EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Potassium selenate (All food producing species)
Sodium selenate (All food producing species)
Sodium selenite (All food producing species)

Selenate and selenite salts have a widespread prophylactic and therapeutic use in veterinary medicines against diseases and disorders related to selenium deficiencies in animals. The substances were previously evaluated by the Committee for Medicinal Products for Veterinary Use in 1997, leading to the establishment of "No MRL required" classifications in all food producing species with no restrictions on the route of administration[1].

On 12 May 2014 the European Commission requested the European Medicines Agency to review the established maximum residue limits. This request followed the CVMPs recommendation of 10 April 2014 on barium selenate and focused on concerns relating to potential consumer exposure to residues at the injection site.

Based on the available data, the Committee for Medicinal Products for Veterinary Use recommended, on 4 December 2014, the maintenance of the existing MRL classifications for potassium selenate, sodium selenate and sodium selenite in all food producing species.

[1] Commission Regulation (EU) No 37/2010, of 22.12.2009

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Potassium selenate, sodium selenate and sodium selenite
Therapeutic class:	Alimentary tract and metabolism/mineral supplements
Procedure number:	EMEA/V/MRL/003225/MODF/0002
Applicant:	European Commission
Target species:	All food producing species
Intended therapeutic indication:	Selenium deficiency
Route(s) of administration:	Oral/Intramuscular

1. Introduction

Selenium is an essential micronutrient for both animals and man. Deficiency syndromes such as growth impairment, muscular degeneration, cardiomyopathy, hepatic degeneration and reproduction disturbances in ruminants and non-ruminants, as well as exudative diathesis and encephalomalacia in poultry have been well documented.

Selenium is ubiquitously present in soils in various chemical forms (selenites, selenates and elemental selenium) but there is great variation between different geographical areas. It is taken up by plants and so is present in feed, and is distributed to the tissues of food producing animals. Foods of animal origin contain the highest selenium levels presumably in form of selenomethionine and other organic selenocompounds. In grains and cereals the level of selenium is generally low but much higher levels can be found in products from the seleniferous areas.

In areas with low levels of selenium in the soil e.g., the Nordic countries, feed is supplemented (0.1 to 0.3 mg/kg) in order to prevent development of deficiency syndrome in domestic animals.

Selenate and selenite salts have a widespread prophylactic and therapeutic use in veterinary medicines against diseases and disorders related to selenium deficiencies in animals. The recommended dose of sodium selenite varies between 0.01 to 0.08 mg selenite/kg bw (0.25-1.5 mg/kg feed) for the preparations used in medicated feed in horses, cattle and sheep, as well as swine and poultry. When selenium is applied as sodium and potassium selenates, the doses range from 0.08-0.24 mg/kg bw. Dosing is given in a single application, divided into 3-5 daily doses or repeated every 2 or 3 weeks. In poultry, supplement feeding for 1-2 weeks with 2-3 week intervals is indicated. Potassium selenite and sodium selenite preparations are also used for parenteral applications (intramuscular) in cattle, swine and sheep, as a single dose of 0.02-0.06 mg selenite/kg bw, or repeated dosing within a one week interval. A slow release bolus, indicated in ruminants, provides a daily dose of 0.05 mg selenium/kg/day for 120 days.

Sodium selenite and sodium selenate have also been approved as feed additives at a maximum concentration of 0.5 mg selenium/kg feed (complete feed).

Selenium based dietary supplements (up to 200 µg selenium/person/day) have a long history of use in human nutrition.

The CVMP previously assessed potassium and sodium salts of selenium in 1997 and estimated a tolerable upper daily intake in humans of 600 µg selenium/person/day (10 µg/kg bw), based on long-term exposure studies in humans. However, in 2000 the European Commission's Scientific Committee on Food reviewed the available data on selenium and established a tolerable upper intake

level of selenium at 300 µg/person per day. This value was accepted by EFSA in 2006, and in 2014, in a review of the MRL classification for barium selenate, it was also supported by the CVMP.

Currently, potassium selenate, sodium selenate and sodium selenite are included in Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Potassium selenate	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY
Sodium selenate	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY
Sodium selenite	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

In the 1997 Summary report for potassium and sodium salts of selenium (EMEA/MRL/249/97-FINAL), which summarises the evaluation on which the above MRL entries were based, the following statement is made: “An accumulation of selenium residue at the injection site may exist shortly after treatment and therefore Member States should consider the establishment of withdrawal times for parenteral preparations”.

On 5 May 2014 the European Commission submitted a request for review of the CVMP opinion on the MRL status for potassium selenate, sodium selenate and sodium selenite under Article 11 of Regulation (EC) No 470/2009 to the European Medicines Agency.

