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Toxicity of repeated oral intake of organic selenium, inorganic selenium, and selenium nanoparticles: A review

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ABSTRACT

Background: To protect from toxicity at supra-essential doses of selenium, it is important to determine dose levels at which adverse effects occur.
Methods: We identified relevant literature on the repeated dosage of selenium and extracted dose descriptors on reported endpoints, except on genotoxicity/carcinogenicity.
Results: Selenium forms with toxicological data were organic ones: selenomethionine, selenocystine/selenocysteine; and inorganic ones, including selenite (SeO_3^{2-}), selenate (SeO_4^{2-}), selenium sulphide (SeS_2), selenide (Se^{2-}) and selenium nanoparticles. Clinical signs of selenium toxicity in humans include a garlicky-smelling breath, hair loss, and nail changes. One human study showed increased mortality following daily ingestion of 300 μg Se per day for 5 years, equal to a lowest-observed-adverse-effect level (LOAEL) of ~4.3 μg/kg bw/days. The corresponding no-observed-adverse-effect level (NOAEL) was ~2.9 μg Se/kg bw/day. One study reported an increased risk of type 2 diabetes after ~2.9 μg Se/kg bw/day, but other studies with similar doses found no increases in mortality or incidence of type 2 diabetes. NOAELs on affected body weight in animal studies were 0.24–1.2 mg Se/kg bw/day. Other endpoints of selenium toxicity in animals include hepatotoxicity with a NOAEL as low as 2 μg/kg bw/day in rats, as well as gastrointestinal, cardiovascular, and reproductive toxicities with NOAELs of 0.6 (gastrointestinal), 0.08, and 0.4 (cardiovascular) and ≥ 0.04 mg Se/kg bw/day (reproductive), respectively.
Conclusions: Dose descriptors describing selenium toxicity were as low as 2–3 μg Se/kg bw/day.

1. Introduction

Selenium is an essential trace element and is a building block of the amino acids selenomethionine, selenocysteine, and an oxidised form of the latter—namely selenocystine [1]. Selenomethionine, an analogue of methionine, is believed to be non-specifically incorporated into the protein pool [2]. Selenocysteine is a building block of transport protein selenoprotein P and the antioxidant enzymes: glutathione peroxidases and thioredoxin reductases [3,4]. Selenium deficiency involves such signs as cardiomyopathy in humans [5] and liver necrosis and muscular dystrophy in animals [1,6].

Selenium forms include organic ones with one or more chemical bonds between selenium and carbon, for example, selenocysteine and selenomethionine, and inorganic ones having no carbon, for example, selenite (SeO_2^{-3}) and selenate (SeO_2^{-4}). Human exposure is via organic selenium in such foodstuffs as fish, shellfish, and organ meats [7–9]; one particularly rich source is Brazil nuts [10]. In addition, food supplements often contain inorganic selenium [11]. Normal intake levels are between 11 and 280 μg Se/day (0.15 and 4 μg Se/kg bw/day) [12–18]. Normal blood levels are around 100 μg/L [15,19–22]. Excessive intake in animals via plants that grow on selenium-rich soil occurs in some parts of the world [23,24], and likewise, the human selenium intake is also different in various parts of the world due to crops grown in soil with different levels of selenium [25–27].

We here review selenium toxicity after repeated intake or dosing via the oral route. Knowledge on at what levels different selenium forms become toxic is important in the risk assessment of this element. This work complements our previous reviews of acute oral toxicity and biokinetics of selenium [28,29]. We collected dose descriptors, NOAELs and LOAELs, of available studies to assess dose levels at which toxicity occurs. Concerning cancer risk, some studies point to a protective effect of selenium, while others point to increased risk. However, to limit the extent of the current article, we omitted carcinogenicity and its associated endpoint, genotoxicity. Selenosis describes severe selenium toxicity

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in livestock after consumption of selenium-rich plants and involves signs such as staggering gait, emaciation, alopecia, erosion of joints, and deformation and shedding of hooves [23,24,30,31]. Due to it being specific to animals, selenosis is not discussed further in this article.

2. Methods

We found relevant literature using the search string "selenium AND oral toxicity", providing 357 hits in the PubMed database [32] and 290 hits in Web of Science [33] (performed in October 2021, and again in November 2022 and May 2023). In addition, we reviewed the reference lists of the retrieved articles to capture studies not identified in the searches. In total, we identified 107 relevant articles.

We summarised dose descriptors in tables in each section on specific toxicity endpoints. Studies for which we set no dose descriptors included those only reporting changes in enzyme levels.[1] Also, we set no dose descriptors on case studies, as these represent only single data points. Doses given in food or drinking water as parts per million (ppm) were converted to doses per kg body weight (bw) by use of European Food Safety Authority (EFSA) default values [34]. If nothing else is mentioned, selenate and selenite were in the form of sodium salts.

3. Human mortality and selenium exposure

One study looked at the long-term mortality after selenium supplementation to investigate whether selenium supplementation prolongs life expectancy by reducing cancer risk. A Danish population of 491 women and men with a baseline plasma selenium of 89 μg/L was supplemented with selenium-enriched yeast for 5 years. Mortality was elevated at 300 μg Se/day (~4.3 μg Se/kg bw/day). The hazard ratio for all-cause mortality when comparing that dose level to a placebo was 1.62 (95% confidence interval (CI), 0.66–3.96) at 5 years of exposure and 1.59 (95% CI, 1.02–2.46) over the entire follow-up period of an additional 10 years. No increase was observed at 100 or 200 μg Se/day (~1.4 and 2.9 μg Se/kg bw/day) ($NOAEL_{increased\ mortality}$: ~2.9 μg Se/kg bw/day) [35] (Table 1).

Two case reports suspected excessive selenium intake to be causative in the deaths of cystic fibrosis patients. In one case, a 17-year-old male who had ingested selenium yeast complex tablets for 14 days had a selenium intake of 400 μg/day (~6 μg Se/kg bw/day). Symptoms before death included vomiting, weight loss, and decreased appetite. The other case was an 11-month-old girl who died one week after the discontinuation of a selenium-enriched yeast, which she had been fed for 2 months (25 μg Se/day ~5 μg Se/kg bw/day[2]). The symptoms leading up to her death were weight loss, respiratory distress, dehydration, and low serum calcium [36] (Table 1).

Table 1
Mortality in humans – dose descriptors.

Mortality in humans – dose descriptors	
NOAEL	LOAEL
Humans, Se-enriched yeast, ~1.4, 2.9, or 4.3 μg Se/kg bw/day, 5 years, $NOAEL_{increased\ mortality}$: 2.9 μg Se/kg bw/day[35]	Humans, Se-enriched yeast, $LOAEL_{increased\ mortality}$: 4.3 μg Se/kg bw/day[35] Humans, selenium yeast complex and selenium-enriched yeast, two case-studies in cystic fibrosis patients reported deaths suspected to be caused by selenium: ~6 μg Se/kg bw/day for 14 days (17-year-old male) and ~5 μg Se/kg bw/day for 2 months (11-month-old girl) [36]

4. Effects on body weight and lethality in animals

4.1. Selenium in food

Baker et al. fed a high selenium diet to pigs by either *Astragalus praelongus* (31.6 ppm Se in feed) (~2.5 mg Se/kg bw/day), *Astragalus bisulcatus* (31.7 ppm, ~2.5 mg/kg bw/day) or selenite (26.6 ppm, ~2.1 mg Se/kg bw/day). The intended treatment period was 9 weeks, but the animals were necropsied after developing ataxia or paralysis. All forms of selenium caused weight loss (selenium in *Astragalus* $LOAEL_{body\ weight}$: 2.5 mg Se/kg bw/day; selenite $LOAEL_{body\ weight}$: 2.1 mg Se/kg bw/day) [37] (Table 3).

Rats were administered 10 ppm selenium given as seleniferous wheat (60 days) (~1.2 mg Se/kg bw/day) or in an unknown form via drinking water (6 weeks) (~1.2 mg/kg bw/day); increased lethality and lower body weight gain were seen as compared with control ($LOAEL_{lethality}$: 1.2 mg Se/kg bw) [38]. Klug et al. administered seleniferous wheat containing 13 ppm selenium (1.6 mg Se/kg bw/day) to rats for 30 days and found a reduced growth rate (seleniferous wheat: $LOAEL_{reduced\ body\ weight\ gain}$: 1.6 mg/kg bw) [39]. Halverson and colleagues dosed seleniferous wheat or selenite to rats via the diet for 6 weeks (~0.2–1.3 mg Se/kg bw/day). Growth reduction was seen at 0.6 mg Se/kg bw/day and above after selenite and at 0.8 mg Se/kg bw/day and above after seliniferous wheat. Deaths occurred at ≥ 1 mg Se/kg bw/day. For selenite, in only one of eight at 1 mg, and one of ten animals at 1.2 and 1.3 mg Se/kg bw/day. In the seliniferous wheat group, death occurred in 5 of 8 and 8 of 8 animals at 1.2 and 1.3 mg Se/kg bw/day, respectively. Selenite $NOAEL_{growth\ reduction}$: 0.4 mg Se/kg bw/day; $NOAEL_{growth\ reduction}$ Se as seleniferous wheat: 0.6 mg Se/kg bw/day (dose descriptors for lethality are in Table 2) [40] (Table 3).

4.2. Selenocystine and selenomethionine

Selenocystine was dosed to mice at 5, 10, 15, or 20 mg Se/kg bw/day by stomach tube, 6 days per week for 30 days. Reduced body weight was seen at all dose levels, while all mice died at doses of 15 and 20 mg Se/kg bw/day (selenocystine $LOAEL_{body\ weight}$: 5 mg Se/kg bw/day, lowest tested dose; $NOAEL_{lethality}$: 10 mg Se/kg bw/day) [41] (Table 3).

