, 15 nm	DI water	100 mg Au L^{-1}	Tobacco (*Nicotiana tabacum*) – Tobacco hornworm (*Caterpillars Manduca sexta*)	Only Au^0 was present within hornworm tissues with no ionic Au as revealed by μXANES analysis	6.2-11.6	Judy et al., 2011
AuNP	Citrate	10, 60, 100 nm	Algal culture medium	3-2, 543 mg Au L^{-1}	Algae (*P. subcapitata*) - Daphnia (*Daphnia magna*) - Zebrafish (*Danio rerio*)	Particulate and ionic Au were distinguished by spICP-MS	<1	Monikh et al., 2021
AuNP*	Citrate	rod-shaped (10 × 45 nm and 50 × 100 nm)	Algal culture medium	17-1, 207 mg Au L^{-1}	Algae (*P. subcapitata*) - Daphnia (*Daphnia magna*) - Zebrafish (*Danio rerio*)	Particulate and ionic Au were distinguished by spICP-MS	<1	Monikh et al., 2021
CeO$_2$	Bare	cubic 67× 8 nm	Soil	1, 000–2, 000 mg Ce kg^{-1}	Bean plants (*Phaseolus vulgaris var. red hawk*) – Mexican bean beetles (*Epilachna varivestis*) – Spined soldier bugs (*Podisus maculiventris*)	-	5.32-6.7	Majumdar et al., 2016
CeO$_2$	Bare	155 nm	Soil	1, 000 μg Ce g^{-1}	Zucchini (*Cucurbita pepo* L.) – Crickets (*Acheta domesticus*) – Wolf spiders (*Family lycosidae*)	-	0.16	Hawthorne et al., 2014
CeO$_2$	Bare	7 nm	Water-saturated potting soil	0, 500, 1, 000 mg Ce kg^{-1}	Lettuce (*Lactuca sativa*) – Land snails (*Achatina fulica*)	Ce(IV) and Ce(III) were present in snail tissues as revealed by XANES analysis	0.0012-0.037	Ma et al., 2016
La$_2$O$_3$	Bare	167 nm	Soil	500 mg La kg^{-1}	Lettuce (*Lactuca sativa*) – Crickets (*Acheta domesticus*)	-	0.012	Roche et al., 2015
La$_2$O$_3$	Bare	167 nm	Soil	500 mg La kg^{-1}	Lettuce (*Lactuca sativa*) – Darkling beetles (*Tenebrionoidea*)	-	0.007	Roche et al., 2015
AuNP	Bare	12 nm	Artificial soil	200 mg Au kg^{-1}	Earthworms (*Eisenia fetida*) – Juvenile bullfrogs (*Rana catesbeina*)	-	< 0.1	Unrine et al., 2012
TiO$_2$ NPs	Bare	96 nm	Aquatic environments	4 μg Ti L^{-1}	Zooplankton – Fishes	Particulate and ionic Ti were distinguished by spICP-MS	< 1	Xiao et al., 2019
TiO$_2$ NPs*	Bare	5-10 nm; *nanotube inner pore diameter of about 2-9 nm	Freshwater	1, 818 mg Ti L^{-1}	Phytoplankton (*Spirogyra* spp.) – Ricefish (*Oryzias sinensis*); Biofilm – Mud snail (*Cipangopaludina chinensis*); Biofilm – Nematodes (*Meloidogyne* sp.)	-	< 1	Yeo and Nam, 2013
TiO$_2$ NPs*	Bare	5-10 nm; *nanotube inner pore diameter of about 2-9 nm	Freshwater	1, 818 mg Ti L^{-1}	Water dropwort (*Oenanthe javanica DC.*) – Nematodes (*Meloidogyne* sp.)	-	0.1-~10	Yeo and Nam, 2013
CuO-NPs	Bare	40 nm	Soil	400 mg Cu kg^{-1}	Lettuce (*Lactuca sativa*)-Crickets (*Acheta domestica*)-Lizards (*Anolis carolinensis*)	Cu$_2$O and Cu$_2$S were detected in lettuce roots as revealed by μ-XANES analysis	-	Servin et al., 2017

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Table 2. Summary of Ag trophic transfer studies using the biodynamic approach. The biodynamics parameters including assimilation efficiency, ingestion rate, and elimination rate constant are listed.

