Selenium and its inorganic compounds

Supplement 2011	
MAK value (2010)	
Selenium and its inorganic compounds	**0.02 mg/m³ I (inhalable fraction).(as selenium)**
Hydrogen selenide	**0.006 ml/m³ ≙ 0.02 mg/m³ (as selenium)**
Peak limitation (2010)	
Selenium and its inorganic compounds	**Category II, excursion factor 8**
Hydrogen selenide	**Category II, excursion factor 8**
Absorption through the skin (2010)	
Selenium and its inorganic compounds	**H**
Hydrogen selenide	**–**
Sensitization	**–**
Carcinogenicity (1999)	**Category 3B**
Prenatal toxicity (1999)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (2010)	**150 µg/l**

Substance name	Chemical formula	Molecular weight	CAS number	Melting point [°C]	Boiling point [°C]
Selenium	Se	78.96	7782-49-2	221	690[1]
Selenium oxide	SeO_2	110.96	7446-08-4	340	n.d.[1]
Selenium sulfide	SeS	111.02	7446-34-6	111	118–119[*4]
Selenium disulfide	SeS_2	143.09	7488-56-4	113	n.d.[1]
Selenious acid	H_2SeO_3	128.97	7783-00-8	70	n.d.[1]
Selenic acid	H_2SeO_4	144.97	7783-08-6	58	260[1]
Hydrogen selenide	H_2Se	80.98	7783-07-5	–65.7	–41.3[1]

The MAK-Collection Part I, MAK Value Documentations 2015
DFG, Deutsche Forschungsgemeinschaft

Substance name	Chemical formula	Molecular weight	CAS number	Melting point [°C]	Boiling point [°C]
Selenious acid, monosodium salt	$NaHSeO_3$	150.96	7782-82-3	n.d.	n.d.[3]
Sodium selenide	Na_2Se	124.94	1313-85-5	>875	n.d.[4]
Selenious acid, disodium salt	Na_2SeO_3	172.94	10102-18-8	710*	n.d.[5]
Selenic acid, disodium salt	Na_2SeO_4	188.94	13410-01-0	n.d.	n.d.[5]
Selenomethionine	$C_5H_{11}NO_2Se$	196.11	3211-76-5	n.d.	n.d.[2]

* Decomposes, [1] SRC 2010, [2] NLM (2010 b), [3] NCBI (2010), [4] ATSDR (2003), [5] NLM (2010 a)

Since the establishment of the MAK value for selenium and its inorganic compounds (see Documentation "Selenium" 1999, not available in English), further studies on the toxicokinetics, empirical results in humans, the reproductive toxicity and genotoxicity of selenium and its inorganic compounds have been published which make a supplement or a re-assessment necessary.

In this supplement to selenium and its inorganic compounds, studies on selenomethionine are also included, as only the selenium ion is considered to be the effective agent in this compound.

Mechanism of Action

Selenium is an essential trace element and, in the form of selenocysteine, is a structural component in a large number of enzymes and functional proteins, responsible for important functions in the cell cycle or in cellular redox systems. Selenium-containing proteins include proteins transporting or binding selenium and selenoenzymes to which belong, among others, glutathione peroxidases and the deiodinases (Documentation "Selenium" 1999, only available in German). In various studies on the tumour-suppressing effect of selenium, its interference with the cellular redox status by modification of the protein-thiol groups and methionine mimicry (Jackson and Combs 2008), effects on cell cycle regulation and apoptosis (Naithani 2008), on DNA repair and tumour suppressor gene regulation (Youn et al. 2001), effects at the signal path level (Rikiishi 2007; Youn et al. 2001) or on angiogenesis (Jackson and Combs 2008) have been postulated as mechanisms.

The mechanism, on which the potentially diabetogenic effect of selenium supplementation at sufficient initial selenium levels is based, has not yet been clarified. Whereas, on the one hand, this effect is attributed to the ability of a number of selenium compounds to form reactive oxygen species and, in this way, to increase

insulin resistance (Bleys et al. 2007 a), other authors draw attention to the development of insulin resistance following over-expression of glutathione peroxidase and thus to reductive stress (McClung et al. 2004).