The request to the CVMP followed on from the Committee’s Opinion of 10 April 2014 in which it recommended that the ‘*No MRL required*’ entry for barium selenate in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 should be amended to include a restriction indicating that the substance may not be administered by injection. The recommendation reflects concerns over the potential consumer exposure to injection site residues. The Commission requested the review of the MRL status for potassium selenate, sodium selenate and sodium selenite in order to consider whether similar concerns may exist in relation to these substances.

2. Scientific risk assessment

This evaluation focuses on the effects of selenium and not on those of potassium and sodium. This is appropriate as the risk to consumers results from the selenium content of potassium selenate, sodium selenate and sodium selenite.

2.1. Safety assessment

Since the original CVMP assessment of sodium selenate, sodium selenite and potassium selenate in 1997, additional information relevant to the consumer safety evaluation of the substance has been

generated. In particular, the European Commission's Scientific Committee on Food recommended a tolerable upper intake level for selenium.

2.1.1. Overview of pharmacological properties

The principal mechanism of action for physiological and pharmacological effects of selenium is its antioxidative effect at the cell membrane against hydrogen peroxide and lipoperoxides. The effects are related to the enzymatic activity of glutathione peroxidases, which contain selenocysteine. Selenocysteine is also an integral component of other functional proteins such as tetraiodothyronine-5'-iodo-deiodinase (involved in metabolism of thyroid hormones) but the full extent of the biochemical mode of action of selenium in the body remains to be elucidated.

Pharmacokinetic properties

Most water-soluble selenium compounds (selenites, selenates, organocompounds) are readily absorbed (80 to 90%) from the gastrointestinal tract of mice, rats and dogs. A high degree of absorption after oral intake of sodium selenite (40 to 85%), selenate (95%) and selenomethioninne (75 to 97%) has also been shown in human studies. The retention of selenium in plasma after administration of selenite seems to be slightly higher in humans with poor selenium status.

In laboratory animals, following absorption, there is a rapid distribution of selenium compounds to most organs. The specific organ accumulation in experimental animals was shown to be influenced by the selenium status as well as the chemical form of administered selenium. The disposition of selenium in man appears to be similar to that in laboratory animals. Several studies have demonstrated that both inorganic and organic forms of selenium cross the placenta and enter milk in experimental animals and man.

Metabolic processes involving selenium are dependent on the chemical form and dose as well as on nutritional status. Major metabolites are methylated selenites. Following a reduction to selenide inorganic selenium is also incorporated into amino acids (as selenocysteine) and cotranslationally into functional proteins. Although significant progress has been made in elucidating the biological role of selenium many aspects of the underlying biochemical mechanisms are not yet fully understood.

Studies in laboratory animals indicate that under normal conditions urine is the major excretory pathway for selenium. However, faecal excretion may dominate in deficiency states. At high or toxic levels as much as 30 to 60% of selenium can be excreted via expired air, predominantly as dimethylselenide. Available data suggest that humans excrete selenium compounds in a way similar to the rat with 40 to 70% of excreted selenium found in urine.

Various biological indicators of selenium exposure are used depending on the chemical form, level of exposure and nutritional status. Toxic levels of selenium in food-producing animals are reflected by increased blood levels of the element. In humans at higher intake levels only, selenomethionine intake from food and supplements seems to be directly reflected in whole blood levels whereas high doses of selenite and selenate are related to an increase in urinary excretion.

In experimental animals a biphasic biological half-life of selenium has been identified with a rapid initial phase of about 3 days and 1.2 days in rat and dog, respectively, followed by a second phase of about 30 to 70 days in most species. In studies in humans after selenite intake three phases of elimination were observed lasting 1 day, 8 to 20 days and 65 to 116 days, respectively. There are indications that the half-life of the third phase may be longer for selenomethionine.

2.1.2. Calculation of pharmacological ADI, if relevant

Relevant pharmacological effects of potassium selenate, sodium selenate and sodium selenite are considered to have been adequately represented in the animal and human studies described below. No additional pharmacological effects that would need further characterisation have been identified. Consequently, and in line with the CVMP guideline on the approach to establish a pharmacological ADI (EMA/CVMP/SWP/355689/2006), no pharmacological ADI is considered necessary.