One study compared inorganic forms of selenium to selenomethionine and selenocystine in rats dosed via diet for 5 weeks. Selenomethionine at 1 and 10 ppm (~0.12 and 1.2 mg Se/kg bw/day) gave a $NOAEL_{no\ effect\ on\ body\ weight}$: 1.2 mg Se/kg bw/day (highest dose). Selenocystine (0.12 and 1.2 mg/kg bw/day) resulted in decreased body weight gain: selenocystine $LOAEL_{body\ weight\ gain}$: 0.12 mg Se/kg bw/day (lowest dose tested). Selenium sulphide 30, 100, and 300 (no survivors) ppm (3.6, 12, and 36 mg/kg bw/day) had an effect, whereas 10 ppm had not (1.2 mg/kg bw/day) (selenium sulphide $NOAEL_{lethality}$: 1.2 mg Se/kg bw/day). Selenide at 10, 30, and 60 ppm (1.2, 3.6, and 7.2 mg/kg bw/day) resulted in decreased body weight gain compared to controls (selenide $LOAEL_{body\ weight\ gain}$: 1.2 mg Se/kg bw/day, lowest tested dose). Selenite at 1 and 10 (0.12 and 1.2 mg/kg bw/day) had no effect, whereas 30 and 100 ppm (3.6 and 12 mg/kg bw/day) caused no survivors (selenite $NOAEL_{lethality}$: 1.2 mg Se/kg bw/day). Selenate decreased the body weight gain in both doses 10 and 30 ppm (1.2 and 3.6 mg Se/kg bw/day) (selenate $LOAEL_{body\ weight\ gain}$: 1.2 mg Se/kg bw/day, lowest tested dose) [42] (Table 3).

Concerning selenomethionine, hamsters were administered diets supplemented with 0.1, 5, or 10 ppm Se as selenomethionine (~0.1, 0.6,

[1] We acknowledge that changes in enzymes originating from tissues/organs of greater than 50% is a starting point to consider adverse according to WHO [105].

[2] At an estimated body weight of 5 kg

Table 2
Lethality in animals.

Effects on lethality in animals – dose descriptors	
NOAEL	LOAEL
Selenium from food	
	Rats, seleniferous wheat, ~1.2 mg Se/kg bw/day, 60 days, $LOAEL_{lethality}$: 1.2 mg Se/kg bw[38]
Rats, seleniferous wheat, ~0.2, 0.4, 0.6, 0.8, 1.0, 1.2 and 1.3 mg Se/kg bw/day, 6 weeks. Seleniferous wheat $NOAEL_{lethality}$: 1.0 mg Se/kg bw/day based on lethality at higher dose and only one dead animal in the 1.0 group [40]	Rats, seleniferous wheat, $LOAEL_{lethality}$: 1.2 mg Se/kg bw/day (5 of 8 animals died, at 1.3 mg Se/kg bw/day 8 of 8 animals died)[40]
Selenomethionine	
Macaques, selenomethionine, doses starting at a range of 0–240 μg Se/kg bw/day, but reduced to 0, 10, 25, 47, 60, 75, 81 and 120 μg Se/kg bw/day during the study, 30 days. One of 2 animals in the 240 μg Se/day-group died, and the other was euthanised for humanitarian reasons, no dose descriptor was set due to a limited number of animals per dose group[44]	
Hamsters, selenomethionine, ~0.1, 0.6 and 1.2 mg Se/kg bw/day, 21 days. $NOAEL_{lethality}$: 1.2 mg Se/kg bw/day (highest tested dose)[43]	
Selenocystine	
Mice, selenocystine, 5, 10, 15, or 20 mg Se/kg bw/day, 6 days/ week for 30 days, $NOAEL_{lethality}$: 10 mg Se/kg bw/day[41]	Mice, selenocystine $LOAEL_{lethality}$: 15 mg Se/kg bw/day[41]
Inorganic selenium	
Rats, selenite, ~0.2, 0.4, 0.6, 0.8, 1.0, 1.2 and 1.3 mg Se/kg bw/day, 6 weeks, $NOAEL_{lethality}$: 1.3 mg Se/kg bw day (highest dose), note that one animal died in this group[40]	
Hamsters, selenite, 0.03, 1.2, 2.4, 4.8 or 9.6 mg Se/kg bw/day, 21 days, $NOAEL_{lethality}$: 4.8 mg Se/kg bw/day [43]	Hamsters, selenite, $LOAEL_{lethality}$: 9.6 mg Se/kg bw/day[43]
	Rats, selenate or selenite, ~1.2 mg/kg bw/day[a], 21 days, selenite/selenate $LOAEL_{lethality}$: 1.2 mg Se/kg bw/day [49]
Rats, selenite or selenate, ~0.2, 0.4, 0.7 or 1.1 mg Se/kg bw/day, 4–6 weeks. Selenite $NOAEL_{lethality}$: 0.4 mg Se/kg bw/day and selenate $NOAEL_{lethality}$: 0.7 mg Se/kg bw/day[50]	Rats, selenite or selenate, Selenite $NOAEL_{lethality}$: 0.7 mg Se/kg bw/day, selenate $LOAEL_{lethality}$: 1.1 mg Se/kg bw/day[50]
Rats, selenium sulphide, ~3.6, 12 and 36 mg Se/kg bw/day, 5 weeks, $NOAEL_{lethality}$: 12 mg Se/kg bw/day Selenide, ~1.2, 3.6 and 7.2 mg Se/kg bw/day, 5 weeks, $NOAEL_{letahlity}$ 7.2 mg Se/kg bw/day (highest tested dose) Selenite, ~0.12, 1.2, 3.6 and 12 mg Se/kg bw/day. The lowest two doses had no effect, whereas 3.6 and 12 mg Se/kg bw/day resulted in no survivors, 5 weeks, $NOAEL_{lethality}$: 1.2 mg Se/kg bw/day Selenate, ~1.2 and 3.6 mg Se/kg bw/day, $NOAEL_{lethality}$: 3.6 mg Se/kg bw/day (highest tested dose) This study also included selenomethionine and selenocystine and both showed no lethality at highest doses, $NOAEL_{lethality}$: 1.2 mg Se/kg bw/day [42]	Rats, selenium sulphide, $LOAEL_{lethality}$: 36 mg Se/kg bw/day (no survivors) Selenite, $LOAEL_{lethality}$: 3.6 mg Se/kg bw/day[42]
Selenium nanoparticles	
None of 4 repeated dose studies included in the table on effects of Se on body weight showed lethality.	

[a]EFSA default values have in this article been used to calculate doses in mg Se/kg bw/day based on levels in feed or in drinking water [106].

and 1.2 mg Se/kg bw/day) or with 0.25–80 ppm selenium as selenite (0.03–9.6 mg Se/kg bw/day) for 21 days. Both substances gave a reduced growth rate at 1.2 mg Se/kg bw/day or greater. Lethality was observed in 3 of 10 animals given selenite at 9.6 mg Se/kg bw/day (selenite $NOAEL_{growth\ rate}$: 0.03 mg Se/kg bw; selenomethionine $NOAEL_{growth\ rate}$: 0.6 mg Se/kg bw/day). On the one hand, we set no LOAEL on lethality as the effect was not statistically significant (in Fischer's exact test); on the other hand, it is hard-pressed to set a NOAEL when 3 of 10 animals died [43] (Tables 2 and 3).

Macaques were administered selenomethionine in doses starting at a range of 25–600 μg/kg bw/day, which was reduced to 25–300 μg/kg bw/day during the 30-day study (10, 25, 47, 60, 75, 81, 120 μg Se/kg bw/day). Body weight was decreased at 75–81 and 120 μg Se/kg bw/day and in two animals in a 600 μg/kg bw/day group (240 μg Se/kg bw/day). The animals in these groups also had to have extra food to prevent death. Further, concerning lethality, one animal in the 240 μg Se/kg bw/day group died suddenly on day 11, and another had to be killed on day 17, with a reduction in body weight of 14% ($NOAEL_{reduced\ body\ weight}$: 60 μg Se/kg bw/day) [44,45]. Pregnant macaques were administered selenomethionine by nasogastric intubation during the foetal organogenesis period (doses: 10, 60, 120 Se/kg bw). Two to three dams were followed until term at approximately gestation day 165, while a remaining seven dams per group had a hysterectomy on gestation day 100. The body weight was reduced at the highest dose ($NOAEL_{reduced\ body\ weight}$: 60 μg Se/kg bw/day) [46] (Tables 2 and 3).

Concerning studies with no lethality, selenium-deficient rats were administered 2 mg/kg selenium to the diet in the form of selenomethionine or selenite for 110 days (~0.2 mg Se/kg bw/day). Animals fed selenomethionine exhibited reduced growth rates (LOAEL: 0.2 mg Se/kg bw/day), while those fed selenite did not [47]. Mice were administered selenite or selenomethionine in the drinking water at 0, 1, 3, or 9 ppm Se for 14 days (~0.2, 0.6 and 1.8 mg Se/kg bw/day). The body weight was decreased at the highest dose of selenite (selenite $NOAEL_{body\ weight}$: 0.6 mg Se/kg bw/day), while even the highest dose of selenomethionine caused no effects on body weight (selenomethionine $NOAEL_{body\ weight}$: 1.8 mg Se/kg bw/day) [48] (Table 3).

4.3. Inorganic selenium

Rats were administered potassium selenate or selenite at 10 ppm of selenium in the diet (~1.2 mg/kg bw/day).[3] After 21 days, the lethality rate of potassium selenate was 17%, and that of selenite was 11%; no deaths occurred in the control group (Selenite $LOAEL_{lethality}$: 1.2 mg Se/kg bw/day; selenate $LOAEL_{lethality}$: 1.2 mg Se/kg bw/day) [49]. Rats were administered selenite or selenate in the drinking water for 4–6 weeks (~0.2, 0.4, 0.7, or 1.1 mg Se/kg bw/day). The two lowest doses caused a small reduction in body weight at both dosage periods. Lethality was observed after exposure levels of 0.7 and 1.1 mg Se/kg bw/day for selenite (4 of 6 died,[4] and 6 of 6 died at the second highest and highest dose, respectively), while only 2 of 6 died after selenate at 0.7 mg Se/kg bw/day (not statistically different by Fischer's exact test). Selenite $NOAEL_{lethality}$: 0.4 mg Se/kg bw/day; selenate $NOAEL_{lethality}$: 0.7 mg Se/kg bw/day, and for both substances: $LOAEL_{body\ weight}$: 0.2 mg Se/kg bw/day) [50]. Rats were dosed with selenite via drinking water for 35 days, 1 or 2 years at 1, 4, 8, 16, and 64 ppm Se (~0.09, 0.36, 0.72, 1.4, and 5.8 mg Se/kg bw/day). Survival was decreased at 35 days at 1.4 mg for 5-week-old animals, while survival was zero at 5.8 mg Se/kg

[3] EFSA default values have in this article been used to calculate doses in mg Se/kg bw/day based on levels in feed or in drinking water [106].

[4] The P value of Fischer's exact test is 0.06 (4 dead of 6), so the results are only borderline statistically significant.

Table 3
Effects on body weight (gain) in animals – dose descriptors.