Toxicokinetics and Metabolism

Orally ingested selenium, in the form of organic compounds, as selenomethionine (from plant products) and selenocysteine (from animal products), or after intake either orally, via inhalation or absorption through the skin mainly in the form of water-soluble inorganic selenium compounds, is reduced after absorption to form selenide, which serves as a common source for the synthesis of selenoproteins and selenium sugars (Ohta and Suzuki 2008). 25 genes coding selenoproteins have been identified in the human genome to date. Their functions are only partly known (Lu and Holmgren 2009). Unlike selenoproteins, the selenosugars, of which three different species have been identified in human urine samples, are excretion products of selenium (Bendahl and Gammelgaard 2004; Gammelgaard and Bendahl 2004; Gammelgaard et al. 2003, 2005; Kobayashi et al. 2002; Kuehnelt et al. 2005). Intermediate selenide is not only metabolized to selenoproteins and selenium sugars, but also to methylated derivatives such as monomethyl and dimethyl selenide and the trimethylselenonium ion. Monomethyl selenide, the metabolite responsible for the anti-oxidative effect of selenium, constitutes an important intermediate: monomethyl selenide can be further methylated to form dimethyl selenide and trimethylselenonium ion or becomes a degradation product of methyl selenocysteine and methyl selenious acid, which can be further converted into selenide (Ohta and Suzuki 2008). Methylselenocysteine, a substance also occurring naturally, and methylseleninic acid are rapidly transformed through the β-lyase and a number of reduction reactions. Studies in rats show that methylselenocysteine is more stable and more efficiently distributed in the organism than methylseleninic acid, and is therefore the most reliable source of methylselenol in most organs (Suzuki et al. 2008). In vitro experiments with simultaneous incubation of ^{77}Se-methylseleninic acid and ^{82}Se selenite in erythrocyte suspensions suggest that the production of selenium sugars or of trimethylselenium ions depends on the metabolic capacity to demethylate methylselenol to selenide (Suzuki et al. 2006).

In earlier studies on the selenium metabolism it was postulated that methylselenide is formed mainly at a low selenium dose (0.1 mg/kg body weight in rats), and the trimethylselenonium ion dose-dependently at higher doses (Itoh and Suzuki 1997; Suzuki et al. 1995). Dimethylselenide is not formed until toxic selenium doses are administered (Mozier et al. 1988; Vadhanavikit et al. 1993). More recent studies question these data. After single oral administration of a subtoxic dose of 300 µg ^{77}selenium in the form of selenite, 11.2% of the dose was found in the form of dimethylselenide in the exhaled air and 18.5% in the form of compounds containing selenium (total selenium) in the urine of a volunteer during the first 10 days. The

major portion of the dimethylselenide was exhaled during the first two days after administration (Kremer et al. 2005). No methylselenol could be detected in the urine using an improved HPLC/ICP-MS method. The fact that it was detected in the earlier studies was attributed to inadequate analytical methods (Francesconi and Pannier 2004). Elimination of the trimethylselenonium ion has in the meantime been clearly confirmed although, normally, only traces of this metabolite are excreted. The concentration of the trimethylselenium ion in urine is subject to high interindividual variation. In some persons, the trimethylselenonium ion can represent the major urinary metabolite (Kuehnelt et al. 2006). In the meantime, it is agreed that selenosugar is generally the most important selenium metabolite in human urine (Bendahl and Gammelgaard 2004; Francesconi and Pannier 2004; Gammelgaard et al. 2003; Kobayashi et al. 2002; Kuehnelt et al. 2005, 2006, 2007).

Effects in Humans

Exposure to selenium at the workplace

Inhalation

In 20 workers aged between 30 and 55 years and active in various fields of selenium refinement, external exposure was measured twice by two-hour personal sampling of the total selenium in air and internal exposure by determining selenium concentrations in plasma and urine. As reference, measurement of the selenium concentrations in plasma and urine in age-matched control persons was carried out. No differentiation of the selenium species in the inhalable dust was possible due to the great variation of activities during the working day. The plasma analyses were carried out after the shift and after holidays, the urinalyses before and after the shift as well as after the holidays. The selenium concentrations in air were between 8 and 950 µg/m^3 I (median 110 µg/m^3 I; 95th percentile 946 µg/m^3 I). The MAK value had been exceeded in 67% of those exposed to selenium. The post-shift plasma selenium concentrations were 12 to 182 µg/L (median 118 µg/l; 95th percentile 181 µg/l). Selenium concentrations of 61 to 103 µg/L (median 75 µg/l; 95th percentile 103 µg/l) and thus significantly lower values ($p = 0.034$) were measured in the plasma samples obtained from 12 workers after their holidays. The selenium concentrations in the control group were significantly below the post-shift values of the exposed persons and varied between 52 and 102 µg/L (median 76 µg/l; 95th percentile102 µg/l). 80% of the post-shift values in the exposed persons exceeded the 95th percentile in the control group used as reference value though, by contrast, the after-holiday values were at the level of the controls. The pre- and post-shift selenium concentrations in urine samples (pre-shift: 10 to 815 µg/g creatinine, median 43 µg/g creatinine, 95th percentile 792 µg/g creatinine; post-shift: 10 to

