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REVIEW ARTICLE

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Toxicological effects of selenium nanoparticles in laboratory animals: A review

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Abstract

This paper provides a comprehensive summary of the main toxicological studies conducted on selenium nanoparticles (NPs) using laboratory animals, up until February 28, 2023. A literature search revealed 17 articles describing experimental studies conducted on warm-blooded animals. Despite some uncertainties, in vivo studies have demonstrated that selenium NPs have an adverse effect on laboratory animals, as evidenced by several indicators of general toxic action. These effects include reductions of body mass, changes in hepatotoxicity indices (increased enzyme activity and accumulation of selenium in the liver), and the possibility of impairment of fatty acid, protein, lipid, and carbohydrate metabolisms. However, no specific toxic action attributable solely to selenium has been identified. The LOAEL and NOAEL values are contradictory. The NOAEL was 0.22 mg/kg body weight per day for males and 0.33 mg/kg body weight per day for females, while the LOAEL was assumed to be a dose of 0.05 mg/kg of nanoselenium. This LOAEL value is much higher for rats than for humans. The relationship between the adverse effects of selenium NPs and exposure dose is controversial and presents a wide typological diversity. Further research is needed to clarify the absorption, metabolism, and long-term toxicity of selenium NPs, which is critical to improving the risk assessment of these compounds.

KEYWORDS
animal study, nanoparticles, review, selenium, toxicity

1 | INTRODUCTION

The impact of selenium on the human body for a long time led to mixed outcomes. Although selenium was previously thought to be extremely toxic, presently, it is considered a vital microelement. Despite its crucial role in normal bodily functioning, the therapeutic and toxic doses of selenium have a narrow range, and even subtoxic doses can have adverse effects on human health. To improve the delivery and absorption of this trace element without causing toxicity, selenium NPs perform the task effectively due to their high bioavailability and low toxicity. Gangadoo et al. (2020) propose the use of nanoselenium in various studies as a viable solution for this purpose.

Despite the widespread use of nanoselenium in various applications, limited information is available regarding its potential toxic effects. The existing literature includes only a handful of studies investigating the toxicity of selenium NPs. Conversely, comprehensive reviews exist on the overall pattern of selenium toxicity in humans (Vinceti et al., 2014, 2018; Vinceti, Filippini, Cilloni, Bargellini, et al., 2017). Therefore, it is crucial to gather and estimate experimental data pertaining to the toxicological properties of selenium NPs and its compounds including oxides.

The present study endeavors to provide an exhaustive review of the relevant toxicological data pertaining to nanoselenium. The overarching aim of this review is to investigate the following research questions:

1. Is there persuasive evidence to suggest that nanoselenium exerts deleterious effects on laboratory animal organisms?
2. Which biological functions and systems are impacted by such adverse effects?
3. Does nanoselenium exhibit any unique toxic mechanisms of action?
4. What is the dose–response relationship between exposure to selenium NPs and resultant adverse effects?

2 | MATERIALS AND METHODS

2.1 | Search strategy

In order to identify pertinent scholarly articles, a systematic bibliographic search was conducted independently by two reviewers utilizing online databases including PubMed, Google Scholar, and Web of Science. The search encompassed English-language publications up to February 28, 2023. To supplement the search results, reference lists were cross-checked for any additional studies that could be considered for inclusion. The literature search was performed using various combinations of keywords, such as selenium nanoparticles, Se NP, toxicity, cytotoxicity, pathology, rats, and mice, across different fields of study, including pathology, biochemistry molecular biology, cell biology, and toxicology (Table 1).

TABLE 1 Different combinations of keywords, which were used for the literature search.

Databases	Keywords
PubMed	Keywords: «selenium nanoparticles» or «SeNP» and «toxicity», «cytotoxicity» or «pathology»
Google Scholar	Keywords: «selenium nanoparticles» or «SeNP» and «toxicity», or «pathology» and «rats» or «mice»
Web of Science	Keywords: «selenium nanoparticles» or «SeNP» and «toxicity», or «pathology». Fields of study: pathology, biochemistry molecular biology, cell biology, toxicology.

2.2 | Study selection

In this study, the titles and abstracts of retrieved articles were examined by the author to identify publications that met the inclusion criteria. The inclusion criteria were restricted to studies involving the use of nanoparticles (NP) of selenium (Se) or its compounds within the range of 1 to 100 nm and in vivo investigations on rats or mice to evaluate the acute, subacute, subchronic, or chronic effects of NP. The effects generated by the NP, such as toxicity and cytotoxicity, were also considered. In contrast, studies that did not specify the particle size or employed particles larger than 100 nm, in vitro studies, investigations on the characterization and synthesis of NP, and research on positive properties, such as antimicrobial or anticancer properties, were excluded from the study.