Effects on body weight (gain) in animals – dose descriptors	
NOAEL	LOAEL
Selenium from food	
	Pigs, *Astragalus praelongus or Astragalus bisulcatus*, ~2.5 mg Se/kg bw/day. The intended treatment period was 9 weeks, but the animals were necropsied after developing ataxia or paralysis. Both forms: $LOAEL_{weight\ loss}$: 2.5 mg/kg bw [37]
	Rats, seleniferous wheat, 1.6 mg Se/kg bw/day, 30 days, $LOAEL_{reduced\ body\ weight\ gain}$: 1.6 mg Se/kg bw[39]
Rats, seleniferous wheat, ~0.2, 0.4, 0.6, 0.8, 1.0, 1.2 and 1.3 mg Se/kg bw/day, 6 weeks, $NOAEL_{reduced\ body\ weight\ gain}$: 0.6 mg Se/kg bw/day[40]	Rats seliniferous wheat, $LOAEL_{reduced\ body\ weight\ gain}$: 0.8 mg Se/kg bw/day[40]
Selenomethionine	
Macaques, selenomethionine, doses starting at a range of 0–240 μg Se/kg bw, but reduced to 0, 10, 25, 47, 60, 75, 81 and 120 μg Se/kg bw/day during the study, 30 days, $NOAEL_{reduced\ body\ weight}$: 0.06 mg Se/kg bw/day [44]	Macaques, selenomethionine, $LOAEL_{reduced\ body\ weight}$: 0.08 mg Se/kg bw/day) (Cukierski et al., 1989)
Pregnant macaques 10, 60, 120 Se/kg bw during the organogenesis period. Two to three dams were followed until term at approximately gestation day 165, while a remaining seven dams per group had hysterectomy on gestation day 100. Reduced body weight was more pronounced at highest dose than in controls, $NOAEL_{reduced\ body\ weight}$: 60 μg Se/kg bw/day[46]	Pregnant macaques, selenomethionine $LOAEL_{reduced\ body\ weight}$: 120 μg Se/kg bw/day[46]
Hamsters, selenomethionine, ~0.6 and 1.2 mg Se/kg bw/day, 21 days, $NOAEL_{reduced\ body\ weight\ gain}$: 0.6 mg Se/kg bw/day[43]	Hamsters, selenomethionine, $LOAEL_{growth\ rate}$: 1.2 mg Se/kg bw/day [43]
Mice, selenomethionine, ~0.2, 0.6 and 1.8 mg Se/kg bw/day, 14 days, $NOAEL_{reduced\ body\ weight\ gain}$: 1.8 mg Se/kg bw/day (highest tested dose) [48]	
	Selenium deficient rats, selenomethionine, ~0.2 mg Se/kg bw/day), 110 days, $LOAEL_{reduced\ body\ weight\ gain}$: 0.2 mg Se/kg bw/day[47]
Rats, selenomethionine, ~0.12 and 1.2 mg Se/kg bw/day), 5 weeks, $NOAEL_{body\ weight}$: 1.2 mg Se/kg bw/day (highest dose)[42]	
Selenocystine	
	Mice, selenocystine, 5, 10, 15, or 20 mg Se/kg bw/day, 6 days per week for 30 days, $LOAEL_{body\ weight}$: 5 mg Se/kg bw/day (lowest tested dose)[41].
	Rats, selenocystine, ~0.12 and 1.2 mg Se/kg bw/day, 5 weeks, $LOAEL_{body\ weight\ gain}$: 0.12 mg Se/kg bw/day) (lowest dose tested)[42]
Inorganic selenium	
Mice, selenite, ~0.2, 0.6 and 1.8 mg Se/kg bw/day, 14 days, $NOAEL_{body\ weight}$: 0.6 mg Se/kg bw/day[48]	Mice, selenite, $LOAEL_{body\ weight}$: 1.8 mg Se/kg bw/day[48]
Selenium deficient rats, selenit, ~0.2 mg Se/kg bw/day, 110 days, ($NOAEL_{reduced\ growth\ rate}$: 0.2 mg Se/kg bw/day (highest dose tested)[47]	
Hamsters, selenite, ~0.03, 1.2, 2.4, 4.8 or 9.6 mg Se/kg bw/day, 21 days, $NOAEL_{growth\ rate}$: 0.03 mg Se/kg bw [43]	Hamsters, selenite, $LOAEL_{growth\ rate}$: 1.2 mg Se/kg bw[43]

Table 3 (*continued*)

Effects on body weight (gain) in animals – dose descriptors	
NOAEL	LOAEL
Rats, selenite, ~0.2, 0.4, 0.6, 0.8, 1.0, 1.2 and 1.3 mg Se/kg bw/day, 6 weeks, $NOAEL_{growth\ reduction}$: 0.4 mg Se/kg bw/day[40]	Rats, selenite, $LOAEL_{growth\ reduction}$: 0.6 mg Se/kg bw/day [40]
	Pigs, selenite, ~2.1 mg Se/kg bw/day, the intended treatment period was 9 weeks but the animals were necropsied after developing ataxia or paralysis. $LOAEL_{weight\ loss}$: 2.1 mg/ kg bw[37]
	Rats, selenite or selenate, ~0.2, 0.4, 0.7 or 1.1 mg Se/kg bw/day, 4–6 weeks, for both substances: $LOAEL_{body\ weight}$: 0.2 mg Se/kg bw/day)[50]
	Rats, selenate, ~0.9 mg Se/kg bw/day, 15 or 18 weeks, $LOAEL_{body\ weight}$: 0.9 mg Se/kg bw/day[52]
Rats, selenite, ~0.02, 0.24 and 0.6 mg Se/kg bw/day, 28 days, $NOAEL_{body\ weight}$: 0.24 mg Se/kg bw/day[53]	Rats, selenite, $LOAEL_{body\ weight}$: 0.6 mg Se/kg bw/day[53]
	Rats, selenite, ~0.6 and 1.0 mg Se/kg bw/day, 9 weeks, $LOAEL_{body\ weight}$: 0.6 mg Se/kg bw/day[54]
	Rats, selenite, 0.2 and 0.5 mg Se/kg bw/day, 5 weeks, $LOAEL_{body\ weight\ gain}$: 0.2 mg Se/kg bw/day[55].
	Mice, selenite, ~9.6 mg/kg bw/day, 46 days, $LOAEL_{body\ weight}$: 9.6 mg Se/kg bw/day[56]
	Rats, selenite, ~2.8 mg Se/kg bw/day, 17 weeks, $LOAEL_{body\ weight}$: 2.8 mg Se/kg bw/day[57]
Rats, selenium sulphide, ~1.2, 3.6, 12 and 36 mg Se/kg bw/day, $NOAEL_{body\ weight\ gain}$: 1.2 mg Se/kg bw/day	Rats, selenium sulphide, $LOAEL_{body\ weight\ gain}$: 3.6 mg Se/kg bw/day
Rats, selenite, ~0.12 and 1.2 mg/kg bw/day, 5 weeks, $NOAEL_{body\ weight\ gain}$: 1.2 mg/kg bw/day[42]	Rats, selenide, ~1.2, 3.6 and 7.2 mg Se/kg bw/day, 5 weeks, $LOAEL_{body\ weight\ gain}$: 1.2 mg Se/kg bw/day (lowest tested dose)
	Rats, Selenate, ~1.2 and 3.6 mg/kg bw/day, 5 weeks, $LOAEL_{body\ weight\ gain}$: 1.2 mg Se/kg bw/day, (lowest tested dose) [42]
Selenium nanoparticles	
Rats, selenium nanoparticles or selenite, 0.05, 0,5 mg Se/kg bw day for both selenium forms and 4 mg for selenium nanoparticles, 28 days, Selenite $NOAEL_{body\ weight}$: 0.05 mg Se/kg bw/day[58]	Rats, selenium nanoparticles or selenite, selenium nanoparticles $LOAEL_{body\ weight}$: 0.05 mg/kg bw (lowest dose tested), Selenite $LOAEL_{body\ weight}$: 0.5 mg Se/kg bw/day[58]
Mice, selenate, hydroselenite, selenium nanoparticles (100–500 nm), an organic form of selenium produced by *Saccharomyces cerevisiae* - Sel-Plex (selenium-enriched yeast), or the bacterially formed selenium nanoparticle preparation Lacto-MicroSelenium, ~0.1, 1, and 10 mg/kg bw/day[a], 14 days. Selenium nanoparticles $NOAEL_{body\ weight\ reduction}$: 1 mg Se/kg bw/day Selenite $NOAEL_{body\ weight\ reduction}$: 1 mg Se/kg bw/day Selenate $NOAEL_{body\ weight\ reduction}$: 1 mg Se/kg bw/day Sel-plex $NOAEL_{body\ weight\ reduction}$: 1 mg Se/kg bw/day Lacto-MicroSelenium $NOAEL_{body\ weight\ reduction}$: 10 mg Se/kg bw/day (highest dose tested)[61]	Mice, selenium nanoparticles $LOAEL_{body\ weight\ reduction}$: 10 mg Se/kg bw/day Selenite $LOAEL_{body\ weight\ reduction}$: 10 mg Se/kg bw/day Selenate $LOAEL_{body\ weight\ reduction}$: 10 mg Se/kg bw/day Sel-plex $LOAEL_{body\ weight\ reduction}$: 10 mg Se/kg bw/day[61]
Rats, selenium nanoparticles (0.2, 0.4, 0.8, 2, 4 or 8 mg Se/kg bw), 14 days. $NOAEL_{body\ weight}$: 0.8 mg se/kg bw/day[59]	Rats, selenium nanoparticles, $LOAEL_{body\ weight}$: 2 mg se/kg bw/day[59]

(*continued on next page*)

Table 3 (*continued*)

Effects on body weight (gain) in animals – dose descriptors	
NOAEL	LOAEL
Mice, selenium nanoparticles, 2.5, 5, 10 and 20 mg/kg (bw), 14 days. $NOAEL_{decreased\ body\ weight}$: 10 mg Se/kg (bw)[60]	Mice, selenium nanoparticles, $LOAEL_{decreased\ body\ weight}$: 20 mg Se/kg (bw)[60]

[a]0.5, 5 and 50 ppm by the authors of that article estimated to correspond to 0.004, 0.04, and 0.4 mg/kg bw/day *Se uptake*. By use of EFSA default value for subacute studies in mice (0.2) to correspond to 0.1, 1 and 10 mg/kg bw/day.

bw/day for both 5- and 12-week-old animals. In addition, the survival was decreased in the 0.36 mg group (2 years, 5-week-old animals) ($NOAEL_{survival}$ 35-day study: 0.72 mg Se/kg bw/day; $NOAEL_{survival}$ 1-year study: 0.36 mg Se/kg bw/day only dose tested; $LOAEL_{survival}$ 2-year study: 0.36 mg Se/kg bw/day, only dose tested) [51] (Tables 2 and 3).