437 µg/g creatinine, median 56 µg/g creatinine, 95th percentile 426 µg/g creatinine) showed no significant difference and no comparable/similar/uniform development during the shift. They were, however, clearly above the reference value of 32 µg/g creatinine in the control persons (range 7 to 33 µg/g creatinine, median 13 g/g creatinine). There was no relationship between the current inhalation exposure and the selenium concentrations in plasma and urine (Schaller et al. 2008).

Also, from the studies already listed in the Documentation of 1999 (Glover 1967, 1970; Kinnigkeit 1962), no relationships can be derived between the selenium concentration in air and the selenium concentrations in serum or urine.

Dermal absorption

Unlike the organic selenium compounds, **selenomethionine** (Burke et al. 1992, 2003) and a **selenotrisulfide** derivative of α-liponic acid (Alonis et al. 2006), no studies on the dermal uptake of selenium and its inorganic compounds are available. However, in case reports, intoxications following skin contact with inorganic selenium compounds have been described.

A female helper aged 19 at a chemical plant who had occupational contact with **selenium dioxide**, lead oxide, tannin and benzyl alcohol, experienced pains in her fingertips and her fingernails turned bright red the day after filling selenium dioxide from a storage container into transportation glasses for the first time. By the following day, papular dermatitis on the stretching sides of both forearms, pronounced swelling of the hands and a bright to brownish red discoloration of all fingernails had developed. The intact rubber gloves worn by the patient during her work were found to have a sweetish-putrid odour, comparable to the smell of organic selenium compounds. The patient reported first having started to fillup the selenium dioxide without the prescribed rubber gloves and then put them on. Two different analytical methods were applied to determine selenium in urine (diaminobenzidine and pyrrol methods), which produced similar results. The selenium concentrations in urine were 97 and 73 µg/100 ml four days after intoxication, 41 and 38 µg/100 ml after 7 days, and 14 and 17 µg/100 ml after 11 days, respectively. Selenium concentrations in the fingernails were 421 and 372 µg per 100 mg nail, respectively, from which 0.3 to 1.0 mg fixed selenium per fingernail was concluded. The authors point out that the intoxication was probably caused by selenious acid, which converts to selenium dioxide in an aqueous medium (Rietschel and Langer 1965).

In the context/ In the course of a skin rash on the head, a 31-year-old worker who has contact with a selenium alloy at his workplace experienced alopecia areata after 6 months, which deteriorated to alopecia universalis after 11 months. The selenium concentrations found were 500 µg/l in blood and 2.04 µg/g in the nails. Average blood values of 50 µg selenium/l were found in colleagues not exposed to selenium (Srivastava et al. 1995).

To treat a skin rash on her head, a woman aged 46 used a hair shampoo containing selenium sulfide (no details on concentration) two to three times per week. After eight months, she experienced arrhythmic tremor in arms and hands, which developed into a severe generalized tremor accompanied by extreme sweating. She had a metallic taste in the mouth and her breath smelt of garlic. This was followed by a diffuse pain in the lower abdomen. She felt weak, lethargic, had no appetite and suffered from sporadic vomiting. She complained of headaches, disturbances of speech, vision and locomotion, and skin rashes, particularly on the skin of her head. Blood pressure, blood count, ECG and radiography of the lungs were normal. In the 24-hour urine 243 mg coproporphyrin/L, 147 mg uroporphyrin/L and 28 mg selenium/L were measured. Four days later, these values had decreased to 48.8 mg coproporphyrin/L and 17.4 mg uroporphyrin/L. Selenium was no longer detectable in the urine. The metallic taste in her mouth continued for a total of five days. The patient was free of symptoms ten days after their appearance (Ransone et al. 1961).

In one worker, daily contact with selenium and **sodium selenite** over 36 years caused an oedematous erythema in face and neck, raised plaques on the back of hands and fingers, reddening of the nasal and pharyngeal mucous membrane, mild conjunctivitis and enlarged liver. In the urine, an increased amount of porphyrins were found (Halter 1938).