2.1.3. Overview of toxicology

The toxicity of selenium salts is thought to occur following its absorption and reduction/metabolism by glutathione to hydrogen selenide (H_2Se) through selenodiglutathione and glutathionylselenol intermediates. Hydrogen selenide is the key metabolite derived from the inorganic forms of selenium, selenite and selenate. It is oxidised to selenium dioxide and probably causes toxicity due to the production of superoxide and other reactive oxygen species, which can induce cell damage. Selenium toxicity is also associated with non-specific incorporation of selenium in place of sulphur in functional proteins leading to protein malfunction and disruption of cellular processes. With acute poisoning, one explanation for selenium toxicity is the depletion of intermediate substrates, such as glutathione and S-adenosyl methionine.

Single-dose toxicity

Water-soluble selenium compounds show a relatively high acute toxicity in laboratory animals. Oral LD_{50} values for sodium selenite were 1 mg selenium/kg bw in rabbit, 3 mg/kg bw in the mouse and 4.8 to 7 mg/kg bw in the rat. A selenium content of 25 mg/kg in feed gives rise to acute toxicity symptoms in most species tested. Gastrointestinal disturbances, cardiotoxic effects as well as signs of neurotoxicity such as convulsions with an ultimate respiratory arrest dominate the clinical picture. In farm animals "the blind stagger" syndrome has been described in livestock after an ingestion of plants known to accumulate selenium. The most pronounced clinical sign is a restricted vision and neurotoxic effects. The acute toxicological profile of selenium has been thoroughly reviewed by Högberg and Alexander (2007)[2]. From acute toxicity studies in laboratory animals LD_{50} values between 1.5 mg/kg bw and 10 mg/kg bw for many selenium compounds and animal species were derived.

Repeated dose toxicity

According to earlier long-term toxicity studies cited in the literature, diets containing 5 mg selenium/kg feed (corresponding to 0.25 mg/kg bw), usually given as sodium selenite, resulted in growth reduction in rats. At higher dietary levels of 6.4 to 8 mg selenium/kg feed (corresponding to 0.3 to 0.4 mg selenium/kg bw) liver changes, anaemia, splenomegaly, pancreatic enlargement and increased mortality were observed. Based on growth retardation and organ toxicity a LOAEL of 0.03 mg selenium/kg bw/day was established. In food-producing animals subclinical toxicity is believed to occur at 2 to 5 mg selenium/kg feed.

In areas with seleniferous soils an "alkali disease syndrome" can develop in horses, cattle and sheep after consumption of plants containing 5 to 25 mg selenium/kg for periods of less than one month. The typical symptoms are emaciation, deformation and shedding of hoofs, loss of long hair and erosions of joints of the long bones and eventually liver cirrhosis.

[2]Högberg, J and Alexander, J (2007): Selenium. In: Handbook on the Toxicology of Metals. 3rd edition, ed by Nordberg, GF; Fowler, BA; Nordberg, M; Friberg, LT. Elsevier Science Publishers, 784-807.

Reproductive toxicity, including developmental toxicity

Contradictory results have been reported on the reproductive toxicity of selenium compounds in laboratory animals. In an older study in mice a failure to breed in the third generation was seen after 0.57 mg selenium/kg bw/day (the only dose level tested) given in the drinking water as sodium selenate. In other published investigations no effects on sperm and oestrus cycle were observed in mice treated with sodium selenite (drinking water for 13 days, doses up to 7 mg selenium/kg bw). Based on altered menstrual cycle after a daily administration of selenomethionine for 30 days to monkeys, a NOAEL of 0.08 mg selenium/kg bw/day was calculated.

Teratogenic effects after exposure to inorganic forms of selenium were suspected in single studies on sheep and pigs but the results were inconclusive.

On the other hand, according to literature, the effects of selenium on reproduction and offspring observed in laboratory rodents were related to the maternal toxicity and nutritional deprivation. Studies on macaques fed selenomethionine (3, 25, 150 and 300 µg selenium/kg bw/day during organogenesis) produced no signs of teratatogenesis, although a dose dependent maternal toxicity was observed. Studies in mice have also indicated a protective effect of selenium against for example, radiation-induced teratogenicity. Overall the available data do not indicate a link between selenium exposure and toxic effects on the embryo or foetus.

Genotoxicity

Both sodium selenite and selenate tested positive in some, but not all, *in vitro* studies in prokaryotic organisms such as *Salmonella typhimurium* (strain TA 100 without metabolic activation) and *Bacillus subtilis* recombination assay. Sodium selenite induced chromosomal aberrations as well as unscheduled DNA synthesis and sister chromatid exchange in eukaryotic test systems (Chinese hamster ovary cells, human fibroblasts). In *in vivo* tests an increased number of micronuclei was observed in the bone marrow of macaques treated by nasogastric intubation with selenomethionine at a dose 0.24 mg selenium/kg bw/day for 2 weeks. On the other hand chromosomal aberrations and sister chromatid exchange were not increased in healthy persons (n=5) given sodium selenite (0.025 mg selenium/kg bw/day) for 2 weeks or in patients (n=9) treated with intramuscular sodium selenite injections or tablets (0.05 to 0.005 mg selenium/kg bw/day) for 1 to 13.5 months. These observations in humans were of limited value because this type of study is of low precision and the only parameters investigated were sister chromatid exchange and clastogenicity, with no consideration of possible gene mutations and possible changes in the number of chromosomes per cell. Consequently, there remains some concern that human exposure to selenium compounds may be associated with a mutagenic risk.