Some studies saw effects on body weight in the absence of lethality: Rats had reduced body weight after selenium was given as 10 ppm selenate in the drinking water for 15 or 18 weeks (~0.9 mg Se/kg bw/day) (selenate $LOAEL_{body\ weight}$: 0.9 mg Se/kg bw/day) [52]. Raines and co-workers administered rats 0.2, 2, or 5 ppm selenium in the diet as selenite for 28 days (~0.02, 0.24, and 0.6 mg Se/kg bw/day). Selenite $NOAEL_{body\ weight}$: 0.24 mg Se/kg bw/day [53]. Kaur and Kaur gave male rats 5 or 8 ppm Se in the diet as selenite for 9 weeks (~0.6 and 1.0 mg Se/kg bw/day). Selenium caused a reduction in the body weight at both doses (selenite $LOAEL_{body\ weight}$: 0.6 mg Se/kg bw/day [54]. Kaur and Parshad dosed rats 2 or 4 ppm selenium of selenite via diet for 5 weeks (~0.2 and 0.5 mg Se/kg bw/day) and saw a dose-dependent decrease in body weight gain as compared to controls (selenite $LOAEL_{depressed\ body\ weight\ gain}$: 0.2 mg Se/kg bw/day) [55]. Selenite was administered to mice in the drinking water for 46 days (selenite $LOAEL_{reduced\ body\ weight}$: 9.6 mg Se/kg bw/day) [56]. Rats were administered selenite at a feed concentration of 50 ppm (~2.8 mg Se/kg bw/day) for 17 weeks (selenite $LOAEL_{body\ weight\ reduction}$: 2.8 mg Se/kg bw/day) [57] (Table 3).

4.4. Selenium nanoparticles in comparison to other formulations

Rats dosed 4 mg/kg bw for males and (0.05, 0.5, and 4 mg Se/kg bw in females) of selenium nanoparticles had a marked decrease in the body weight gain in both males and females in a 28-day oral gavage study. Direct comparisons in females of selenite and selenium nanoparticles at the two lowest doses showed the following: selenium nanoparticles decreased the body weight gain, while selenite had this effect only at the highest dose (selenium nanoparticles $LOAEL_{decreased\ body\ weight\ gain}$: 0.05 mg Se/kg bw/day, the lowest dose tested; Selenite $NOAEL_{decreased\ body\ weight\ gain}$: 0.05 mg Se/kg bw/day) [58]. Rats were administered selenium nanoparticles at doses of 0.2, 0.4, 0.8, 2, 4, or 8 mg Se/kg bw by gavage for 14 days. The body weight decreased at 2, 4, and 8 mg Se/kg bw/day ($NOAEL_{body\ weight\ changes}$: 0.8 mg Se/kg bw/day) [59]. Mice were administered bacterially produced selenium nanoparticles. Doses given by gavage were 2.5, 5, 10, and 20 mg Se/kg (bw) for 14 days. The $NOAEL_{decreased\ body\ weight}$ was 10 mg Se/kg bw/day [60] (Table 3).

Mice were administered selenium forms: selenate, hydroselenite, selenium nanoparticles (100–500 nm), an organic form of selenium produced by *Saccharomyces cerevisiae* - Sel-Plex (selenium-enriched yeast), or the bacterially formed selenium nanoparticle preparation Lacto-MicroSelenium. Doses were 0.5, 5, and 50 ppm in feed (~0.1, 1, and 10 mg Se/kg bw/day) for 14 days. Reduced body weight was observed at the highest dose for selenite, selenate, Sel-Plex, and selenium nanoparticles, whereas Lacto-MicroSelenium had no effect (NOAELs detailed in Table 3) [61] (Table 3).

4.5. Summary of dose descriptors for lethality and body weight in animal studies

In animal studies, NOAELs of lethality are between 1 and 12 mg Se/kg bw/day (Table 2) (Figs. 1 and 2), and those of reduced body weight as compared to controls are in the range of 0.24–1.2 Se/kg bw/day, except one nanoparticle study with a NOAEL of 10 mg Se/kg bw/day (Table 3).

5. Gastrointestinal toxicity

5.1. Data on humans

MacFarquhar et al. described an outbreak of acute selenium poisoning in 201 humans after the intake of a liquid dietary supplement labelled as containing 200 μg selenium (as selenite) per 30 mL. However, the supplement contained 200 times more selenium; and 201 cases

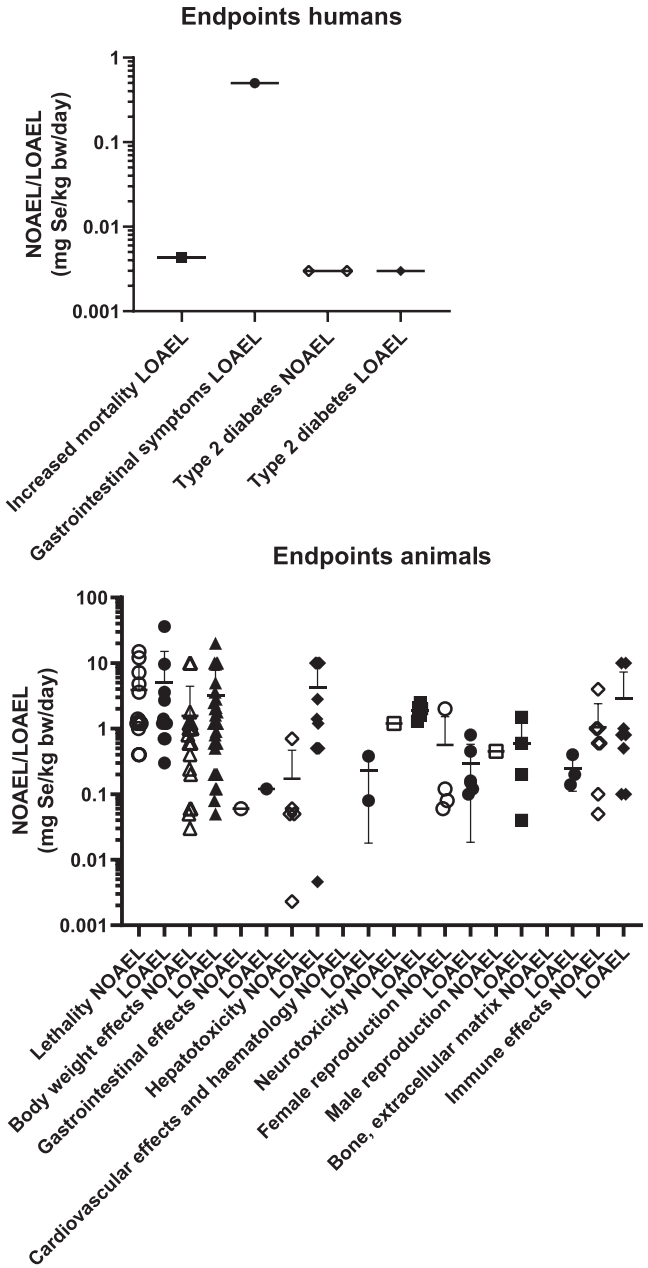

Fig. 1. Dose descriptors irrespective of selenium form in human and animal studies.

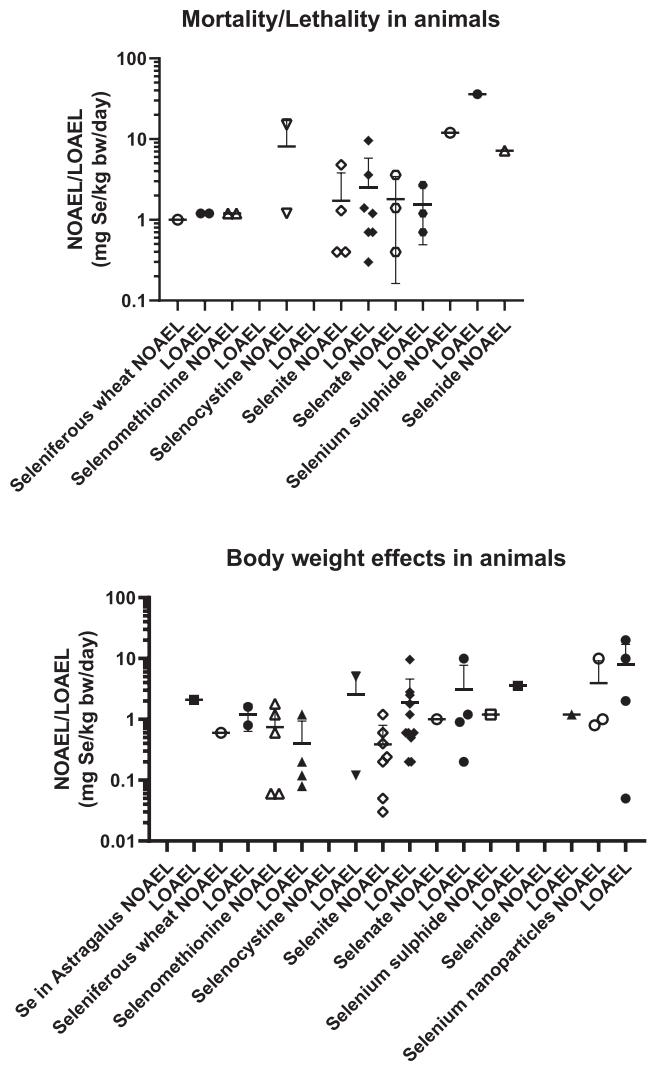

Fig. 2. Dose descriptors on different selenium forms on mortality, lethality and body weight effects in animals The data on hydroselenite, Sel-Plex, and Lacto-Micro-selenium from Benko [61] were not plotted.

of intoxication were identified. The median estimated dose of selenium was 12.8 mg/kg (bw) per 29 days (0.44 mg/kg bw/day). Diarrhoea was seen in 78% of the patients ($LOAEL_{abdominal\ symptoms}$: 0.5 mg Se/kg bw/day) [62]. Aldosary et al. reported additional data on this outbreak: Five men and four women ingested an estimated cumulative dose of 1.3 g selenium over periods of 10–60 days (~0.5 mg Se/kg bw/day, over a mean period of 37.5 days). In each case, the toxicity manifested within one week and involved blisters on the tongue, metallic taste in the mouth, dyspepsia, abdominal pain, constipation, and diarrhoea ($LOAEL_{abdominal\ symptoms}$: 0.5 mg Se/kg bw/day) [63]. Another case of selenium toxicity was likely caused by a nutritional supplement (form of selenium not specified). A 55-year-old woman presented with a 6-week history of diarrhoea and serum selenium of 534 μg/L. Her daily selenium intake was approximately 24 mg (0.34 mg Se/kg bw/day). The ingestion had started one week before the onset of diarrhoea [64]. A man developed diarrhoea following 2 weeks of ingestion of a supplement. He ingested an estimated 416–832 μg selenium per day (~60–120 μg Se/kg bw/day) [65]. A 51-year-old man and a 44-year-old woman had, as part of a fasting cure, ingested a food supplement containing selenium, magnesium, and zinc, among other substances. The selenium dose was accidentally 10 times higher than intended, but an estimated dose was not reported. The pair developed diarrhoea and nausea. Serum selenium levels were 347 and 387 μg/L [66] (Table 4).