Workers at a car tyre workshop ("repair shop"?), in whose urine a mean concentration of 126 µg selenium/L (maximum 1268 µg/l, normal value about 75 µg/l) was found, complained merely of burning or irritation of the skin after contact with **selenious acid** (no other details) and of "whiskers" (hairlike precipitations of selenium dioxide crystals) in the region of the mouth. Irritation of the upper airways occurred only occasionally. As most frequent symptom, the workers described a metallic taste in the mouth lasting for two to three days (Vaillancourt and Robin 1994). Assuming a saturated aqueous selenium solution, calculations with the models of Guy and Potts (1993), Wilschut et al. (1995) and Fiserova-Bergerova et al. (1990), yield dermal fluxes of 0.002, 0.004 and 0.012 mg/cm^2 and hour, respectively. This would correspond to a total uptake of 3.7, 7.1 and 23.6 mg selenium, respectively, if both hands and forearms (approximately 2000 cm^2) were exposed for one hour.

On the basis of a 10% aqueous **selenious acid,** dermal fluxes of 0.0002, 0.002 and 0.032 mg/cm^2 and hour are calculated from the models cited above. This would correspond to a total uptake of 0.3, 3.7 and 64.5 mg selenious acid, respectively, if both hands and forearms (approximately 2000 cm^2) were exposed for one hour. This would mean that a total uptake of 0.2, 2.3 and 39.5 mg selenium, respectively, is obtained after conversion.

Chemopreventive effects

In the Documentation of 1999 (Documentation "Selenium" 1999, only available in German), various prospective studies were listed, from which indications could be

gained as to the preventive effect of an adequate selenium uptake in the context of tumour development in the gastrointestinal and respiratory tracts, and in the prostate gland. A further study, which appeared to confirm this effect of selenium in humans, was the "Multicenter Cancer Prevention Trial" by the Nutritional Prevention of Cancer Study Group (Clark et al. 1996). An inverse association between serum selenium levels and tumour incidence has also been reported in a region within China where the epidemic occurrence of squamous cell carcinomas of the oesophagus and adenomatous cancers of the gastric cardia was observed (Mark et al. 2000). However, the results of two more recent studies have clearly dampened the hope of an effective cancer prevention through selenium supplementation which these preceding studies had nourished. In the SELECT Study (The Selenium and Vitamin E Cancer Prevention Trial), a double blind, placebo-controlled phase 3 study involving 35533 men without prostate conditions, daily administration of 200 µg selenium in the form of **L-selenomethionine** had no effect on the development of prostate cancer. The results were obtained independently of whether vitamin E was administered simultaneously or not. The study was prematurely terminated due to a possible increased risk of type 2 diabetes mellitus from the selenium (Lippman et al. 2009). In a further study with 1312 participants (Nutritional Prevention of Cancer (NPC) Trial) receiving a daily selenium supplementation (200 µg, administered in the form of baker's yeast containing about 60% L-selenomethionine) no effect on the risk of cancer, in this case skin cancer, was observed (Stranges et al. 2007).

The objective of the study described in greater detail under "Reproductive and developmental toxicity" was, among others, to investigate whether the cardio-vascular diseases observed under a low selenium status can be counteracted by selenium supplementation.

In 22 volunteers, daily selenium supplementation (300 µg selenium, 48 weeks) did not improve vascular endothelial responsiveness of peripheral blood vessels (Hawkes and Laslett 2009).

Selenium and diabetes mellitus

In the study by Stranges et al. (2007) here described under "Chemopreventive effects", 97 new cases of type 2 diabetes mellitus were diagnosed during the observation period of 7.7±2.7 years, corresponding to an incidence of 10.5 cases per 1000 person-years. Of the 97 new diabetes cases, 58 were study participants with selenium supplementation and 39 were in the placebo group (12.6 cases per 1000 person-years in the selenium group and 8.4 cases in the placebo group; hazard ratio (HR) 1.55; 95% confidence interval (CI) 1.03–2.33; $p = 0.03$). After stratifying the results by age, sex, smoker status and BMI (body mass index), the group supplemented with selenium showed an increased risk. The risk difference was, however,