Several studies have demonstrated that there are significant differences in the biological effects of nanoparticles and ions (Cho et al., 2012; Cronholm et al., 2013) as well as between nanoparticles and microparticles (Sutunkova, 2017). Therefore, we excluded studies that examined toxicity modeling involving particles larger than 100 nm. It is worth noting that particles with dimensions ranging from 1 to 100 nm in three directions can be classified as nanosized particles (U.S. Environmental Protection Agency, 2022; Vert et al., 2012), although some researchers may apply the term to particles up to 500 nm, such as fibers and tubes that are less than 100 nm in two dimensions (Zhang et al., 2013). Nonetheless, we did not include publications that deviated from the primarily spherical shape of nanoparticles, including green synthesis selenium nanoparticles (e.g., Cavalu et al., 2017; Kalishwaralal et al., 2016; Wadhwani et al., 2017) and bovine serum albumin (BSA) stabilized selenium nanoparticles (e.g., Zhang et al., 2001), selenium nanoparticles prepared through laser ablation from selenium sheet plates (Sutunkova et al., 2021), and selenium nanoparticles synthesized through femtosecond laser-induced plasma shock wave (Tzeng et al., 2020).

The present review excluded studies that investigated the toxic effects of the nanomaterial referred to as NP through in vitro experiments. This is due to the complex nature of extrapolating toxicity data from in vitro studies to that of the whole organism (Zhang et al., 2018). Moreover, caution should be exercised when generalizing such findings (Dubaj et al., 2022; García-Contreras et al., 2012). The review included any form of exposure to nanoselenium, such as

sharp, subacute, subchronic, or chronic, and any route of ingestion or administration. The focus of this review is on the adverse effects of nanoselenium; thus, studies on its synthesis and applications, as well as those that highlight its positive properties, such as its antibacterial, antimicrobial, anticancer, and dietary supplement functions, were excluded.

3 | RESULTS

A comprehensive electronic search was conducted on various databases until February 28, 2023, resulting in the identification of 17 relevant articles. Notably, some of the publications were authored by the same research team, namely:

Zhang et al. (2001), Zhang et al. (2005), Wang et al. (2007), and Zhang et al. (2008) from the University of Science and Technology of China;

Loeschner et al. (2014), Hadrup et al. (2016), and Hadrup et al. (2019) from the National Food Institute at the Technical University of Denmark.

3.1 | Body weight

In the context of experimental animal exposure to selenium nanoparticles (Se NP), several studies have reported varied changes in body weight when compared to control groups. Specifically, decreases in body weight were observed in some studies (Hadrup et al., 2019; He et al., 2014; Urbankova et al., 2021; Wang et al., 2007; Zhang et al., 2005, 2008), while other studies reported no changes (Hadrup et al., 2016) (Table 2). Notably, the absence of changes in body weight in response to a dose of 0.5 mg Se NP/kg reported by Hadrup et al. (2016) cannot be solely attributed to low dose exposure or the absence of intoxication, since decreases in body weight were observed at doses of 0.05 mg/kg Se NP (Hadrup et al., 2016) and 2 (Bhattacharjee et al., 2019), 20 mg/kg Se NP (Shakibaie et al., 2013), and 5 mg Se/kg food (Benko et al., 2012), but not at doses of 0.2, 0.4, 0.5, 2.5, 5, and 10 mg Se NP/kg (Hadrup et al., 2016, 2019; He et al., 2014; Shakibaie et al., 2013). Based on these observations, a nonlinear dose–response relationship is presumed for this indicator.

3.2 | Liver

Several studies have investigated the impact of selenium on liver function and histology. While some studies have reported an increase in alanine aminotransferase (ALT) activity (Wang et al., 2007; Zhang et al., 2005, 2008), others have observed a reduction (Urbankova et al., 2021; Zhang et al., 2019) or no change in ALT activity (He et al., 2014). As for aspartate aminotransferase (AST) activity, some studies reported no change (Shakibaie et al., 2013; Urbankova et al., 2021; Zhang et al., 2005), while others reported an increase (He et al., 2014) or a decrease (Zhang et al., 2019). Selenium species and compounds have been shown to increase oxidative stress, potentially resulting in toxic effects (Jablonska et al., 2016; Naderi et al., 2017). However, increasing selenium intake to levels required for optimal selenoprotein expression, specifically selenoprotein P expression, may have detrimental metabolic effects and increase the risk of type 2 diabetes and liver disease (Urbano et al., 2021; Vinceti, Filippini, Cilloni, Bargellini, et al., 2017; Vinceti et al., 2021; Wang et al., 2021).

TABLE 2 Experimental animal studies assessing effect on body weight under Se NP exposure.

Reference	Animals	NP, size. Dose, mg Se/kg, exposure duration	Effect
He et al. (2014)	Male rats	SeNPs, 79.88 ± 23.68 nm. 0.2, 0.4, 0.8, 2.0, 4.0, or 8.0 mg Se/kg, orally during 14 days	Decrease
Zhang et al. (2005)	Male Kunming mice	NPs of BSA-stabilized red amorphous elemental selenium, 20–60 nm. SeNPs orally: (1) 6 mg/kg body mass during 12 days (2) 2 and 4 mg/kg body mass during 15 days	
Wang et al. (2007)	Male Kunming mice	NPs of BSA-stabilized red amorphous elemental selenium, 20–60 nm, orally 5.0 for 7 days in succession.	
Zhang et al. (2008)	Male Kunming mice	NPs of BSA-stabilized red amorphous elemental selenium, 20–60 nm, orally 5.0 for 7 days in succession.	
Hadrup et al. (2019)	Female Wistar rats, SPF	NPs of BSA-stabilized (4 g/L) red amorphous elemental selenium, 32–38 nm on average, orally 0.05/0.5/4 mg/kg of Se during 28 days	
Urbankova et al. (2021)	Male Wistar albino rats	Elemental SeNPs, <100 nm, orally at a dose of 0.5, 1.5, 3.0, and 5.0 mg se/kg	
Hadrup et al. (2016)	Female Wistar rats, SPF	NPs of BSA-stabilized (4 g/L) red amorphous elemental selenium, 19 nm on average (from 10 to 80 nm), orally 0.5 mg of SeNP/kg during 14 days	No effect