Table 4
Gastrointestinal symptoms in humans and macaques – dose descriptors.

Gastrointestinal symptoms in humans and macaques – dose descriptors	
NOAEL	LOAEL
Humans	
None	Humans, $LOAEL_{abdominal\ symptoms}$: 0.5 mg Se/kg bw/day[62], at a mean period of 37.5 days[63]
Macaques	
Pregnant macaques, selenomethionine during the organogenesis period, 10, 60, 120 μg Se/kg bw, $NOAEL_{maternal\ anorexia\ and\ vomiting}$: 60 μg Se/kg bw/day[46]	Pregnant macaques, selenomethionine, $LOAEL_{anorexia\ and\ vomiting}$: 120 μg Se/kg bw/day[46]

5.2. Data in macaques

Pregnant macaques were administered selenomethionine during the organogenesis period (10, 60, 120 Se/kg bw). Two to three dams were followed until term at approximately gestation day 165, while a remaining seven dams per group had a hysterectomy on gestation day 100. Dose-dependent maternal toxicity involved frequent bouts of anorexia and intermittent episodes of vomiting (5 of 10 animals at highest dose) ($NOAEL_{anorexia\ and\ vomiting}$: 60 μg Se/kg bw/day) [46]. Gastrointestinal distress was observed in macaques administered selenomethionine at 120 μg Se/kg bw/day [44] (Table 4).

5.3. Summary of dose descriptors for gastrointestinal toxicity

A LOAEL of gastrointestinal effects is 0.5 mg Se/kg bw/day in humans. One study in macaques had a NOAEL of 0.6 and a LOAEL of 0.12 mg Se/kg bw/day (Table 4).

6. Hepatotoxicity in animals

6.1. Selenium in food

Rats were, during gestation and lactation, given 0.5 or 4.5 ppm Se in the diet via a sesame seed meal (~0.06 and 0.5 mg Se/kg bw/day), where after the offspring received either the same doses or 1.2 mg Se/kg bw/day for 14 weeks. Based on a higher incidence of liver lesions in the offspring, a $NOAEL_{liver\ lesions}$ was 0.06 mg Se/kg bw/day [67]. Rats were given 10 ppm selenium as seleniferous wheat for up to 60 days (~1.2 mg Se/kg bw/day). Liver toxicity was seen as atrophy and cirrhosis ($LOAEL_{liver\ toxicity}$: 1.2 mg Se/kg bw/day) [38] (Table 5).

6.2. Selenite

Rats were administered selenite at 2.3 or 4.6 μg Se/kg bw/day for 3 months. Swelling of Kupffer cells was observed in dilated sinusoidal vessels at the highest dose, and liver enzymes were affected at both doses ($NOAEL_{swelling\ of\ Kupffer\ cells}$: 2.3 μg Se/kg bw/day) [68]. Syrian hamsters were given a diet with selenite for 42 days (~0.007, 0.07, 0.4, 0.7, and 1.4 mg Se/kg bw/day[5]). Degenerative liver changes were seen at 1.4 mg Se/kg bw day (NOAEL 0.7 mg Se/kg bw/day) [69]. Rats were administered selenite at 0.05 mg/g feed (~2.8 mg Se/kg bw/day) for 17 weeks, causing degeneration of the hepatic cells (selenite $LOAEL_{degeneration\ of\ hepatic\ cells}$: 2.8 mg Se/kg bw/day) [57] (Table 5). Studies reporting only changes in liver enzymes are summarised in the Supplemental Materials.

[5] The dose estimated by the authors of the study.

Table 5
Hepatotoxicity.

Hepatotoxicity – dose descriptors	
NOAEL	**LOAEL**
Selenium in food	
Rats, Se in the diet via a sesame seed meal, ~0.06 and 0.5 mg Se/kg bw/day, during gestation and lactation, $NOAEL_{liver\ lesions}$: 0.06 mg Se/kg bw/day[67]	Rats, Se in the diet via a sesame seed meal, $LOAEL_{liver\ lesions}$: 0.5 mg Se/kg bw/day
	Rats, seleniferous wheat, ~1.2 mg Se/kg bw/day, 60 days or 6 weeks, $LOAEL_{liver\ toxicity}$: 1.2 mg Se/kg bw/day [38]
Selenite	
Hamsters, selenite, ~0.007, 0.07, 0.4, 0.7, and 1.4 mg Se/kg bw/day, 42 days, $NOAEL_{degenerative\ changes\ in\ liver}$: 0.7 mg Se/kg bw/day[69]	Hamsters, selenite, $LOAEL_{degenerative\ changes\ in\ liver}$: 1.4 mg Se/kg bw/day[69]
	Rats, selenite, ~2.8 mg Se/kg bw/day, 17 weeks, $LOAEL_{degeneration\ of\ hepatic\ cells}$: 2.8 mg Se/kg bw/day[57]
Rats, selenite, 2.3 and 4.6 μg Se/kg bw/day, 3 months, $NOAEL_{swelling\ of\ Kupffer\ cells}$: 2.3 μg Se/kg bw/day[68]	Rats, selenite, $LOAEL_{swelling\ of\ Kupffer\ cells}$: 4.6 μg Se/kg bw/day[68]
Selenium nanoparticles	
Rats, selenium nanoparticles or selenite, 0.05, 0,5 for both selenium forms and 4 mg for selenium nanoparticles Se/kg bw day, 28 days, Selenium nanoparticles and selenite $NOAEL_{increased\ relative\ liver\ weight}$: 0.05 mg Se/kg bw/day[58]	Rats, selenium nanoparticles and selenite, $LOAEL_{increased\ relative\ liver\ weight}$: 0.5 mg Se/kg bw/day[58]
Mice, selenium nanoparticles, selenate, hydroselenite, selenium nanoparticles, Sel-Plex, and Lacto-MicroSelenium, 0.1, 1, or 10 mg Se/kg bw/day, 14 days, Selenite $NOAEL_{decreased\ relative\ liver\ weight}$: 0.1 mg Se/kg bw/day and selenium nanoparticles $LOAEL_{decreased\ relative\ liver\ weight}$: 1 mg Se/kg bw/day. NOAELs not set on the other forms due to non-monotonous dose response curves[61]	Mice, selenium nanoparticles, selenate, hydroselenite, selenium nanoparticles, Sel-Plex, and Lacto-MicroSelenium, 0.1, 1, or 10 mg Se/kg bw/day, 14 days, Selenite $LOAEL_{decreased\ relative\ liver\ weight}$: 1 mg Se/kg bw/day and selenium nanoparticles $LOAEL_{decreased\ relative\ liver\ weight}$: 10 mg Se/kg bw/day[61]

6.3. Selenium nanoparticles

Relative liver weight was increased in rats dosed with selenium nanoparticles at 0.5 and 4 mg Se/kg bw/day for 28 days and for selenite in the same setup, but only tested at up to 0.5 mg Se/kg bw/day (selenium nanoparticles/selenite $NOAEL_{increased\ relative\ liver\ weight}$: 0.05 mg Se/kg bw/day) [58,70]. For 14 days, mice were administered 0.1, 1, or 10 mg Se/kg bw/day of selenium nanoparticles, selenate, hydroselenite, Sel-Plex, or Lacto-MicroSelenium. Decreased relative liver weight was seen in some groups, but only selenite and selenate exerted the effect at the highest dose (dose descriptors detailed in Table 5) [61].

6.4. Summary of dose descriptors for hepatotoxicity

One study with selenite in rats and swelling of Kuppfer cells found a NOAEL of 2.3 μg Se/kg bw/day (corresponding LOAEL: 4.6 μg Se/kg bw/day). NOAELs in other animal studies were 0.05, 0.06, 0.1, 0.7, and 1 mg Se/kg bw/day (Table 5).

7. Neurotoxicity

7.1. Data in humans

After taking a nutritional supplement containing more than 200 times more selenium (selenite) than reported on the label, five men and four women had ingested estimated cumulative doses of selenium of 1.3 g over a mean of 37.5 days (~0.5 mg Se/kg bw/day). Neurotoxicity in the form of memory difficulties manifested in 6 of the 9 patients ($LOAEL_{memory\ difficulties}$: 0.5 mg Se/kg bw/day) [63]. After ingesting a nutritional supplement containing selenium in an unknown form, a man developed paraesthesia at ~60–120 μg Se/kg bw/day for 14 days. The condition resolved after two months [65]. Difficulty of concentration was seen in a case of selenium poisoning after an estimated intake of 0.34 mg Se/kg bw/day over 6 weeks [64] (Table 6).