significant only in men (HR 1.62; 95% CI 1.04–2.55; p = 0.03) and in the mean BMI tertile (23.72–26.76 kg/m^2; HR 2.81; 95% CI 1.12–7.04; p = 0.03). A significant exposure-effect relationship was found across the tertiles of the baseline plasma selenium levels (p = 0.038). In an isolated assessment of the individual tertiles, however, only the participants in the highest tertile of baseline plasma selenium values (>121.6 µg/L plasma) were at a significantly higher risk of developing a type 2 diabetes mellitus (HR 2.70; 95% CI 1.30–5.61; p = 0.008). The diabetes risk of the participants with a baseline selenium level (HR 2.50; 95% CI 1.31–4.77; p = 0.005) above the median (113.4 µg/L plasma) was significantly increased to a similar extent. The authors emphasize various limitations of the study: the diabetes incidence was not the primary endpoint of the study, the "diabetes mellitus type 2" diagnosis was based on information from study participants, other risk factors, such as a predisposition to diabetes in the family, body fat distribution and physical activity were not included, and the study population consisted of elderly, mostly Caucasian (average age 63.2 years) with a non-melanotic skin cancer in their patient history. Had there been only a few diabetes cases more in the placebo group would have yielded a different result.

Also in the SELECT study, participants who had received selenium only had a somewhat higher diabetes risk than those in the placebo group, though the risk increase was not significant (RR 1.07; 99% CI 0.94–1.22; p = 0.16). In 277 of the 8752 men taking selenium only and in whom the selenium concentrations in the serum had been determined at the start of the study, the selenium levels were on average 135 µg/l (123.4–145.9 µg/l). At the last control before termination of the study, a mean selenium concentration in the serum of 251.6 µg/L (218.7–275.0 µg/l) was measured in 72 participants in this group (Lippman et al. 2009). Although the diabetes risk in the group of persons with selenium substitution was only discretely and not significantly higher, the termination of the study was defended in subsequent publications not only by the lack of a protective effect on the development of prostate carcinomas, but also by a possibly significant diabetogenic effect of selenium substitution if the study had been continued.

No studies are available from Germany or other European states in which a diabetes risk from selenium supplementation has been investigated. In the French Su. VI.MAX Study (Supplementation en Vitamines et Minéraux Antioxydants), however, effects of selenium supplementation on the fasting plasma glucose level were observed. In this randomized, placebo-controlled study, in which the 1533 participants in the intervention group received **selenomethionine** (100 µg selenium) in addition to vitamin C, vitamin E, β-carotene and 20 mg zinc in a capsule as diet additive for 7.5 years on a daily basis, a statistically significant positive association between the baseline selenium plasma levels and the fasting glucose values at the beginning and end of the study (regression coefficient 0.03 ± 0.008; p = < 0.0001) was found on multivariate longitudinal sectional analysis (Czernichow et al. 2006).

Apart from the studies described in which selenium was supplemented, a number of other studies are available which indicate an interaction between selenium and glucose metabolism in humans. In the Health Professionals Follow-up Study, male

diabetics were found to have a lower selenium concentration in their toenails than the persons of the control group (Rajpathak et al. 2005). Data from the 1980s (NHANES III) and the years 2003 to 2004 (NCHS 2003-2004) are available from the NHANES (National Health and Nutrition Examination Survey). A cross-sectional analysis with 8876 participants ≥ 20 years by NHANES III revealed mean selenium levels of 126.5 µg/L serum in participants with diabetes mellitus and of 125.7 µg/L in persons without it. After adjustment for age, sex, ethnic group and BMI, the corresponding concentrations were 126.8 µg/l serum and 124.7 µg/l, respectively. The adjusted difference of 2.1 µg/L was statistically significant (95% CI 0.4-3.8; p = 0.02). Diabetes was defined as the presence of a fasting plasma glucose ≥ 126 mg/dl, a self-report of a physician's diagnosis of diabetes, or current use of insulin or oral antidiabetics The multivariable adjusted odds ratio for diabetes mellitus comparing the highest (≥ 137.66 µg/L serum) to the lowest (≤ 111.62 µg/l) quintile of selenium levels was 1.57 (95% CI 1.16-2.13). In the opinion of the authors, it is not possible to derive, from these data, whether the high selenium level is the cause or the result of diabetes mellitus (Bleys et al. 2007 a, b). In the corresponding analysis of the NHANES data from 2003 to 2004, the selenium levels determined in the serum were 143.7 ± 18.3 µg/L in the diabetics and 136.4 ± 19.9 µg/l in the non-diabetics. The corresponding plasma glucose levels were 149.9 ± 48.9 mg/dl and 96.9 ± 9.6 mg/dl, respectively. As diabetics, those persons with a fasting plasma glucose value ≥ 126 mg/dl plasma were considered, who reported current use of insulin or oral antidiabetics. The multivariable adjusted odds ratio for diabetes mellitus comparing the participants' quartile with the highest selenium concentrations (≥ 147 µg/L serum) with the lowest (< 124 µg/l) was 7.64 (95% CI 3.34-17.46). In spline regression models, the prevalence of diabetes as well as glucose and glycosylated haemoglobin levels increased with increasing selenium concentrations up to 160 µg/L serum (Laclaustra et al. 2009).