Carcinogenicity

Several earlier studies indicated an increased incidence of tumours in laboratory animals after oral exposure to selenium. The significance of these studies has been questioned because of serious shortcomings in design and conduct. On the other hand a number of investigations showed a protective effect against certain types of tumours. Overall, international evaluations conclude that the data seems to indicate that the compounds studied will not act as carcinogens at low or moderate doses[3].

Studies of other effects including immunotoxicity and neurotoxicity

No studies of immunotoxicity or neurotoxicity were available.

[3] Alexander J, Melzer HM. Selenium. In: Oskarsson A (editor). Risk evaluation of essential trace elements – essential versus toxic levels of intake. Copenhagen: Nordic Council of Ministers Nord, 1995: 18: 9-54

2.1.4. Calculation of the toxicological ADI or alternative limit

The data available does not allow a toxicological ADI to be established for potassium selenate, sodium selenate or sodium selenite. However, based predominantly on the available human data, a number of bodies have made recommendations on safe limits for selenium intake. The CVMP conclusion on the safe limit for selenium intake is presented in section 2.1.9 on the overall conclusions on the ADI.

2.1.5. Overview of microbiological properties of residues

No microbiological data were available which is acceptable as no microbiological effects are expected.

2.1.6. Calculation of microbiological ADI

As no microbiological effects are expected the establishment of a microbiological ADI is not relevant.

2.1.7. Observations in humans

In humans, cases of selenium poisoning have been described after oral ingestion of selenium although, in general, selenium exposure levels associated with documented poisonings are lacking. Gastrointestinal and neurological symptoms predominated. Intake of 250 mg selenium as a single dose or in multiple doses of 25–30 mg resulted in acute toxic effects, such as nausea, vomiting, nail changes, dryness of hair, hair loss, tenderness and swelling of fingertips, fatigue, irritability and garlicky breath. In Sweden, several cases of toxicity in children occur each year due to accidental overconsumption of selenium tablets. Acute symptoms such as vomiting have been observed. Clinically significant selenium toxicity was reported in 13 individuals after prolonged and regular ingestion of supplements containing 27.3 mg (27,300 µg) selenium per tablet due to a manufacturing error.

In an episode involving 12 people, ingestion of 'health' tablets led to daily doses of 27 to 31 mg selenium (selenite), with a total dose of 27 to 2387 mg, resulted in nausea, vomiting, hair loss, fatigue, irritability and garlicky breath. The highest serum levels reached 530 µg selenium/l 4 days after the last tablet. A high simultaneous intake of vitamin C might have alleviated the toxicity.

In a review of selenium poisoning in humans (Nuttall, 2006[4]) case reports and corresponding estimated doses of selenium intake were given. The data indicate that oral doses of 5 mg to 22.3 mg selenium/kg bw (as sodium selenite or sodium selenate) were acutely toxic, sometimes resulting in a fatal outcome.

In studies involving 400 persons from seleniferous areas in China, typical signs of selenosis such as hair loss or nail loss, nail abnormalities, mottled teeth, skin lesions and changes in peripheral nerves were observed after a dietary intake of about 1200 µg selenium/day. The pathological changes were reversible and disappeared as soon as the diets were changed. The LOAEL for clinical selenosis was 900 to 1000 µg selenium per day. While one man taking 913 µg selenium per day (as selenite) exhibited clinical signs of selenosis, no clinical signs were seen in people with an intake estimated at approximately 850 µg/day. The NOAEL for clinical symptoms of selenosis was therefore considered to be 850 µg selenium/person per day. Marginally prolonged prothrombin times were observed in subjects estimated to have a selenium intake of around 850 µg/day.

In a 2-year study, performed in the United States of America, on 142 persons no clinical signs of

[4] Nuttall, KL (2006): Review: Evaluating Selenium Poisoning. Annals of Clinical and Laboratory Science, 36,4, 409-420.

toxicity were observed after a dietary intake of 68 to 724 µg selenium/day (mean intake of 239 µg selenium/day). At the highest intake level no prothrombin time prolongation or other biochemical changes were seen except for a slight increase of alanine aminotransferase enzyme in the serum. The latter values were however within the reference range and considered clinically insignificant. Thus a dose 724 µg selenium/person corresponding to 12 µg selenium/kg bw could be considered a NOAEL.