TABLE 3 Histological assessment of Se NP on the liver of laboratory animals.

Reference	Animals	NP, size. Dose, mg Se/kg, exposure duration	Effect discovered by histology
Urbankova et al. (2021)	Male Wistar albino rats	Elemental SeNPs, <100 nm, orally at the doses 0.5 and 1.5 for 28 days	Moderate dystrophic parenchyma of liver
Urbankova et al. (2021)	Male Wistar albino rats	Elemental SeNPs, <100 nm, orally at the doses 3.0 for 28 days	Mild parenchyma dystrophy with intact trabecular organization
He et al. (2014)	Male rats	SeNPs, 79.88 ± 23.68 nm, 2.0 and 4.0 for orally during 14 days	Pathological changes of various extent, mainly including hyperplasia and edema
Urbankova et al. (2021)	Male Wistar albino rats	Elemental SeNPs, <100 nm, orally at the doses 5.0 for 28 days	Liver parenchyma with mild multifocal autolytic damage and signs of congestion
Wang et al. (2007), Zhang et al. (2008)	Male Kunming mice	NPs of BSA-stabilized red amorphous elemental selenium, 20–60 nm, orally 5.0 for 7 days in succession.	Hydropic degeneration of hepatocytes pertaining to reversible and moderate pathological changes
He et al. (2014)	Male rats	SeNPs, 79.88 ± 23.68 nm, 8.0 for orally during 14 days	Pathological changes, including liver degeneration and focal necrosis of hepatocytes

In terms of liver histology, studies have shown no dystrophic changes with selenium supplementation (Urbankova et al., 2021; Wang et al., 2007; Zhang et al., 2008). However, high doses of selenium have been found to lead to the destruction of hepatocytes (Urbankova et al., 2021) (Table 3).

3.3 | Accumulation in the organism

Selenium nanoparticles have been shown to accumulate in the liver (Lesnichaya et al., 2020; Loeschner et al., 2014; Urbankova et al., 2021; Zhang et al., 2019) and kidneys (Lesnichaya et al., 2020; Loeschner et al., 2014) of the organism, but not in the brain (Lesnichaya et al., 2020; Loeschner et al., 2014), stomach, lungs, muscles, blood plasma, or urine (Loeschner et al., 2014).

3.4 | Organism's antioxidant protection system

A dose-dependent decrease in the level of reduced glutathione in the liver has been observed, indicating an imbalance of redox reactions and impaired hepatocyte function (Zhang et al., 2005). The malondialdehyde (MDA) content either decreased (Zhang et al., 2005, 2019) or increased (Wang et al., 2007; Zhang et al., 2008), suggesting the occurrence of oxidative stress. It is worth noting that these effects were observed at similar doses of nanoparticles studied by the authors. Superoxide dismutase (SOD) activity either remained unchanged (Zhang et al., 2005) or decreased (Urbankova et al., 2021; Zhang et al., 2019), while catalase (CAT) activity was found to be elevated (Zhang et al., 2005).

3.5 | Selenium-dependent enzymes

Exposure to nanoparticles of selenium and its compounds has been repeatedly shown to increase the activity of selenium-dependent enzymes, including the selenium-containing forms of glutathione peroxidase (Urbankova et al., 2021; Wang et al., 2007; Zhang et al., 2001, 2005, 2008, 2019), phospholipid hydroxyperoxide glutathione peroxidase (Zhang et al., 2001), thioredoxin reductase (Wang et al., 2007; Zhang et al., 2001, 2008, 2019), and glutathione S-transferase (Wang et al., 2007; Zhang et al., 2005, 2008).

3.6 | Effects of NP of Se or its compounds on laboratory rodents shown by one team of authors

Upon reviewing the literature, we have found that the following changes, although not consistently replicated by other research teams, are significant for assessing the adverse impacts of Se NP on laboratory animals (Table 4).

Se NP have been observed to cause local alopecia (Hadrup et al., 2019) and impair fatty acid, protein (Hadrup et al., 2016), lipid (He et al., 2014), and carbohydrate (Urbankova et al., 2021) metabolisms.

Blood composition has also been affected, with a drastic reduction in the number of white blood cells at higher Se concentrations up to 77%, and reductions in bone marrow cell numbers caused by Se NP (20%) (Benko et al., 2012).

Histological examinations of the spermaries have revealed atrophy of seminiferous tubules and disturbed spermatogenesis (He et al., 2014), while histological examination of the thymus in rats exposed to nanoselenium showed cortex thinning and an unclear boundary between cortex and medulla (He et al., 2014).