In two cross-sectional studies with participants from France (Coudray et al. 1997) and Singapore (Hughes et al. 1998), no statistically significant correlation was found between the selenium levels in the plasma and the fasting glucose values or diabetes prevalence.

Indirect indications for an interaction of selenium and glucose homoeostasis have been derived from a number of studies. Chen and coworkers report a strong positive correlation between the activity of glutathione peroxidase in the erythrocytes and insulin resistance in non-diabetic women during pregnancy (Chen et al. 2003). The activity of glutathione peroxidase in the erythrocytes represents the accumulation of selenium over the preceding 120 days (see Documentation "Selenium" 1999, only available in German). After administration of **sodium selenite**, a reduced circulation of the IGF 1 (insulin-like growth factor 1) was found. The substance has a documented effect on the control of glucose homoeostasis (Grønbaek et al. 1995).

An earlier case report showed that exposure to **hydrogen selenide** possibly also affects the glucose metabolism. After hydrogen selenide poisoning, a chemist developed severe hyperglycaemia, which could only be brought under control by increasingly high insulin doses (Rohmer et al. 1950).

Allergenic effects

Sensitizing effects on the skin

Four workers in a glass factory exposed to **barium** and **sodium selenite** for 5 months, 7 years (2 workers) or 9 years complained of skin or mucosal changes. In one worker each with acute contact dermatitis in face and neck or with recurrent eyelid eczema, patch tests with 0.1% sodium selenite in petrolatum were clearly or weakly positive and also reproducible after 15 months or 4 and 8 weeks. Irritant conjunctivitis was diagnosed in one worker with negative patch testing for **barium** and **sodium selenite**, and an irritant dermatitis suspected in another, as the originally occurring weakly positive reaction in the patch test after 48 hours was not reproducible 8 months later. Of the five control persons, two showed irritant reactions to 1% **barium selenite** and four no reaction to a 0.1% selenite preparation (Richter et al. 1987). During the preparation of nutrient (das ist richtig) oder: culture media containing selenite for bacterial cultures, a female laboratory assistant developed pruriginous vesicular skin changes between the fingers. This also spread over her face and neck, and bronchial asthma occurred twice. Triple positive results were obtained after patch testing with 0.1% **sodium selenite** in water, whereas an intracutaneous test with selenite (no other details) was negative. No reactions were obtained in the patch test with the 15 controls (Senff et al. 1988).

Sensitizing effects on the airways

There are no reports available.

Reproductive toxicity

A large number of publications show that both selenium deficiency and increased selenium uptake are able to cause impairment of sperm function and consequently a reduction in male fertility (Hawkes et al. 2009).

In a double-blind study lasting 120 days, no adverse effects on sperm parameters and reproductive hormones were found in men whose diet contained a high or a low quantity of **sodium selenite**. In this study, all eleven participants aged between 20 and 45 years were fed diets providing selenium intake levels of 0.6 µg/kg body weight and day for 21 days. Over the subsequent 99 days, six participants received a diet with a selenium concentration of 0.2 µg/kg body weight and day and five volunteers with a selenium concentration of 4 µg/kg body weight and day. Investigations were carried out in weeks 3 (baseline values), 8, 13 and 17 (final values). To assess sperm quality, the concentration, number and motility of the sperm and the sperm volume were determined and sperm morphology examined histologically. In