2.1.8. Findings of EU or international scientific bodies

In 1991 The UK Committee on Medical Aspects of Food Policy (COMA) recommended a maximum safe intake of selenium from all sources of 450 µg selenium/person/day for adults.

A 1995 report (Nordic Council of Ministers, Copenhagen, 1995) proposed a safe tolerable dietary intake of 4 to 5 µg selenium/kg bw/day, corresponding to 240 to 300 µg selenium/person, based on effects seen in humans.

In 2000 the European Commission's Scientific Committee on Food recommended a tolerable upper intake level of 300 µg/person (5 µg/kg bw), based on effects seen in humans.

In 2006 the EFSA Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) accepted the tolerable upper intake level recommended by the Scientific Committee on Food.

2.1.9. Overall conclusions on the ADI

A formal ADI cannot be established as the necessary studies are not available. However, based on human data a safe limit for selenium intake can be established.

In its 1997 report the CVMP established a safe level for long term ingestion of selenium in man being 600 µg/person per day (10 µg/kg bw/day). This figure was based on consideration of the available human data. In particular, it was noted that in seleniferous geographical areas in the United States of America (in which people are assumed to have a nutritional status similar to that of European consumers) no clinical effects were observed after long-term exposure to doses of up to 720 µg selenium/day.

In 2000 the European Commission's Scientific Committee on Food reviewed the available data on selenium and established a tolerable upper intake level of selenium at 300 µg/person per day. This figure was based on studies conducted in seleniferous areas in China (reported above) in which the LOAEL for clinical symptoms of selenosis was considered to be 900 to 1000 µg of selenium/person per day and the NOAEL was 850 µg/person per day. The Scientific Committee on Food considered that sensitive individuals were likely to have been included in the study and that consequently an uncertainty factor of 3 was appropriate for derivation of a tolerable upper intake level of selenium. The tolerable upper intake level of selenium was therefore established as 300 µg/person per day, to cover intake from all sources (including food and supplements).

The CVMP supports the evaluation undertaken by the Scientific Committee on Food and confirms the tolerable upper intake level of 300 µg selenium/person per day as being appropriate for use in the MRL evaluation of potassium selenate, sodium selenite and sodium selenate.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

The only available pharmacokinetic data in target species are those presented in the residue depletion studies section below.

2.2.2. Residue depletion studies

There are numerous reports on selenium tissue levels in various domestic animals after a continuous intake of feed supplemented either directly (additive) or through, for instance, fertilizer with lower (prophylactic) doses of the element. However, proper depletion studies after the application of selenium-based medicines to the indicated animal species are lacking. The selenium contents of skeletal muscle and internal organs show a linear increase with the intake and plateau with rising dose. Highest levels were found in the edible organs such as kidney and liver followed by lower concentrations in the muscle. However, there seems to be a great variation both in the ratios between various tissues and with regard to the absolute concentrations, depending on whether the selenium is supplied in the inorganic or organic (presumably present in plants) form. The differences in bioavailability between various chemical forms present in different diets of various animal species have not yet been fully elucidated.

Oral administration

Studies in sheep (n=4) have shown that after ingestion for 10 days of feed supplemented with 3 mg selenium/kg feed derived from sodium selenite (corresponding to approximately 0.12 mg selenium/kg bw) the concentrations were 1.4 mg selenium/kg in the kidney, 0.84 mg selenium/kg in the liver and 0.16 mg selenium/kg in muscle. In comparison, control animals (exposed to 0.2 mg selenium/kg feed) had 0.34 mg selenium/kg in the kidney, 0.26 mg/kg in the liver and 0.08 mg selenium/kg in the muscle. In pigs (n=6), after 17 weeks of daily feeding, a diet supplemented with 2.6 mg selenium/kg feed from sodium selenite (0.10 mg/kg bw) resulted in no increase in selenium levels in muscle (0.4 mg selenium/kg), a 1.3 fold increase in selenium levels in kidney (2.15 mg selenium/kg) and a 4-fold increase in selenium levels in liver (2.43 mg selenium/kg) as compared to control animals receiving 0.5 mg selenium/kg feed. The supplement in the two studies corresponded to the highest levels currently recommended for sodium selenite medical preparations used in feed.