The histology of kidneys also revealed contractions of the glomeruli in the Bowman capsule, which is a sign of glomerulonephritis, and signs of necrobiosis in some renal tubular cells of rats exposed to 8.0 mg Se/kg bw (He et al., 2014).

According to the literature, Se nanoparticles (Se NP) have been shown to have the ability to penetrate the blood–brain barrier (Lesnichaya et al., 2020), but they do not accumulate in the brain (Lesnichaya et al., 2020; Loeschner et al., 2014). Histological examination of the brain has revealed a decrease in astroglial cells, which

TABLE 4 Effects of Se NP or its compounds on laboratory rodents shown by one team of authors.

Reference	Animals	NP, size. Dose, mg Se/kg, exposure duration	Effects of NP
Benko et al. (2012)	10-week-old BDF1 male mice	Nano Se of 100 to 500 nm, 0.5, 5, or 50 ppm to the diet	The number of white blood cells was drastically reduced up to 77%, bone marrow cell numbers—up to 20%
He et al. (2014)	Male rats	SeNPs, 79.88 ± 23.68 nm, 0.2, 0.4, 0.8, 2.0, 4.0, or 8.0 mg Se/kg, orally during 14 days	Se NP can impair lipid metabolisms. Histological examination showed that (1) an atrophy of seminiferous tubules and disturbed spermatogenesis; (2) cortex thinning and an unclear boundary between cortex and medulla of the thymus; (3) kidneys showed contractions of the glomeruli in the Bowman capsule, which is a sign of glomerulonephritis. In some renal tubular cells of rats exposed to 8.0 mg Se/kg bw, the researchers found signs of necrobiosis.
Hadrup et al., 2016	Female Wistar rats, SPF	NPs of BSA-stabilized (4 g/L) red amorphous elemental selenium, 19 nm on average (from 10 to 80 nm), orally 0.5 mg of SeNP/kg during 14 days	Se NP can impair fatty acid, protein metabolisms.
Hadrup et al. (2019)	Female Wistar rats, SPF	NPs of BSA-stabilized (4 g/L) red amorphous elemental selenium, 32–38 nm on average, orally 0.05/0.5/4 mg/kg of Se during 28 days	Local alopecia
Khubulava et al., 2019	Male and female albino rats	SeNPs <100 nm, orally 1000 mg/kg, 5000 mg/kg once, and 500 mg/kg during 90 days	A single dose of Se NP at 1000 mg/kg caused destructive changes in the intestines (signs of initial epithelial erosion and desquamation; marked eosinophilia and abundant cellular infiltration in criptae zones). A single NP dose of 5000 mg/kg provoked signs of disorganization of mucosa and muscular layers in the large intestine (lesion and lymphoid infiltration of mucosal layer). It is interesting that no appreciable changes were discovered after a 90-day exposure to a dose of 500 mg/kg.
Lesnichaya et al., 2020	Male rats	NPs of SeO nanocomposite (NC) (6.8 and 24.5 nm), stabilized by k-carrageenan biocompatible polysaccharide, 500 μgr/kg body mass during 10 days	Se NP can penetrate through the blood–brain barrier, but they do not accumulate in the brain
Urbankova et al., 2021	Male Wistar albino rats	Elemental SeNPs, <100 nm, orally at a dose of 0.5, 1.5, 3.0 and 5.0 mg Se/kg	Se NP can impair carbohydrate metabolisms. Changes were found in intestines as well. Thus, oral administration led to changes of various degrees in the mucous lining of the intestines, from complete absence and deformation of intestinal villi in response to a dose 0.5 mg Se/kg to severe alterations in the mucous lining at a dose of 5.0 mg Se/kg (Urbankova et al., 2021).

Lesnichaya et al. suggest may be due to the action of Se nanoparticles on the astroglial elements of the sensorimotor cortex. The authors postulate that such selectivity may lead to essential alterations in the functional state of the sensorimotor cortex during the post-contact period (Lesnichaya et al., 2020).

Se NP also induce changes in the intestines. Oral administration of Se NP caused changes in the mucous lining of the intestines, ranging from complete absence and deformation of intestinal villi at a dose of 0.5 mg Se/kg to severe alterations in the mucous lining at a dose of 5.0 mg Se/kg (Urbankova et al., 2021). A single dose of Se NP at 1000 mg/kg resulted in destructive changes in the intestines, including initial epithelial erosion and desquamation, marked eosinophilia, and abundant cellular infiltration in criptae zones. Moreover, a single dose of 5000 mg/kg of Se NP provoked signs of disorganization of mucosa and muscular layers in the large intestine, including lesions and lymphoid infiltration of the mucosal layer (Khubulava et al., 2019). However, no significant changes were observed after a 90-day exposure to a dose of 500 mg/kg (Khubulava et al., 2019).

3.7 | NOAEL and LOAEL

According to Jia et al. (2005), the no-observed-adverse-effect level (NOAEL) for nanoselenium (20–60 nm NP of BSA-stabilized red amorphous elemental selenium) was determined to be 0.22 mg/kg body weight per day for males and 0.33 mg/kg body weight per day for females after 13 weeks of oral exposure in Sprague–Dawley rats. However, the findings of Hadrup et al. (2019) contradict these results, as they suggest that the lowest-observed-adverse-effect level (LOAEL) for nanoselenium is 0.05 mg/kg.