addition, the activities of the reproductive hormones in the serum (testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, oestradiol and progesterone) and also the levels of the thyroid hormones (T3 and TSH) in the serum were measured. No effects on the serum levels of the reproductive hormones were observed. The selenium concentration increased in the blood plasma by 70% and in the seminal plasma by 50% compared with the baseline values. Selenium supplementation had no effect on selenium concentration in the sperm. The serum level of thyroid hormone T3 decreased and that of the TSH increased. In both groups, by the end of the study, a significant decrease in sperm concentration and number compared with baseline values was observed. There was no significant difference in results between the groups. At week 13, the mean sperm motility in both groups was significantly different, but not however at weeks 8 or 17. In the volunteers with the higher selenium supplementation, the fraction of motile sperm decreased by an average of 32% but was only 17% lower than the baseline value at the end of the study. The authors drew attention to the low number of volunteers and possible seasonal differences in spermatogenesis (maximum in winter, minimum in summer). Also, environmental or dietary influences on sperm motility could not be excluded (Hawkes and Turek 2001). In a further study performed by the same working group with a greater number of volunteers and longer study duration, it was found that sperm motility does not depend on selenium dose. This investigation involved 42 male volunteers between 18 and 45 years. Of these, 22 received yeast tablets containing selenium (300 μg selenium) for 48 weeks and the standard placebo yeast tablets with a selenium content of ≤ 1.3 μg per tablet. Selenium administration increased the selenium concentration in blood plasma, and seminal plasma by at least half the baseline values. Selenium supplementation had no effect on selenium concentration in the sperm, the level of testosterone or luteinizing hormone in the serum, and sperm quality. There was a negative association between sperm motility and air temperature, and it was higher in the winter than in the summer. At week 24, in the serum of the selenium supplementation volunteers compared with that of participants in the placebo group, a significant increase in prostate-specific antigen (PSA), a biomarker for prostate cancer, was found. This increase could not be definitely attributed to selenium supplementation, as the baseline values of these persons compared with controls was already higher and both groups were found to have comparable PSA concentrations by the end of the recovery period (week 96) (Hawkes et al. 2009).

Between 1972 and 1988, the selenium levels in the drinking water of an Italian community in Reggio Emilia were 7 to 9 μg/L (in the form of **selenate**, calculated intake 10–20 μg/day). Compared with women from the same community whose drinking water had a selenium concentration of <1 μg/L, a slight, non-significant increase in spontaneous abortions (RR = 1.73; 95% CI 0.62–4.80) was found. In the offspring of 18 women whose drinking water had a higher selenium content, body weight and length of the offspring was unchanged (Vinceti et al. 2000). As the selenium level in the drinking water cannot be considered high (maximum threshold value for selenium in drinking water is 10 μg/l; EC 1998; WHO 2003), data on

selenium status are lacking, and only insufficient information is available as to confounders, the validity of this study is limited.

Genotoxicity

Nine patients suffering from neuronal ceroid lipofuscinosis received intramuscular injections or oral administration of **sodium selenite** (5 to 50 µg selenium/kg body weight and day) for one month or up to 13.5 months. As controls, five healthy persons received sodium selenite (25 µg selenium/kg body weight and day) orally for two weeks. No increased number of chromosome aberrations or sister chromatid exchanges were found in the lymphocytes of all treated patients (Norppa et al. 1980 b).

Carcinogenicity

In the Italian community already mentioned, 2065 inhabitants drank water with a selenium concentration between 7 and 9 µg/L between 1972 and 1988. The size of the reference cohort consisting of community members whose drinking water had a selenium content of <1 µg/L was not given. According to the authors' report, after a 10-year observation period, the incidence of melanomas in those high exposed was 3.9 times higher than in those low exposed (95% CI 1.8–7.4). The SMR was 5.0 (95% CI 1.6–12.0) for men and 3.2 (95% CI 1.0–7.7) for women. The authors estimated the daily intake of selenium in this area to be 45 to 50 µg/day and the excess selenium taken in via the drinking water to be 10 to 20 µg/day (Vinceti et al. 1998). As the selenium concentration in the drinking water was below the threshold value (10 µg/l), no individual measurements of selenium exposure were made (individuals were classed as exposed and non-exposed depending on their place of residence), data on the selenium status are lacking and the information on confounders is inadequate, this study cannot be used in assessing carcinogenicity.

Since the 1999 Documentation (see Documentation "Selenium" 1999, only available in German), no epidemiological studies on the carcinogenicity of selenium in humans have been published. However, the studies described under the headings "Selenium and diabetes mellitus" or "Chemopreventive effects" revealed no cancer risk after 7 to 12 years daily selenium supplementation with 200 µg **L-selenomethionine** in 35 533 (SELECT Study; Lippman et al. 2009) or 1312 men (NPC Study; Stranges et al. 2007).