Using the lower level (corresponding to 4.5 µg selenium/kg bw) of feed supplemented with sodium selenite or plant selenium for 90 days in milking cows (n=15), an American study showed a mean concentration in milk of 18 µg selenium/l. Comparable results were obtained in a 2-year investigation in milking cattle (n=10) given feed supplemented with sodium selenite or yeast selenium in Sweden. Based on a daily consumption of 1.5 litres milk consumer intake would be approximately 22 µg selenium/person/day. Levels to up to 60 µg selenium/litre milk were reported in earlier studies from Denmark.

It should be pointed out that in all the relevant studies a significantly higher increase in the tissue and milk selenium concentrations could be detected when the supplement was in the form of organic selenium (plant, yeast) as compared to feed fortification with sodium selenite.

Administration by injection

In an investigation using radiolabelled ^{75}Se-sodium selenite, groups of lambs (n=5) received varying

doses of selenium (0.05 mg, 0.25 mg and 0.6 mg selenium/kg bw) given as a single intramuscular injection. Thirty and 56 days after injection the animal tissues were analysed for the content of selenium. There was a dose-dependent linear increase in selenium tissue concentration. The mean levels of selenium measured at 30 days after administration of the highest two doses were 0.005 and 0.011 mg/kg in the muscle, 0.112 and 0.470 mg/kg in the liver as well as 0.070 and 0.130 mg/kg in the kidney. The selenium concentration at the injection site did not differ significantly from that in muscle. However, it should be pointed out that selenium concentration at the injection site after post injection times shorter than 30 days were not determined and hence no information on the pattern of depletion from the site of injection was available in this study.

In a study by Van Vleet (1975)[5] tissues from calves, lambs and pigs (four animals of each species) without selenium supplementation were analysed to establish baseline selenium concentrations. The following mean selenium content was found in calves, lambs and pigs respectively: liver, 0.12, 0.16 and 0.19 mg/kg; renal cortex, 0.63, 0.89 and 0.70 mg/kg; muscle, 0.05, 0.05 and 0.06 mg/kg. Subsequently, additional calves, lambs and pigs (eight animals of each species) were injected with a commercial selenium-vitamin E preparation at dose levels of 0.08, 0.055 or 0.06 mg of selenium (as selenite) per kg bw. Selenium content of tissues was measured in animals killed at 1, 7, 14 and 23 days after injection. In calves, concentrations in liver and kidney rapidly increased to moderate values and then slowly decreased, with mean concentrations at 23 days still somewhat greater than base line values (0.22 and 0.82 mg/kg respectively). Concentrations for injection site tissue also rapidly increased to moderate values, but had decreased to base line values by 23 days after injection. In lambs, selenium content of liver was moderately increased after injection, but had decreased to base line values after 14 days; kidney and injection site did not have increased selenium content after injection. In pigs, liver and kidney had moderate initial increases in concentration of selenium, but these were at base line values after 14 days and no increase occurred at injection sites. Increased selenium content in tissue at the injection site was found in calves, but not in lambs or pigs.

Another study conducted by Stephenson and Grant (1979)[6] provides data on residue concentrations in 24 sheep treated by subcutaneous injection at a dose rate of 5 mg selenium per 25 kg bw (corresponding to 0.2 mg/kg bw). Selenium concentrations increased in blood as well as in tissues within some minutes after injection, showing rapid uptake of selenium from the injection site. Highest values were measured in kidney (2450 µg/kg at 8.5 hours) and in liver (2400 µg/kg at 12 hours). As decline from the injection site was not measured, the study does not provide information on the safety of residues concerning this aspect.

In a study with subcutaneous injections of 0.15 mg selenium/kg bw as sodium selenite the concentration of selenium in cows' milk was 168 µg/l on the first day and 69 µg/l on the second day compared to concentrations of 26 µg/l in control animals. Smaller amounts, 1 to 5 mg selenium per animal as sodium selenite fed daily did not affect the selenium content of milk.

Only limited data were available from Member States on how withdrawal periods have been set.

A study in sheep was provided where ewes were given a single subcutaneous injection of 2 ml/45 kg bw as potassium selenate, corresponding to 0.06 mg selenium /kg. The first time point analysed was 28 days after treatment and there was no difference between injection site and non-injection site muscle. The likely daily exposure was determined using the food basket and was estimated to be 109 µg (fat residues were not included).

[5] Van Vleet JF (1975) American Journal of Veterinary Research 36(9) 1335-1340

[6] Stephenson and Grant (1979) New Zealand Veterinary Journal 27(11) 232

In another study pigs and calves were given an injection with 0.06 mg selenium /kg bw and were slaughtered 12 or 14 days after treatment respectively. In pigs, residues in injection site and non-injection site muscles were similar, but in calves the injection site contained higher levels (see table below). Only a summary of the study was provided without any details or complete data. The likely daily exposure determined using the food basket with the injection site as the muscle portion was estimated to be 102 µg (fat residues were not included).