7.2. Data in animals

Pigs were given 2.86 mg selenite/kg bw/day (1.3 mg Se/kg bw/day) by oral capsules resulting in signs related to porcine focal symmetrical poliomyelomalacia. This effect occurred after two days of administration (death subsequently occurred at a mean period of 6.5 days) ($LOAEL_{porcine\ focal\ symmetrical\ poliomyelomalacia}$: 1.3 mg Se/kg bw/day) [71]. Another study of pigs compared the toxicity of selenomethionine, selenite, and selenium in *Astragalus bisulcatus* plants. The dosage was ~2 mg Se/kg bw/day for up to 6 weeks or until development of paralysis. All five pigs fed *Astragalus bisulcatus* developed neurological signs of paralysis within 5 days of treatment. Four pigs fed selenite developed paralysis occurring at 4–21 days of treatment. In pigs fed selenomethionine, this effect occurred in only 2 of 5 pigs (*Astragalus*/selenite $LOAEL_{paralysis}$: 2 mg Se/kg bw/day, no dose descriptor set on selenomethionine as the result was ambiguous) [72]. Baker et al. fed a high selenium diet to pigs by either *Astragalus praelongus* or *Astragalus bisulcatus* (~2.5 mg/kg bw/day) or selenite (~2.1 mg/kg bw/day) for 9 weeks. All groups developed poliomalacia of the spinal cord and brain stem ($LOAEL_{poliomalacia\ of\ the\ spinal\ cord\ and\ brain\ stem}$: 2.1–2.5 mg Se/kg bw/day) [37]. Mahan and Moxon gave swine selenite in the diet at 2.5–40 ppm Se for 37 days (~0.2, 0.4, 0.6, 0.8, 1.2, 1.6, and 3.2 mg Se/kg bw/day[6]). The two highest dose groups exhibited an inability to coordinate their walk ($NOAEL_{coordination\ inability}$: 1.2 mg Se/kg bw/day) [73].

Mice were administered selenite or selenomethionine in the drinking water at ~0.2, 0.6, and 1.8 mg Se/kg bw/day for 14 days. Dihydroxyphenylacetic acid was increased in the striatum at the two highest doses [48]. Basher et al. administered pregnant mice selenite at ~0.1 and 0.4 mg Se/kg bw/day in the diet from day 7 of gestation to the 15th day of birth. Sensory motor reflexes were inhibited, the active avoidance test indicated impaired learning, and acetylcholine was decreased in pups ($LOAEL_{neurological\ effects}$: 0.1 mg Se/kg bw/day) [74] (Table 7).

7.3. Summary of dose descriptors for neurotoxicity

Memory difficulties in humans had a LOAEL of 0.5 mg Se/kg bw/day (Table 6). Neurotoxicity in animals occurred at a NOAEL of 1.2 (corresponding LOAEL: 1.6). LOAELs in other studies were: 0.1, 1.3, and 2.1 mg Se/kg bw/day (Table 7).

Table 6
Neurotoxicity in humans.

Neurotoxicity: Data in humans – dose descriptors	
NOAEL	**LOAEL**
	Five men and four women, cumulative doses of selenium of 1.3 g over a mean of 37.5 days (~0.5 mg/kg bw/day). Based on occurrence in 6 of 9 persons, $LOAEL_{memory\ difficulties}$: 0.5 mg Se/kg bw/day[63]

[6] Estimated using a bw of 25 kg and a feed intake of 2 kg

Table 7
Neurotoxicity in animals.

Neurotoxicity: Data in animals – dose descriptors	
NOAEL	LOAEL
	Pigs, selenite, 1.3 mg Se/kg bw/day, 2 days, LOAEL porcine focal symmetrical poliomyelomalacia: 1.3 mg Se/kg bw/day[71]
	Pigs, selenomethionine, selenite and selenium contained in *Astragalus bisulcatus* plants, ~2 mg Se/kg bw/day, up to 6 weeks or until they developed paralysis. All 5 pigs fed *Astragalus bisulcatus* developed neurological signs of paralysis within 5 days of treatment. Four pigs fed selenite developed paralysis occurring at 4–21 days of treatment. In pigs fed selenomethionine this occurred only in 2 of 5 pigs, *Astragalus*/selenite $LOAEL_{paralysis}$: 2 mg Se/kg bw/day) (no dose descriptor set on selenomethionine as the effect was borderline)[72]
Swine, selenite, ~0.2, 0.4, 0.6, 0.8, 1.2, 1.6 and 3.2 mg Se/kg bw/day, 37 days, $NOAEL_{coordination\ inability}$: 1.2 mg Se/kg bw/day[73]	Swine, selenite, $LOAEL_{coordination\ inability}$: 1.6 mg Se/kg bw/day[73]
	Pigs, *Astragalus praelongus* (~2.5 mg Se/kg bw/day), *Astragalus bisulcatus* (~2.5 mg Se/kg bw/day) or selenite (~2.1 mg/kg bw/day), 9 weeks, $LOAEL_{poliomalacia\ of\ the\ spinal\ cord\ and\ brain\ stem}$: 2.1–2.5 mg Se/kg bw/day[37]
	Pregnant mice, selenite, ~0.1 and 0.4 mg Se/kg bw/day, starting from day 7 of gestation to the 15th day of birth, $LOAEL_{neurological\ effects}$: 0.1 mg Se/kg bw/day[74]

8. Reproductive and developmental toxicology

8.1. Female reproductive toxicology and developmental toxicology

Pregnant macaques were administered selenomethionine during the organogenesis period (10, 60, 120 μg Se/kg bw). Two to three dams were followed until term at approximately gestation day 165, while a remaining seven dams per group had a hysterectomy on gestation day 100. One embryonic death and two foetal deaths occurred in the high-dose group (three dams were followed until term). No teratologic effects or differences in growth morphology were observed for foetuses in any of the dose groups ($NOAEL_{no\ teratologic\ effects}$: 120 μg Se/kg bw/day, highest tested dose) [46]. In an earlier study from the same group, macaques given selenomethionine for 30 days had menstrual disturbances, reduced serum progesterone, reduced luteal phase length, longer intermenstrual intervals, and decreased excretion of oestrogen ($NOAEL_{menstrual\ disturbances}$: 0.06 mg Se/kg bw/day) [44]. Swine were administered selenite at ~0.8 mg Se/kg bw/day[7] over a period covering the production of two litters, both of which exhibited decreased weights at weaning ($LOAEL_{decreased\ weaning\ weight}$: 0.8 mg Se/kg bw/day) [75] (Table 8).

Pregnant hamsters were administered selenomethionine during the critical stages of embryogenesis—days 5–8 of pregnancy (1.5 or 2.0 mg Se/kg bw/day). Foetal length and frequency of malformations were normal (Selenomethionine $NOAEL_{foetal\ length/malformations}$: 2.0 mg Se/kg bw/day, highest tested dose) [76] (Table 8).

Mice were given 3 ppm selenium as selenate in the drinking water starting from 4 weeks of weaning (~0.45 mg Se/kg bw/day). The mice were allowed to breed, but with selenium dosage, the strain started to die out in the third (F3) generation, while controls bred normally ($LOAEL_{reduced\ litter\ size}$: 0.45 mg Se/kg bw/day) [77]. Selenite was not teratogenic in mice at doses of ~0.16 and 0.32 mg Se/kg bw/day[8] for 30 days before gestation until day 18 of gestation, but retarded foetal growth was observed at the highest dose ($NOAEL_{retarded\ foetal\ growth}$: 0.16 mg Se/kg bw) [78]. Pregnant mice were administered selenite at 1 or 4 ppm in the diet (~0.09 and 0.36 mg Se/kg bw/day) from day 7 of gestation to the 15th day of birth. This resulted in a $LOAEL_{body\ weight\ of\ pups}$ of 0.09 mg Se/kg bw/day [74]. Pregnant rats were given a regimen of potassium selenate at 1.5–7.5 ppm Se in the drinking water (~0.08, 0.15, and 0.45 mg Se/kg bw/day) and allowed to breed five times during one year. Fewer offspring were reared by the second generation of mothers at mid-dose, while reproduction was abolished at the highest dose ($NOAEL_{reproductive\ effects}$: 0.08 mg Se/kg bw/day based) [79] (Table 8).

Table 8
Female reproductive toxicology and developmental toxicology – dose descriptors.

Female reproductive toxicology and developmental toxicology – dose descriptors	
NOAEL	**LOAEL**
Pregnant macaques, 10, 60, 120 μg Se/kg bw, during the organogenesis period, $NOAEL_{(no\ teratologic\ effects)}$: 0.12 mg Se/kg bw/day (highest tested dose)[46]	
Macaques, selenomethionine, 10, 25, 47, 60, 75, 81, 120 μg Se/kg bw/day, 30 days, $NOAEL_{menstrual\ disturbances}$: 60 μg Se/kg bw/day[44]	Macaques, selenomethionine, $LOAEL_{menstrual\ disturbances}$: 80 μg Se/kg bw/day)[44].
	Swine, selenite at ~0.8 mg Se/kg bw/day, over a period covering the production of two litters, $LOAEL_{decreased\ weaning\ weight}$: 0.8 mg Se/kg bw/day[75]
Pregnant hamsters, selenomethionine (1.5, 2.0 mg Se/kg bw/day, on day 5, 6, 7 and 8 of pregnancy at, $NOAEL_{foetal\ length/malformations}$: 2.0 mg Se/kg bw/day, highest tested dose)[76]	
	Mice, selenate, ~0.45 mg Se/kg bw/day, from 4 weeks of weaning. The mice were allowed to breed up to an age of six months, $LOAEL_{reduced\ litter\ size}$: 0.45 mg Se/kg bw/day[77]
	Mice, selenite, ~0.16 and 0.32 mg Se/kg bw/day, for 30 days before gestation and thereafter up to day 18 of gestation, retarded foetal growth was observed at the highest dose, $NOAEL_{retarded\ foetal\ growth}$: 0.16 mg Se/kg bw[78]
	Pregnant mice, selenite, ~0.1 and 0.4 mg Se/kg bw/day, starting from day 7 of gestation to the 15th day of birth, $LOAEL_{lower\ body\ weight\ of\ pups}$: 0.1 mg Se/kg bw/day[74]
Pregnant rats, selenate, ~0.08, 0.15, and 0.45 mg Se/kg bw/day. The animals were bred five times and kept on the Se diet for the whole experiment (1 year), $NOAEL_{reproductive\ effects}$: 0.08 mg Se/kg bw/day[79]	Pregnant rats, $LOAEL_{reproductive\ effects}$: 0.15 mg Se/kg bw/day[79]

8.2. Male reproductive toxicology

8.2.1. Studies in humans

Twelve men ingested a diet with 47 μg Se/day over a 21-day period and then either 13 or 297 μg/day for the next 99 days (~~0.2 or 4 μg

[7] Calculated using a body weight of 25 kg, a feed intake of 2 kg, and a concentration of 10 ppm in the feed.

[8] 0, 11.4, or 22.8 μmol/L in the drink water for 30 days before gestation and thereafter up to day 18 of gestation (~0.9 and 1.8 ppm selenium ~0.16 and 0.32 mg Se/kg bw/day).

Se/kg bw/day). The fraction of motile sperm was decreased by 18% in the high-selenium group, and the difference to low dose was statistically significant at 13 weeks but not at 8 and 17 weeks (no dose descriptors set as there was no control group) [80] (Table 9).