3.8 | The median lethal dose for the NP of Se and its compounds

According to various researchers, the median lethal dose (LD50) for Se NP is presented in Table 5. In Kunming mice, Zhang et al. (2001) reported an LD50 of 113.0 mg/kg with a 95% confidence interval of 89.9–141.9 mg/kg, while Wang et al. (2007) and Zhang et al. (2008) found an LD50 of 92.1 mg Se/kg with a 95% confidence interval of 71.1–131.1 mg/kg. For SPF-grade ICR male mice, Zhang et al. (2019) determined an LD50 of 72 mg Se/kg, whereas for female mice, it was 61.6 mg Se/kg. Zhang et al. (2019) also reported an LD50 of over 36 Se/kg for male and female rats. Lesnichaya et al. (2020) found an LD50 of over 2000 mg/kg for mice, while Khubulava et al. (2019) reported an LD50 of over 5000 mg/kg for rats.

4 | DISCUSSION

There is a body of evidence indicating that laboratory animals are negatively impacted by selenium nanoparticles. Research conducted by various teams has demonstrated the following effects, as shown in Figure 1:

- alterations in body weight, manifested as either a decrease or an increase;
- elevated activity of liver enzymes, particularly ALT and AF;
- heightened concentrations of selenium in the liver, with lesser effects seen in the kidneys;
- adverse effects on the organism's antioxidant defense system;
- enhanced activity of selenium-dependent enzymes.

4.1 | Body weight

According to Zhang et al. (2019), a reduction in body weight (as shown in Table 2) may be a characteristic but non-specific feature of nanoselenium toxicity. This observation is consistent with numerous pathologies induced by gold nanoparticles (Chen et al., 2009; Zhang et al., 2010), silver nanoparticles (Kim et al., 2010), and pesticides (Wang et al., 2019), which have also been found to result in changes in body weight.

4.2 | Liver

Based on the data presented in Table 3, a linear dose–response relationship for histomorphological indicators of liver condition is assumed. However, no specific indicators or their combinations have been identified in the literature as being exclusively associated with nanoselenium toxicity.

4.3 | Accumulation in the organism

The enhanced accumulation of Se NP in the liver can be attributed to the peculiarities of selenium metabolism, with the liver serving as the primary storage organ (Shang et al., 2019) and target site for its toxic effects (Diskin et al., 1979). However, the hepatic accumulation of nanoparticles cannot be considered a unique manifestation of selenium nanoparticle toxicity, as it is a common feature of various NP types, such as gold (Yang et al., 2017) and titanium dioxide (Jia

TABLE 5 Determination of LD50 for NP of Se and its compounds.

Reference	Animals, sample size	NP, size; exposure duration	LD50
Zhang et al. (2001)	Kunming male and female mice, 10 animals in each group	NP BSA-stabilized red amorphous selenium, 20–60 nm; orally administered	113.0 mg/kg with a 95% confidence interval of 89.9–141.9 mg/kg
Wang et al. (2007), Zhang et al. (2008)	Male Kunming mice	Nano-Se in the size range of 20–60 nm; orally administered	92.1 mg Se/kg (with a 95% confidence interval of 71.1–131.1)
Zhang et al. (2019)	SPF-grade ICP mice, males and females, 10 animals in each group	Selenium nanoparticles polysaccharide-protein complex (PTR-Se NP) from *Pleurotus tuber-regium*, 20 nm; orally administered	61.6 mg Se/kg for female and 72 mg Se/kg
Lesnichaya et al. (2020)	Nonlinear male mice, 10 animals in each group	Nanocomposite NP SeO, stabilized by κ-carrageenan biocompatible polysaccharide, 6.8 and 24.5 nm; orally administered	Over 2000 mg/kg
Khubulava et al. (2019)	Male and female albino rat	SeNPs, particle size below 100 nm; orally administered	Over 5000 mg/kg