	Pigs (day 12)		**Calves (day 14)**			
Tissue	Injection site	Muscle	Injection site	Muscle	Liver	Kidney
Selenium concentration	97 µg/kg	110 µg/kg	129 µg/kg	72 µg/kg	273 µg/kg	720 µg/kg

Selection of marker residue and marker to total residues ratio

While it is not possible to distinguish between treatment and non-treatment related selenium in tissues, the only feasible marker residue would be selenium with a marker to total residue ratio definition of 1.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report are available.

2.2.4. Analytical method for monitoring of residues

No analytical method was provided in the original MRL application. This was considered acceptable since a 'No MRL required' classification was recommended. No analytical method is available for review.

2.2.5. Findings of EU or international scientific bodies

No such findings are available.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

As the substance is not expected to possess antimicrobial activity no effect on microorganisms used for industrial food processing is expected.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

Selenium intake needs to be kept within a relatively narrow window as both deficiency and excess can have severe health consequences. Animal products provide approximately 50% of the total dietary

selenium intake, with the most important sources being fish, edible organs, meat, dairy products and eggs. Other dietary components rich in selenium include nuts, seeds, mushrooms and whole grains. The average total dietary selenium intake in European countries is estimated to be between 35 and 100 µg per adult per day. Various international expert bodies have set recommended dietary selenium intake levels ranging from 20 to 70 µg/adult/day.

A supplementation of human diet with selenium compounds based on the postulated protective effect of the element against cardiovascular diseases, immunodeficiency and cancer has been extensively debated but no internationally accepted recommendation has been adopted. In several countries selenium preparations have been marketed, for example as "health foods" or nutritional supplements, in recommended doses up to 120 µg selenium/person/day.

In its 1997 evaluation the CVMP noted that there were no data available on the depletion rate of selenium from the injection site after parenteral treatment and recommended Member States to implement withdrawal periods for injectable preparations in order to avoid any possible risks to the consumer. No data have been provided or found that would justify a change in this recommendation. The available data indicate that the intake of injection site tissues from treated animals would only pose a risk to the consumer for a relatively short time interval after treatment. While it is considered unlikely that animals would be sent for slaughter during this time interval it would nevertheless be appropriate to set a precautionary withdrawal period. In the absence of numerical MRLs competent authorities may do this by following the approach described in the section on injection site residues in the CVMP Note for guidance: approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95 FINAL), i.e., by establishing a withdrawal period that ensures that residues in a standard foodbasket including 300g of injection site muscle remain below the established tolerable daily intake.

While oral selenium can be used for prophylactic purposes, injectable products are considered to be critical for use in the treatment of acute selenium deficiency. As there are no other available treatments for acute selenium deficiency, restricting the use of potassium selenate, sodium selenate and sodium selenite to administration by routes other than injection would have a negative impact on animal welfare.

The option of controlling consumer exposure to selenium derived from potassium selenate, sodium selenate and sodium selenite by setting numerical MRLs is not appropriate in the case of these substances. This is because selenium is a naturally occurring element and consequently residue monitoring authorities would not be able to discriminate between residues of selenium resulting from selenium present naturally in feed and selenium derived from veterinary medicinal products containing potassium selenate, sodium selenate or sodium selenite. In addition, selenium residues may also occur as a result of selenium administered in veterinary medicinal products containing barium selenate[7], which has a 'No MRL required' classification and could, in principle, lead to selenium residues in animal produce. It is also noteworthy that a suitable analytical method validated for detection of selenium residues has not been provided.

The substances are not used as pesticides. However, it should be noted that consumers are exposed to selenium from other sources, including nutritional supplements and food derived from animals treated with selenium containing feed supplements. As intake from these sources is highly variable and cannot easily be quantified, it is not possible to provide a sound proposal for the portion of the tolerable upper intake level for selenium that should be reserved for sources of selenium other than veterinary

[7] Note that, in April 2014 the CVMP recommended, based on concerns over residues at the injection site, that barium selenate should not be administered by injection

medicinal products.

No additional relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

Oral administration of veterinary medicinal products containing selenium is not considered to represent a consumer safety concern and numerical MRLs are not considered necessary. Using the available data following oral administration of sodium selenite leads to the following worst case consumer intake calculations.