8.2.2. Studies in animals

The number of abnormal spermatozoa was increased in rats given selenite as 6 or 8 ppm Se (~0.6 and 0.8 mg Se/kg bw/day) for 6 or 9 weeks. This was accompanied by reduced body, testes, and cauda epididymidis weights (Selenite $LOAEL_{abnormal\ spermatozoa}$: 0.6 mg Se/kg bw/day, lowest dose tested) [54]. Kaur and Parshad dosed rats with selenite at 2 or 4 ppm Se in the diet for 5 weeks (~0.2 and 0.5 mg Se/kg bw/day) and saw a dose-dependent reduction in testes and cauda epididymidis weights. Additional effects were on concentration, motility, and percentage of live spermatozoa (and increased abnormal forms) ($LOAEL_{sperm\ concentration\ and\ morphology}$: 0.2 mg Se/kg bw/day) [55]. Interrupted spermatogenesis and reduced testicular weight were seen in rats given wheat with 12.5 ppm Se for 4 weeks ($LOAEL_{spermatogenesis/testicular\ weight}$: ~1.5 mg Se/kg bw/day) [81]. Sperm concentration and motility were decreased in rabbits given selenite at 0.3 mg Se/kg bw weekly for 6 weeks (mode of administration not specified) ($LOAEL_{sperm\ parameters}$: 0.04 mg Se/kg bw/day) [82]. No effects were seen on reproduction in male rats in an aforementioned study with selenium given over more generations ($NOAEL_{male\ fertility}$ and 0.45 mg Se/kg bw/day, highest dose tested) [79] (Table 9).

8.3. Summary of dose descriptors for reproductive and developmental toxicity

Female reproductive toxicity NOAELs in animals: 0.08 and 2.0 LOAELs 0.1, 0.15, 0.16, 0.45, and 0.8 mg Se/kg bw/day (Table 8). Male reproductive toxicity investigated in animals: 0.04, 0.2, 0.6, and 1.5 mg Se/kg bw/day were LOAELs, and one NOAEL in animals was 0.45 mg Se/kg bw/day (Table 9).

9. Bone toxicity and collagen disturbances

9.1. Studies in animals

Rats were given 5 mg selenite/L drinking water for 90 days (~0.2 mg Se/kg bw/day); changes were observed in macroscopic and microscopic structures of the femoral bone tissue ($LOAEL_{bone\ effects}$: 0.2 mg Se/kg bw/day) [83]. Rats were given selenite at 4.2 mg Se/kg diet (~0.4 mg Se/kg bw/day) for 12–14 weeks and had decreased crystallinity, mineral content, and biomechanical strength of the bones ($LOAEL_{bone\ effects}$: 0.4 mg Se/kg bw/day) [84]. Administration of selenite to mice at a daily dose of 0.3 mg/kg bw for 10 weeks (~0.14 mg Se/kg bw/day) resulted in increased collagen in the skin and decreased collagen in the lung, liver, and kidney ($LOAEL_{collagen\ disturbances}$: 0.14 mg Se/kg bw/day) [85] (Table 10).

Table 9
Male reproductive toxicology – dose descriptors.

Male reproductive toxicology – dose descriptors	
NOAEL	**LOAEL**
	Rats, selenite ~0.6 mg Se/kg bw/day, for 6 or 9 weeks, $LOAEL_{abnormal\ spermatozoa}$: 0.6 mg Se/kg bw/day[54]
	Rats, selenite via diet (~0.2 and 0.5 mg Se/kg bw/day), for 5 weeks, $LOAEL_{sperm\ concentration\ and\ morphology}$: 0.2 mg Se/kg bw/day[55]
	Rats, wheat containing selenium, ~1.5 mg Se/kg bw/day, 28 days, $LOAEL_{spermatogenesis/testicular\ weight}$: 1.5 mg Se/kg bw/day[81]
	Rabbits, selenite, 0.3 mg Se/kg bw *weekly* for 6 weeks, $LOAEL_{sperm\ concentration\ and\ motility}$: 0.04 mg Se/kg bw/day[82]
Rats, selenate, ~0.45 mg Se/kg bw/day, given over more generations, $NOAEL_{male\ fertility}$: 0.45 mg Se/kg bw/day, highest dose tested[79]	

10. Cardiovascular toxicity

10.1. Animal studies

Rats were given selenite at 4.2 mg Se/kg diet (~0.38 mg Se/kg bw/day) for 12–14 weeks. Heart contractile performance was decreased; heart rate and coronary perfusion pressure were increased (Selenite $LOAEL_{contractile\ performance}$: 0.38 mg Se/kg bw/day) [86]. Grotto et al. investigated the effect of selenium supplementation on systolic blood pressure in rats. Selenite was dosed at 2 or 6 mg/L drinking water for 85 days. Estimated by the authors to correspond to ~0.5 and 1.5 mg Se/kg bw/day, while with EFSA default values, the levels are estimated to 0.08 and 0.24 mg Se/kg bw/day. Systolic blood pressure was increased from day 42 to the end of the study. $LOAEL_{hypertension}$: 0.08 mg Se/kg bw/day [87] (Table 11).

11. Type 2 diabetes

Stranges et al. investigated the effect of 200 μg of selenium given daily over an average follow-up of 7.7 years on type 2 diabetes incidence (study period: 1983–1996). The setup was a double-blind, randomised, placebo-controlled trial with 1312 participants. The participants were recruited at seven dermatology clinics in the Eastern United States and had a plasma selenium of 114 μg/L. Selenium was given to 621 participants and a placebo to 629. The hazard ratio was 1.52 (95% CI, 1.02–2.27) [88]. Daily supplementation with 200 μg of selenium as selenised yeast for colorectal adenoma prevention was given to 685 patients who had colorectal adenomas removed (plasma selenium: 135 μg/L). The duration was 33.0 months, ranging from 0 to 82.6 months. For selenium, the hazard ratio for new-onset type 2 diabetes was 1.25. However, this was not statistically significant (95% CI, 0.74–2.11). However, a significant effect was seen among older participants with a relative risk of 2.21 (95% CI, 1.04–4.67) [89]. In another study, there was no significant increase in the incidence of type 2 diabetes in a cancer prevention trial with 200 μg/day of selenium as L-selenomethionine. The study included 35,533 men with a baseline selenium of 135 μg/L. Follow-up periods were between 7 and 12 years. The relative risk of type 2 diabetes was 1.07 (99% CI, 0.94–1.22) [90]. Another study suggested no effect of selenium on type 2 diabetes risk. Algotar and co-workers conducted a longitudinal study on selenium's effect on serum glucose in 699 men. The study was a randomised, double-blind, placebo-controlled study of the effects of 200 or 400 μg Se/day on the incidence of prostate cancer. The period of study was 6 months to 5 years, and baseline selenium was 126 μg/L. There were no changes in serum glucose measured every 6 months [91]. Stranges et al. studied the effect of selenium supplementation for 6 months or 2 years

Table 10
Bone toxicity and effects on the extracellular matrix and collagen.

Bone toxicity and effects on the extracellular matrix and collagen – in animals – dose descriptors	
NOAEL	**LOAEL**
-	Rats, selenite, ~0.2 mg Se/kg bw/day, 90 days, $LOAEL_{bone\ effects}$: 0.2 mg Se/kg bw/day[83]
-	Rats, selenite, ~0.4 mg Se/kg bw/day, 12–14 weeks. $LOAEL_{bone\ effects}$: 0.4 mg Se/kg bw/day[84]
	Mice, selenite, ~0.14 mg Se/kg bw/day, 10 weeks, $LOAEL_{collagen\ disturbances}$: 0.14 mg Se/kg bw/day[85]

Table 11
Cardiovascular effects.

Cardiovascular toxicity and haematology in animals – dose descriptors	
NOAEL	**LOAEL**
	Rats, selenite, ~0.38 mg Se/kg bw/day, 12–14 weeks, $LOAEL_{contractile\ performance}$: 0.38 mg Se/kg bw/day[86] Rats, selenite, ~0.5 and 1.5 mg Se/kg bw/day or with EFSA default values ~0.08 and 0.24 mg Se/kg bw/day, 85 days, $LOAEL_{hypertension}$: 0.5 or with EFSA default values: 0.08 mg Se/kg bw/day[87]

on glycated haemoglobin (HbA1c) in a population of 491 volunteers with low selenium status (90 μg/L) aged between 60 and 74 years. Selenium doses were 100, 200, or 300 μg selenium/day given as selenium-enriched yeast. HbA1c was unchanged by selenium [92] (Table 12).

12. Immune effects

12.1. Studies in animals

Relative spleen weight was increased in rats dosed with selenite at 0.5 mg Se/kg bw/day for 28 days. No effect on this organ was seen for selenium nanoparticles up to 4 mg Se/kg bw/day (selenium nanoparticles $NOAEL_{unchanged\ relative\ spleen\ weight}$ 4 mg Se/kg bw/day—highest tested dose) (selenite $NOAEL_{increased\ relative\ spleen\ weight}$: 0.05 mg Se/kg bw/day) [58]. Mice were administered 0.1, 1, or 10 mg Se/kg bw/day for 14 days as selenium nanoparticles, selenate, hydroselenite, selenium nanoparticles, Sel-Plex, or Lacto-MicroSelenium. Spleen weight and white blood cell numbers were affected, as described in Table 12 [61]. Post-weaning rats were dosed 1.6, 3.2, 4.8, 6.4, 8.0, 9.6, or 11.2 ppm Se as either selenite or seleniferous wheat (~0.2–1.3 mg Se/kg bw/day) for 6 weeks, Enlarged spleens were observed at 8 ppm (0.8 mg Se/kg bw/day) and higher. The pancreas was enlarged at 8 ppm (0.8 mg Se/kg bw/day) and above (selenite/seleniferous wheat: $NOAEL_{spleen\ weight}$: 0.6 mg Se/kg bw/day) [40] (Table 13).

Table 12
Type 2 diabetes.