Ag species	**Capping**	**Particle size**	**NP exposure media**	**NP concentration in the media**	**Food chain**	***In vivo* fate**	**Assimilation efficiency (AE)**	**Ingestion rate (IR, g g^{-1} d^{-1})**	**Elimination rate constant (K_e, d^{-1})**	**TTFs**	**Reference**
AgNP	Citrate, humic acid	17 nm	Moderately hard water	64-7, 700 ng Ag L^{-1}	L. stagnalis – Freshwater snails (*Lymnaea stagnalis*)	-	49-58%	0.24-0.29	0.051-0.058	-	Croteau et al., 2011
Ag^+	-	-	Moderately hard water	43-6, 400 ng Ag L^{-1}	L. stagnalis – Freshwater snails (*Lymnaea stagnalis*)	-	73%	0.91	0.004	-	Croteau et al., 2011
AgNP	PVP	37 nm	Hydroponics, concurrently exposed to Ag_2S-NPs via their roots and to ^{109}AgNPs via their leaves	8 μg Ag L^{-1}; 0-50 mg Ag L^{-1}	Soybeans (*Glycine max* L.) – Terrestrial snails (*Achatina fulica*)	Particulate and ionic Ag was distinguished by spICP-MS	62–85%	-	-	-	Chen et al., 2019
AgNP	Citrate	20, 80 nm	Seawater	0-1, 000 μg Ag L^{-1}	Brine shrimp (*Artemia salina*) – Marine medaka (*Oryzias melastigma*)	-	< 6 %	1.39 E-5		0.009-0.011	Wang and Wang, 2014
Ag^+	-	-	Seawater	0-1, 000 μg Ag L^{-1}	Brine shrimp (*Artemia salina*) – Marine medaka (*Oryzias melastigma*)	-	< 6 %	2.45-2.78 E-5		0.044	Wang and Wang, 2014
$^{110m}Ag^+$	-	-	Seawater	74 kBq ^{110m}Ag L^{-1}	Phytoplankton – Marine snails (*Thais clavigera*)	-	80%	-	-	-	Cheung and Wang, 2005
$^{110m}Ag^+$	-	-	Seawater	0.5 kBq ^{110m}Ag mL^{-1}	300-mm pellets (*Biomar*, France) – Turbots (*Scophthalmus maximus*)	-	< 3 %	-	-	-	Pouil et al., 2015
$^{110m}Ag^+$	-	-	Seawater	0.04 μg Ag L^{-1}	Nereis – Plaice (*Pleuronectes platessa*)	-	4.20%	-	-	-	Pentreath, 1977
$^{110m}Ag^+$	-	-	Seawater	0.04 μg Ag L^{-1}	Nereis – Thornback ray (*Raja clavata* L.)	-	49%	-	-	-	Pentreath, 1977
$^{110m}Ag^+$	-	-	Seawater	492 ng Ag L^{-1}	Fish food – Snow crabs (*Chionoecetes opilio*)	-	67-100%	-	< 0.001	-	Rouleau et al.,2000
$^{110m}Ag^+$	-	-	Seawater	492 ng Ag L^{-1}	Fish food – American plaice (*Chionoecetes opilio*)	-	4-16%	-	< 0.1	-	Rouleau et al.,2000
AgNP	PVP	15 nm	Hydroponics	Foliar exposure, 0.1-30 mg Ag L^{-1}	Lettuce (*Lactuca sativa* L.) – Terrestrial snails (*Achatina fulica*)	-	62-85%	0.08-0.11	0.0093 ± 0.0037	-	Chen et al., 2017
Ag^+	-	-	Hydroponics	Foliar exposure, 0.1-10 mg Ag L^{-1}	Lettuce (*Lactuca sativa* L.) – Terrestrial snails (*Achatina fulica*)	-	64-88%	0.05-0.08	0.019 ± 0.0077	-	Chen et al., 2017
AgNP	Alkane	3-8 nm	Soil	30, 60 mg Ag kg^{-1}	Alder leaves – Isopod (*Porcellionides pruinosus*)	-	-	0.019-0.028	0.004-0.011	-	Tourinho et al., 2016
Ag^+	-	-	Soil	30, 60 mg Ag kg^{-1}	Alder leaves – Isopod (*Porcellionides pruinosus*)	-	-	0.005-0.008	0.015-0.018	-	Tourinho et al., 2016
AgNP	Alkane	3-8 nm	Soil	30, 60 mg Ag kg^{-1}	Contaminated soil – Isopod (*Porcellionides pruinosus*)	-	-	0.19-0.79	0.01-0.26	-	Tourinho et al., 2016
Ag^+	-	-	Soil	30, 60 mg Ag kg^{-1}	Contaminated soil – Isopod (*Porcellionides pruinosus*)	-	-	0.17-0.48	0.17-0.48	-	Tourinho et al., 2016
AgNP	PVP	36 nm	Synthetic freshwater	1-43 ng Ag L^{-1}	Diatom (*Nitzschia palea*) – Freshwater snail (*Lymnaea stagnalis*)	-	67-100%	0.15-0.36	-	-	Oliver et al., 2014