Calculation of theoretical daily intake of residues

Sheep tissues	**Daily consumption (kg)**	**Observed selenium level (µg/kg)**	**Ratio of the marker/total residue**	**Amount per edible tissue or product**
Muscle	0.30	160	1	48
Fat	0.05	-	1	-
Liver	0.10	840	1	84
Kidney	0.05	1400	1	70
Total intake				202 µg/person

Pig tissues	**Daily consumption (kg)**	**Observed selenium level (µg/kg)**	**Ratio of the marker/total residue**	**Amount per edible tissue or product**
Muscle	0.30	400	1	120
Fat	0.05	-	1	-
Liver	0.10	2430	1	243.0
Kidney	0.05	2150	1	107.5
Total intake				470 µg/person

The above worst case consumer exposure calculations after oral administration result in levels below the acceptable level of 300 µg for sheep tissues. While the intake calculation resulting from ingestion from pig tissues exceeds the acceptable level of 300 µg, it should be noted that in the study from which these data are derived, animals were treated daily for 17 weeks, which is very much longer than recommended for any authorised product. Most products are authorised for single use or short treatment duration. Also taking into consideration that natural selenium levels may vary considerably and can be expected to be low in animals that need treatment, it is expected that the oral administration to pigs will not substantially increase the long-term dietary exposure of the consumer to selenium.

For adult cattle, only milk data are available and the results are not very consistent, making it hard to make any calculation on daily exposure for the consumers. While some older studies have reported selenium levels of up to 60 µg/l in milk other long term studies have reported levels of approximately 15 µg/l. As, in practice, treated cattle are expected to be selenium deficient, residues in milk are expected to be closer to the lower end of the reported range and not to represent a hazard to the

consumer.

In relation to injectable potassium selenate, sodium selenate and sodium selenite, studies in lambs and sheep indicate no difference in residue levels in injection site and ordinary muscle. A similar result was obtained in pigs. In calves there is an indication that, two weeks after administration, selenium residues in injection site muscle were greater than in non-injection site muscle. Overall, the available data are too limited to conclude with certainty that the pattern of depletion of residues at the injection site differs between animal species. However, it is clear that persistent residues at the injection site do not occur. Worst case consumer exposure calculations using the data from the Van Vleet study and using the injection site as the muscle portion result in selenium intake below the acceptable intake level of 300 µg already at day 1 (based on one animal only). In the study by Stephenson in sheep the dietary exposure is below 300 µg at 17 hours, and only slightly above at 12 hours. However, injection sites were not analysed in this study. But in other studies in sheep residue levels in injection site and non-injection site muscle were similar.

Overall, injectable potassium selenate, sodium selenate and sodium selenite represent valuable veterinary medicines for which alternatives are not available. However, the possibility that ingestion of tissues from animals slaughtered shortly after treatment via injection may lead to a consumer exposure above the acceptable level cannot be completely ruled out. It is therefore proposed that the 'No MRL required' classification should be maintained for injectable potassium selenate, sodium selenate and sodium selenite but that competent authorities should set withdrawal periods for injectable products and these should be derived in a manner that ensures that that consumer exposure to residues from a foodbasket including injection site muscle remains below the ADI.

When considering the residue data and intake calculations reported above it should be noted that "normal" selenium levels in animal tissues may vary very considerably between different regions. There are some references where tissue levels in untreated animals given a normal diet (i.e. without selenium supplementation) would lead to an estimated dietary exposure above 300 µg/person. Consequently the establishment numerical MRLs for and potassium selenate, sodium selenate and sodium selenite in any tissue would be of questionable value.

3.4. Considerations on possible extrapolation of MRLs

The existing maximum residue limits status covers all food producing species. The current proposal is to maintain this situation and therefore considerations on possible extrapolation are not applicable.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the most relevant hazards to human health associated with exposure to residues of sodium selenate, sodium selenite and potassium selenite are due to the selenium content of the molecules,
- selenium is an essential element and a normal constituent of the diet in humans,
- a tolerable upper intake level of selenium has been established at 300 µg/person per day and is appropriate for use in the consumer safety evaluation,
- the use of sodium selenite, sodium selenate or potassium selenate in prophylaxis and therapy of deficiency diseases in food-producing animals is not expected to increase substantially the long-term dietary exposure of the consumer to selenium,
- the possibility of elevated selenium residues at the injection site shortly after treatment cannot be excluded and therefore Member States should consider the establishment of withdrawal times for parenteral preparations

the CVMP recommends the maintenance of the existing entries for potassium selenate, sodium selenate and sodium selenite in Table 1 of the Annex to Commission Regulation (EU) no 37/2010.

4. Background information on the procedure

Request for review	5 May 2014
Steps taken for assessment of the substance	
Clock started	12 May 2014
CVMP opinion adopted	4 December 2014