Type 2 diabetes – dose descriptors	
NOAEL	**LOAEL**
	Humans, selenium-yeast, 200 μg of selenium given daily over an average follow-up of 7.7 years, $LOAEL_{increased\ incidence\ of\ type\ 2\ diabetes}$: 2.9 μg Se/kg bw/day[88]
Humans (patients who had had colorectal adenomas removed), selenised yeast, 33.0 months, with a range of 0–82.6 months, For selenium, the hazard ratio for $NOAEL_{new\text{-}onset\ type\ 2\ diabetes}$: 2.9 μg Se/kg bw/day (a significant effect was seen among older participants[89]	
Humans, selenomethionine, 200 μg Se/day. Follow-up periods were between 7 and 12 years, $NOAEL_{relative\ risk\ of\ type\ 2\ diabetes}$: 2.9 μg Se/kg bw/day.[90]	
Humans, form of selenium not specified, 200 or 400 μg Se/day, 6 months to 5 years. $NOAEL_{no\ changes\ in\ serum\ glucose}$: 5.8 μg Se/kg bw/day[91]	
Humans, selenium-enriched yeast. 100, 200 or 300 μg selenium/day, 6 months to 2 years NOAEL: $_{No\ change\ in\ glycated\ hemoglobin}$: 4.3 μg Se/kg bw/day (highest dose tested)[92]	

Table 13
Immune effects – dose descriptors.

Immune effects – dose descriptors	
NOAEL	**LOAEL**
Rats, selenium nanoparticles or selenite, 0.05, 0.5 for both selenium forms and 4 mg for selenium nanoparticles Se/kg bw day, 28 days, Selenite $NOAEL_{increased\ relative\ spleen\ weight}$: 0.05 mg Se/kg bw/day, selenium nanoparticles $NOAEL_{increased\ relative\ spleen\ weight}$: 4 mg Se/kg bw/day (highest tested dose)[58]	Rats, Selenite $LOAEL_{increased\ relative\ spleen\ weight}$: 0.5 mg Se/kg bw/day[58]
Mice, selenium nanoparticles, selenate, hydroselenite, Sel-Plex, and Lacto-MicroSelenium, 0.1, 1, or 10 mg Se/kg bw/day, 14 days. Selenium nanoparticles $NOAEL_{spleen\ weight}$: 0.1 mg Se/kg bw/day Hydroselenite $NOAEL_{spleen\ weight}$: 1 mg Se/kg bw/day Sel-Plex $NOAEL_{spleen\ weight}$: 1 mg Se/kg bw/day	Mice, Selenium nanoparticles $LOAEL_{spleen\ weight}$: 1 mg Se/kg bw/day Selenate $LOAEL_{spleen\ weight}$: 0.1 mg Se/kg bw/day Hydroselenite $LOAEL_{spleen\ weight}$: 10 mg Se/kg bw/day Sel-Plex $LOAEL_{spleen\ weight}$: 10 mg Se/kg bw/day Lacto-MicroSelenium $LOAEL_{spleen\ weight}$: 0.1 mg Se/kg bw/day In addition, white blood cells were decreased for several of the substances: selenate, Sel-Plex and selenium nanoparticles at highest dose and mid dose, while selenite was also decreased at the middle dose, and decreased for all substances at the lowest dose $LOAEL_{fewer\ white\ blood\ cells}$: 1 mg Se/kg bw/day [61]
Rats, selenite or seleniferous wheat, ~0.2–1.3 mg Se/kg bw/day, 6 weeks, NOAEL for both selenite/seleniferous wheat: $NOAEL_{spleen\ weight}$: 0.6 mg Se/kg bw/day[40]	Rats, selenite or seleniferous wheat, LOAEL for both selenite/seleniferous wheat, $LOAEL_{increased\ spleen\ weight}$: 0.8 mg Se/kg bw/day)[40]

12.2. Summary of dose descriptors for immune toxicity

Immunotoxicity NOAELs were seen for animals at 0.1–0.6 mg Se/kg bw/day, while LOAELs were 0.1–0.6 (Table 13).

13. Kidney effects

Increased urinary pH was seen after selenite and selenium nanoparticle exposure, and increased creatinine clearance was seen after nanoparticles in rats, suggesting the kidney could be affected by selenium exposure [58]. However, in light of the absence of other findings, selenium does not seem to exert toxicity in the kidney; and has actually been shown to protect the kidney from other toxicities [93–95].

14. Other clinical signs in humans

Clinical signs and additional toxicological effects reported in humans are provided in Table 14.

15. Human studies in which no toxic effects were observed

Twenty-four cancer patients with a baseline plasma selenium of 102 μg/L ingested 400 μg Se as either selenite, methyl-selenocysteine, or selenomethionine daily for 8 weeks (~6 μg Se/kg bw/day). No significant toxicity was observed [96]. No toxicity was reported in several human supplementation studies, including a) lung cancer patients given selenium as selenised yeast at 200 μg/day (~3 μg Se/kg bw/day) for 48 months [97]; b) cancer patients with baseline plasma selenium of 114 μg/L, given 200 μg selenium/day as high-selenium brewer's yeast (~3 μg Se/kg bw/day) for 4.5 years [98]; and c) healthy humans with baseline plasma selenium of 141 μg/L, given 200 μg selenium per day

Table 14
Clinical signs and additional toxicological effects reported in humans.

Endpoint	References
Alopecia/hair loss	[62–66,101, 102]
Seborrhoea-like scaling with some acneiform papules on the scalp	[101]
Nail discoloration or brittleness (Hair brittleness was reported in one man in[103])	[62,65,101, 103]
Mees lines – white lines of discoloration across the finger and toe nails	[64,66,104]
Dystrophic fingernail changes	[63]
Onycholysis (nail separates from its nail bed) of all nails of the hands and feet	[66]
Fatigue	[62,65];
Joint pain	[62]
Garlic-like breath and metallic taste to the mouth	[63,103]
Blisters on the tongue	[63]
Muscle cramps	[64]
Headache	[66]

for 28 months as selenomethionine (~3 μg Se/kg bw/day) [99].

16. Discussion of toxicological effect levels in relation to human exposure levels

16.1. Critical effect and point of departure

Concerning humans, the Rayman et al. study gave a $NOAEL_{increased\ mortality}$ of ~3 μg Se/kg bw/day and a corresponding LOAEL of ~4.3 μg/kg bw/day. However, other human studies with healthy people and individuals who had had cancer with similar intake levels did not show elevated mortality. A similar picture is seen for increased risk of type 2 diabetes. One human study had a LOAEL of ~3 μg/kg bw/day, another the same LOAEL level when considering old people only, while two studies reported no increased risk at similar intake levels. One explanation for the different findings in the studies could be differences in basal selenium intake levels (e.g. from habitual diet), as the levels of supplemental selenium at which the adverse effects occur will depend on this. Yet the baseline plasma levels in the relevant studies do not point to this: The level in Rayman et al. was 89 μg selenium/L, while those in studies not showing toxicity were 102, 114, and 141 μg/L, and a similar picture was seen for the studies on type 2 diabetes.

Concerning animal data, a NOAEL on hepatotoxicity was 2.3 μg Se/kg bw/day with a corresponding LOAEL of 4.6 μg Se/kg bw/day, while reproduction effects started at 0.04 mg Se/kg bw/day (a LOAEL for male reproduction).

Overall, several endpoints are candidates for the critical effect, including increased mortality, type 2 diabetes, and hepatotoxicity, while reproductive toxicity had somewhat higher dose descriptors. The level of NOAELs and NOAELs is around 3–4 μg Se/kg bw/day dosed on top of basal intake in humans, and one animal study had a LOAEL of hepatotoxicity of 2.3 μg Se/kg bw/day (Fig. 1).

16.2. Comparison of normal intake and toxic levels of selenium

LOAEL levels of 3–4 μg Se/kg bw/day in humans and a LOAEL for hepatotoxicity in animals of 2.3 μg Se/kg bw/day are close to normal intake levels, which are between 0.15 and 4 μg/kg bw/day [12–18]. Notably, to extrapolate the animal study finding to humans, one would need to consider the division with assessment factors, suggesting an even lower safe dose in humans. Thus, taking both the human and animal findings into account, the window between normal intake levels and toxicity is narrow. As aforementioned, we should take into account that the investigated humans and animals had a basal selenium intake, on top of which the tested doses were added—the dose descriptors thus describe the supplemental intake.

16.3. Is there a difference in potency among various forms of selenium?

Concerning differences in potency, in our previous review of the biokinetics of selenium, we found that, overall, organic forms of selenium, for example selenomethionine, are more bioavailable than inorganic forms such as selenite, which were more bioavailable than elemental selenium in the form of nanoparticles [29]. Nonetheless, it is not obvious whether the increased bioavailability of organic forms of selenium translates into toxicity occurring at lower dose levels than what is seen with inorganic selenium and selenium nanoparticles. First, such a pattern is not obvious when looking at a graphical presentation of dose descriptors (Fig. 2). Second, several studies with different selenium forms tested head-to-head showed equal potencies: Astragalus vs. selenate [37,72], seleniferous wheat vs. selenite [100], selenomethionine vs. selenite [43,48]; and selenite vs. selenate [50]. Though we note that different potencies were seen in some head-to-head studies: selenocystine was more potent than selenite and other inorganic selenium forms in [42], selenomethionine was more potent than selenite in [47], while it was the other way around in [48].

Overall, it seems at present not obvious that organic forms of selenium result in toxicity occurring at lower dose levels than what is seen with inorganic selenium and selenium nanoparticles.

17. Summary

A human study showed increased mortality following the daily ingestion of 300 μg Se a day over 5 years, giving a LOAEL of ~4.3 μg/kg bw/day and a NOAEL of ~2.9 μg/kg bw/day (200 μg Se/day). Other studies were negative for increased mortality with equal intake levels. Increased risk of type 2 diabetes occurred with selenium supplementation at ~2.9 μg/kg bw/day in one study and another study with the same dose only when looking at the oldest people, while two other studies with the same dose level showed no increase. NOAELs in animal studies describing reduced body weight as compared to controls are 0.24–1.2 mg Se/kg bw/day. Other endpoints of selenium toxicity include hepatotoxicity with a NOAEL as low as 2 μg/kg bw/day, gastrointestinal, cardiovascular, and reproductive toxicities with NOAELs of 0.6 (gastrointestinal), 0.08, and 0.4 (cardiovascular) and ≥ 0.04 mg Se/kg bw/day (reproductive), respectively. Clinical signs of selenium toxicity in humans include a garlicky-smelling breath, hair loss, and nail changes. Genotoxicity and carcinogenicity were not evaluated. In conclusion, NOAELs/LOAELs were as low as 2–3 μg (0.002–0.003 mg) Se/kg bw/day. Normal intake levels are between 0.15 and 4 μg/kg bw/day. Thus, the window between normal and toxic levels is narrow, though one should consider that the dose descriptor levels are investigated on top of the normal intake level of humans and animals.

CRediT authorship contribution statement

Niels Hadrup: Conceptualization, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Gitte Ravn-Haren:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtemb.2023.127235.

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