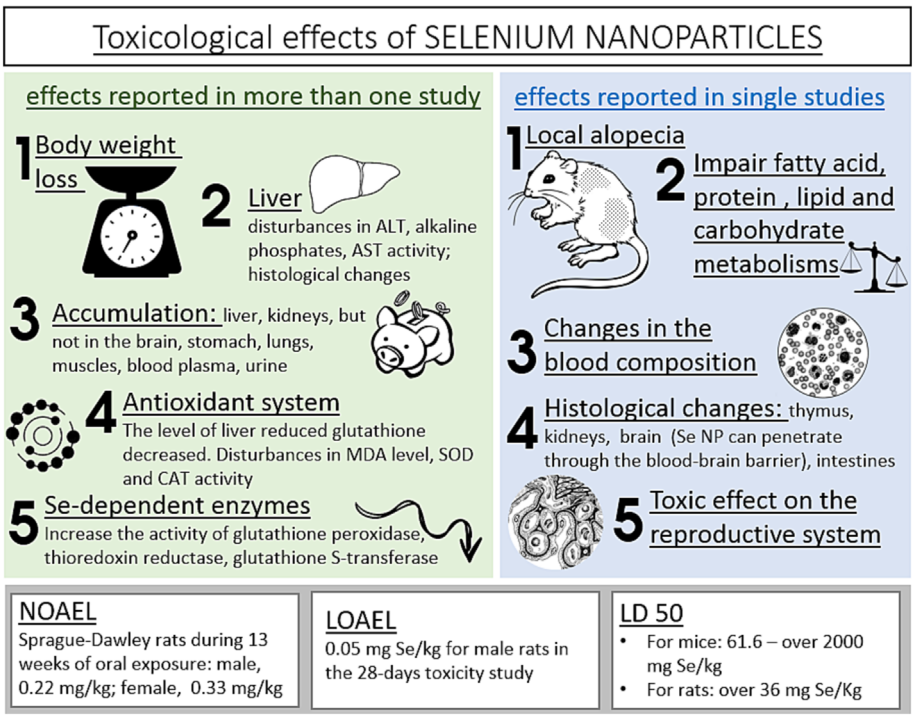

FIGURE 1 Effects of selenium nanoparticles on the organism of laboratory animals.

et al., 2017). The liver functions as a biological filtration system that intercepts 30%–99% of ingested nanoparticles from the bloodstream (Zhang et al., 2016).

4.4 | Organism's antioxidant protection system

In our view, exposure to nanoparticles (NP) of selenium and its compounds may gradually induce oxidative stress and reduce the adaptability of the organism. Changes in the antioxidant protection system are not exclusive to NP of selenium. For instance, oxidative stress can also be induced by cobalt oxide nanoparticles (Savi et al., 2021) or copper nanoparticles (Zou et al., 2021). Furthermore, macrophage and neutrophil activation due to gold NP (Zhang et al., 2003) or zinc oxide NP (Kennedy et al., 2009) may indirectly trigger ROS production.

4.5 | Selenium-dependent enzymes

It is plausible that upregulation of selenoproteins represents a compensatory response to oxidative stress, which is initiated by selenium exposure (Vinceti et al., 2022).

4.6 | Effects of NP of Se or its compounds on laboratory rodents shown by one team of authors

According to a study by Hadrup et al. (2019), the administration of selenium nanoparticles (Se NP) to laboratory rodents caused local alopecia, which is consistent with previous reports on the ability of selenium to induce hair loss in cases of acute poisoning (MacFarquhar et al., 2010). MacFarquhar et al. (2010) reported hair loss in 72% of cases of overdose with selenium-containing vitamin supplements, where the dose was as high as 41.749 μg/day, as compared to the recommended dose of 55 μg/day. In the study by Hadrup et al. (2019), the dose of Se NP administered was also found to be substantial for the experimental animals, necessitating a reduction in dosage on day 9 for females and on day 11 for males from 4 to 1 mg/kg. Eventually, on day 16, practically all animals in both groups had to be euthanized. It is plausible that hair loss due to Se NP could occur only at extremely high doses.

In relation to carbohydrate metabolism, Zhao Z. et al. investigated the potential effect of high doses of dietary selenium on the development of diabetes in pigs, and found evidence of an impact on the regulation of protein, carbohydrate, and lipid metabolism. Specifically, high levels of selenium consumption led to the accumulation of lipids in the liver and was associated with the stimulation of lipogenesis and gluconeogenesis, the suppression of lipolysis, and increased protein concentrations in the liver and muscles (Zhao et al., 2016). Epidemiological studies conducted in the United States in 2008–2010 also suggested a link between high levels of selenium in plasma and an increased risk of type 2 diabetes and hyperglycemia (Steinbrenner et al., 2011; Vinceti et al., 2021). However, the exact mechanisms underlying this relationship remain unclear, and it is not yet known whether excessive selenium disturbs signal transmission and/or insulin secretion or whether carbohydrate metabolism disorders influence selenium metabolism (Liao et al., 2020; Steinbrenner et al., 2011, 2022). The effect of selenium on glucose metabolism is believed to follow a nonlinear U-shaped dose–response curve (Kong et al., 2016; Wang et al., 2016), and it is unclear whether the effects of Se NP on

carbohydrate metabolism are similar, as no studies on changes in the dose–response relationship under the impact of nanoparticles and their ions have been conducted to date.

He et al. (2014) is the only available study on the potential toxicity of selenium nanoparticles (Se NP) on the reproductive system. Although selenium deficiency is often linked to male infertility, selenium is also essential for the proper functioning of the reproductive system (Oguntibeju et al., 2009; Qazi et al., 2019; Watanbe & Endo, 1991). Thus, the impact of altered Se levels should not be dismissed. Reduced fertility and germ cell numbers have been observed in association with altered Se levels and with decreased cjun and cfos mRNA levels (Shalini & Bansal, 2005).

While thymus pathology is typically associated with selenium deficiency (You et al., 2014), excessive consumption of selenium (>5.0 mg Se/kg sodium selenite) has been found to cause thymus lesions and a reduction in T-cell subpopulations in broiler chickens (Peng et al., 2010, 2011). Nevertheless, no studies investigating the direct effect of nanoselenium on the thymus were found.