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Figure 1. Keyword co-occurring networks of papers concerning “silver trophic transfer” between 1991 and 2020. The bibliometric analysis was performed using CiteSpace (Version 5.5 R2) based on the database from Web of Science (WOS) between 1991 and 2020. The topic search used syntax “TS= ((silver OR Ag OR "particulate Ag" OR "Nano Ag" OR ((silver or Ag) AND (nanoparticle* OR particle*))) AND ("food chain*" OR "food web*" OR trophic OR diet) AND (toxic*))”. Circle size is proportional to the number of publications. Co-citation rings and links within the same decades are shown in a unique color.

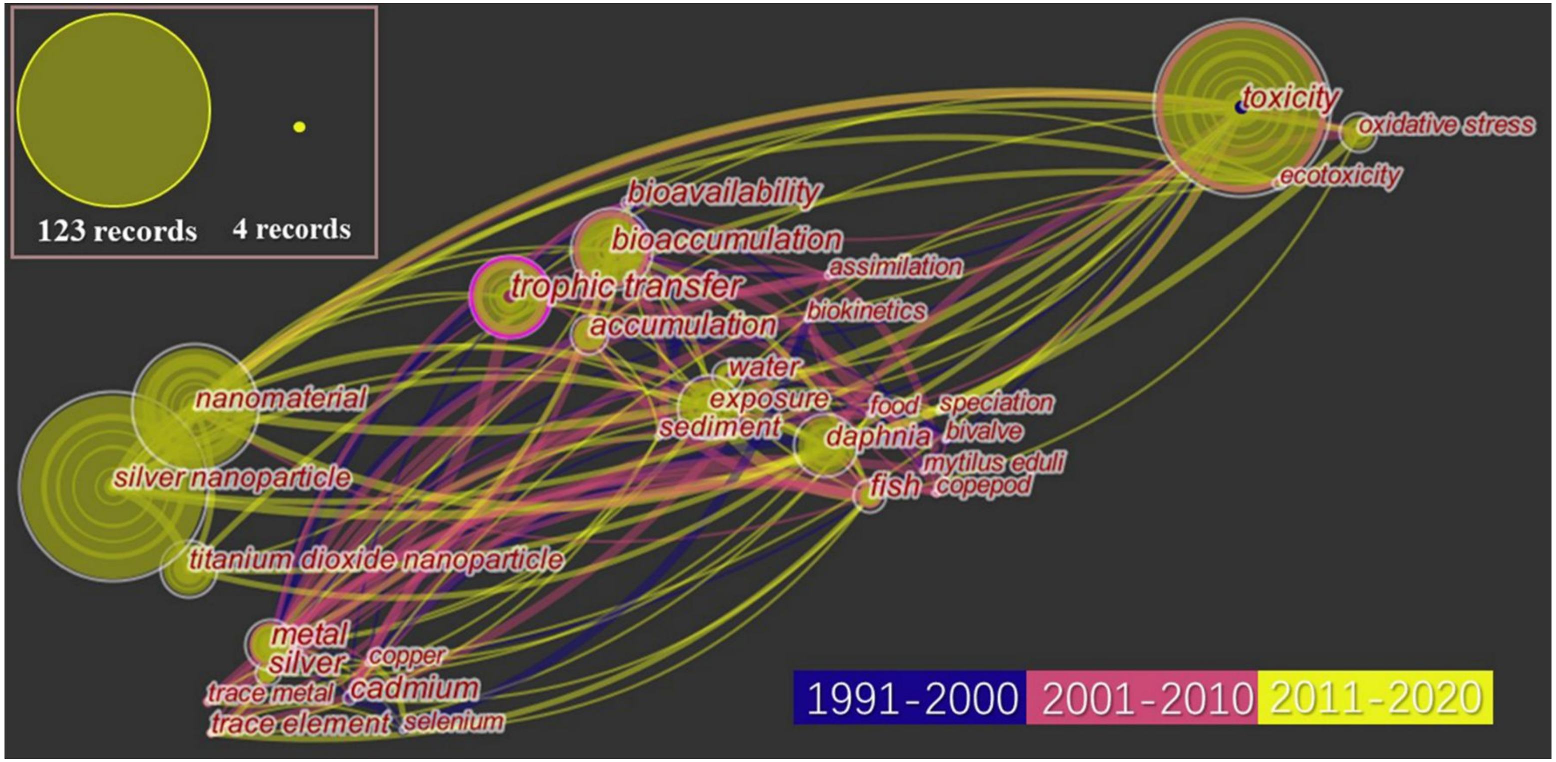

Figure 2. Evolution of the field of silver trophic transfer and co-occurrence of keywords. All data used were retrieved from Web of Science (WOS) from 1991 to 2020.

The font size of topic description text is proportional to the number of publications.

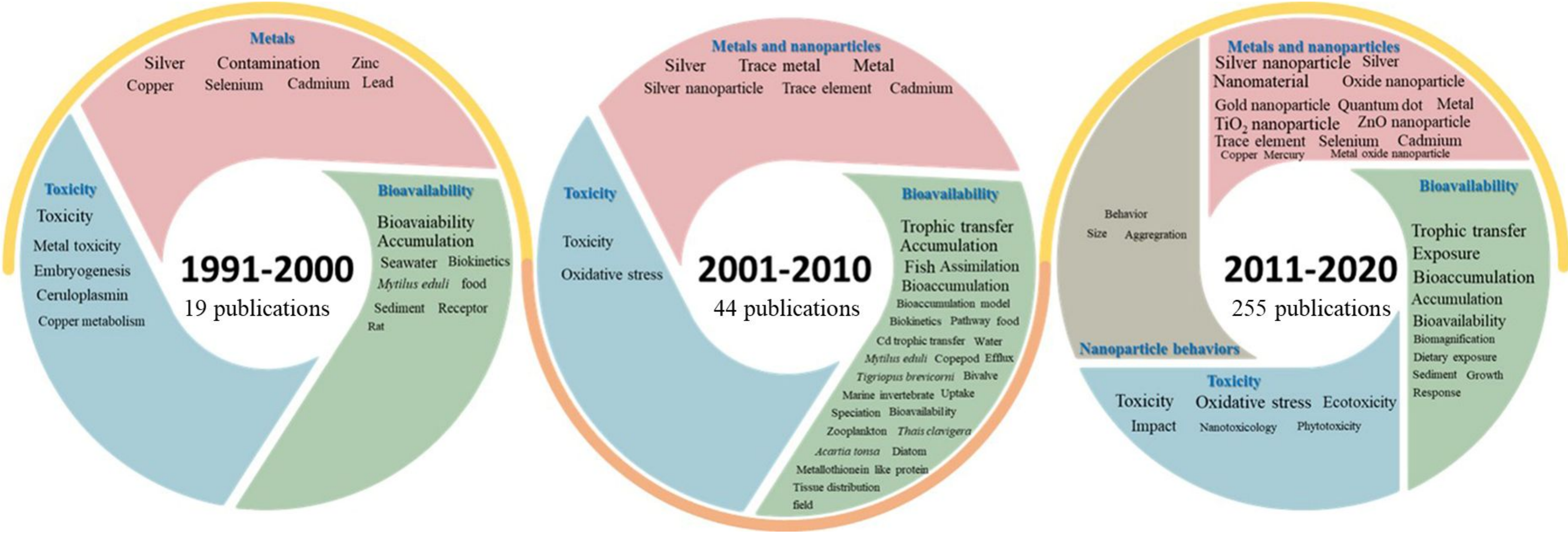

Figure 3. Paradigm for AgNP trophic transfer and the associated toxicity focusing on the biodynamic approach, *in vivo* fate of AgNPs and omics-based approaches. Trophic transfer factors and traditional toxic endpoints were used in previous studies.