We were unable to locate additional information on the potential renal toxicity of selenium and its compounds, including those in nano-size form. However, a clinical report documented a case of acute selenium poisoning resulting in acute renal failure, which resolved within 8 weeks (Kamble et al., 2009).

Damage to specific brain regions, such as the substantia nigra, has been linked to Parkinson's disease (Conte et al., 2013; Deng et al., 2021; Nelson et al., 2018), which has been attributed to both excessive and insufficient selenium levels in the body (Ellwanger et al., 2016), as such imbalances may elevate oxidative stress levels (Ellwanger et al., 2016; Kondaparthi et al., 2019; Zheng et al., 2020).

Some researchers have associated the observed intestinal alterations reported by Khubulava et al. (2019) with the fact that this organ is involved in detoxification processes (Strubelt et al., 1996).

4.7 | NOAEL and LOAEL

The LOAEL identified for rats is significantly higher than that for humans, which has been estimated to be approximately 0.04 mg/kg based on research conducted by Vinceti, Filippini, Cilloni, and Crespi (2017) and Vinceti et al. (2018).

4.8 | The median lethal dose for the NP of Se and its compounds

Khubulava et al. (2019) did not aim to determine the LD50. The study was conducted on nanoparticles with a size under 100 nm, with each group consisting of one female rat and two male rats receiving single doses of 1000 mg/kg and 5000 mg/kg. Despite the small number of animals involved, which typically increases the probability of random errors, the doses reported by the authors were not lethal. Considering interspecies differences between rats and mice, we refrain from making comparisons with this study.

The comparable LD50 value reported in the studies by Wang et al. (2007), Zhang et al. (2008), and Zhang et al. (2001) could be attributed to the fact that these studies were conducted by the same team of authors on the same line of male mice (Kunming), using identical particles of BSA-stabilized red amorphous selenium with a size of 20–60 nm.

The toxicity and bioavailability of selenium compounds vary significantly between different series of compounds (Nuttall, 2006; Vinceti, Filippini, Cilloni, & Crespi, 2017). For rats administered orally, the LD50 values are established as 7 mg Se/kg of body weight for sodium selenite, 138 mg Se/kg for selenium sulfides, and 6700 mg Se/kg for elemental selenium (Nuttall, 2006). It can be assumed that the toxicity of different nanosized selenium

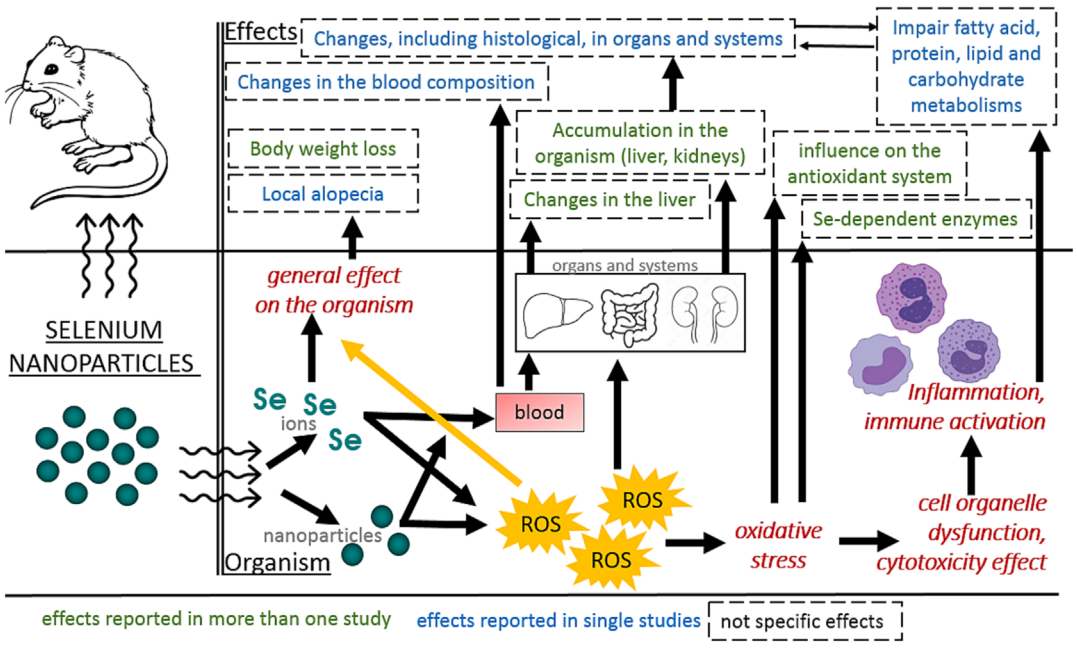

FIGURE 2 The proposed mechanism of action of nanoselenium based on the literature review.

compounds may also vary. Furthermore, although elemental selenium is considered to be the most inert (Poluboyarinov et al., 2019), the reviewed studies do not mention protein corona. The protein corona of nanoparticles and the biological response to it is crucial in nanotoxicology (Corbo et al., 2016; Durán et al., 2015), as it plays a critical role in the interaction between nanoparticles and cells, the rate of their elimination from the bloodstream, toxicity, and distribution in the organism (Bochkova et al., 2020).

Lesnichaya et al. (2020) proposed that fine nanoparticles of selenium exhibit higher chemical and biological activity, leading to increased biochemical interactions with organic compounds. Conversely, larger particles may be partially eliminated from the body through natural routes due to their low reactivity. However, the relationship between organ-systemic toxicity and size within the nanorange is not straightforward, as it depends on the inherent biological aggressiveness of specific nanoparticles and the mechanisms that control their toxicokinetics (Sutunkova et al., 2019).

The models used may significantly influence the outcome of studies, although the difference in LD50 between studies conducted by Zhang et al. (2019), Zhang et al. (2001), Wang et al. (2007), and Zhang et al. (2008) is insignificant. Linear animals possess certain biological characteristics that are passed down through generations. Studies performed on linear animals produce comparable results that can be replicated at any time in the future, as demonstrated by the studies conducted by Zhang et al. (2001), Wang et al. (2007), and Zhang et al. (2008). Genetic variations are crucial not only for the study of diseases but also for understanding responses to toxic agents (Festing, 1993). As such, researchers are advised to use more "stable" inbred strains instead of outbred stocks in toxicological research (Festing, 1979, 2010).

Figure 2 illustrates the hypothetical mechanism of nanoselenium's effects on the organism.

5 | CONCLUSIONS

5.1 | Summary of answers the research question

The objective of the present review was to address a series of questions posed in the introduction. Through a comprehensive evaluation of experimental data, we are now able to provide the following responses.

1. Can the adverse impact of nanoselenium on laboratory animal organisms be substantiated by compelling evidence?
   Based on a review of the available literature, it can be concluded that there is compelling evidence of nanoselenium's adverse impacts on laboratory animal organisms, as evidenced by the indicators of general toxic action such as decreased body weight and hepatotoxicity (increased activity of hepatic enzymes and accumulation of selenium in the liver).
2. Which bodily functions and systems are affected by these adverse effects?
   The impact of selenium nanoparticles and its compounds is not limited to the liver, which is the primary depot for their toxic action. These NPs affect various organs and systems, including the reproductive, nervous, and excretory systems. Moreover, Se NPs can also cause changes in carbohydrate, lipid, and protein metabolism.
3. Does nanoselenium feature any specific toxic action?
   No specific toxic action was found in the reports reviewed that unique to nanoselenium.
4. What is the relationship between the adverse effects of selenium nanoparticles and exposure dose?
   The relationship between the adverse effects of selenium NPs and exposure dose is characterized by a wide typological variety. The dose–response relationship for indicators such as body weight, activity of selenium-dependent enzymes, organism's antioxidant system performance indices, and selenium species is assumed to be complex and nonlinear. Additionally, the effect of selenium supplements, including nanoforms, on glucose metabolism is thought to exhibit a U-shaped dependence. On the other hand, a linear dose–response relationship is expected for the histomorphological indicators of the liver and the activity of some selenium-dependent enzymes.

5.2 | Significance of the conclusions and recommendations for further research

Nanomaterials are increasingly utilized in various human activities. Possible exposure to selenium and its compounds, including nanoforms, can occur in various industrial sectors such as glassmaking, ceramics production, rubber and chemical industries, electronics and optoelectronics, and metallurgy (Kulchitsky & Naumov, 2014; Lebed et al., 2015; Vrček, 2018). However, exposure to Se NPs is not limited to industrial workers, and other groups are also at risk. Nanoselenium has demonstrated potential applications in medicine as antibacterial (Gangadoo et al., 2020) and anticancer agents (Gangadoo et al., 2020; Kuršvietienė et al., 2020), drug delivery vehicles (Guan et al., 2018; Khurana et al., 2019), and for the treatment of neurodegenerative diseases (Sun et al., 2019). Nanoselenium is also used as a food additive (Skalickova et al., 2017) to prevent and treat selenium metabolism disorders in farm animals (Gangadoo et al., 2020), to enrich food (Folmanis et al., 2018), in plant growth (Yurkova & Omel'chenko, 2015), and in balneology (Nastueva et al., 2019).

Based on the aforementioned, we can see that this scientific inquiry has not been thoroughly researched despite the available literature. Therefore, it is imperative to conduct further investigations on Se NPs and evaluate its toxicity and potential hazards regarding various modes of exposure, to develop efficacious measures in preventing any potential adverse effects of this element.

AUTHOR CONTRIBUTIONS

Study concept and design: Yuliya V. Ryabova, Marina P. Sutunkova, and Ilzira A. Minigalieva. *Literature search and data collection*: Yuliya

V. Ryabova, Ilzira A. Minigalieva, and Lada V. Shabardina. *Data analysis*: Yuliya V. Ryabova, Marina P. Sutunkova, Tommaso Filippini, and Ilzira A. Minigalieva. *Writing—original draft preparation*: Yuliya V. Ryabova. *Review and editing*: Marina P. Sutunkova, Tommaso Filippini, and Aristides Tsatsakis. All authors contributed to a critical revision of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

REGISTRATION AND PROTOCOL

The review was not registered. The review protocol was not prepared.

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