Animal Experiments and in vitro Studies

Repeated exposures

Ingestion

Twelve male and twelve female Sprague Dawley rats were treated for 13 weeks with **sodium selenite** at 0, 2, 3, 4 or 5 mg/kg diet (males: 0, 0.14, 0.22, 0.31 or 0.40 mg selenium/kg body weight and day; females: 0, 0.20, 0.33, 0.42 or 0.48 mg/kg body weight and day). Degeneration of liver cells occurred dose-dependently with increasing severity from 0.22 mg selenium/kg body weight. From 0.31 mg selenium/kg body weight and day, changes in body weight, haematological parameters, clinical chemistry, relative organ weights and histopathological parameters were observed. From 0.4 or 0.48 mg selenium/kg body weight and day, necrotic epithelial cells were found in the renal medulla. The NOAEL was 0.14 mg selenium/kg body weight and day for males and 0.20 mg selenium/kg body weight and day for females (Jia et al. 2005).

Absorption through the skin

In the 90-day study already described in the 1999 Documentation (see Documentation "Selenium" 1999, only available in German), 0, 1, 5, 10, 25 or 50 mg **selenium sulfide** (application volume 0.1 ml, suspended in 0.5% carboxymethylcellulose) was applied to the skin of ten male and ten female ICR-Swiss mice each five times per week for 13 weeks. Most of the mice developed reddening and irritation at the application side, occurring after application of 1 mg selenium sulfide after 39 applications, and of 5 or 10 mg selenium sulfide after 14 applications. The conditions were, however, not severe enough to justify termination. Above 25 mg selenium sulfide, the mice had hunched posture, cyanosis, weight loss, tremor, dull coat and reduced activities during the initial weeks. At 25 mg selenium sulfide, three male and five female mice died and, at 50 mg selenium sulfide, eight males and all females. Focal calcifications in the liver were found in one female only at 5 mg selenium sulfide. One dose-dependent case of nephritis occurred at 5 mg selenium sulfide. In the liver, focal coagulation necroses in one animal of each sex were observed after administration of 5 and 10 mg selenium sulfide, in two animals after 25 mg, and in the two surviving mice after 50 mg (NCI 1980).

Reproductive and developmental toxicity

Fertility

In the context of fertility, a LOAEL of <0.1 mg selenium/kg body weight and day for mice and a NOAEL of 0.15 mg selenium/kg body weight and day for rats were

derived in the Documentation of 1999. The relevant studies are described in short below. Further investigations not contained in the Documentation (1999) (see Documentation "Selenium" 1999, only available in German) are given in greater detail.

Generation studies

The LOAEL for the mouse was obtained from a four-generation study with five pairs of Charles River mice each in which administration of 3.0 mg **sodium selenate**/L (about 0.1 mg selenium/kg body weight and day) with their drinking water resulted in reduced mating frequency, an increased number of runts and increased mortality in the offspring before weaning. The fourth generation (F3) produced only three litters totalling 23 offspring, of which 16 were runts (Schroeder and Mitchener 1971). In this study only one dose was tested and data as to whether sodium selenite caused toxic effects in the parents were lacking. In another study by the same working group, the same dose, i.e. 3.0 mg **sodium selenate**/L (about 0.1 mg selenium/kg body weight and day), resulted in reduced physical activity, poor general condition and unkempt coat (Schroeder and Mitchener 1972). From this it can be assumed that the dose applied in the study by Schroeder and Mitchener (1971) producing toxic effects in the parents also had an adverse effect on the offspring.

The NOAEL of 0.15 mg selenium/kg body weight and day for rats (1.5 mg selenium/L drinking water in the form of **potassium selenate**) is derived from a two-generation study with five pregnant Wistar rats. Though the highest dose tested of 7.5 mg selenium/L (about 0.75 mg selenium/kg body weight and day) produced sterility in the females, it had no effect on the males (Rosenfeld and Beath 1954).

In a screening test (one-generation study), 10 male and 10 female Sprague Dawley rats were given 0, 7.5, 15 or 30 mg **sodium selenate**/L (male animals: 0, 0.4, 0.7 or 1 mg sodium selenate/kg body weight and day; corresponding to 0, 0.18, 0.3 or 0.46 mg selenium/kg body weight and day; female animals: 0, 0.5, 0.8 or 1.1 mg sodium selenate/kg body weight and day; corresponding to 0, 0.23, 0.37 or 0.5 mg selenium/kg body weight and day) with their drinking water. Treatment was during and after mating, altogether 26 days for the male rats, and started 6 days prior to mating. Total treatment lasted 30 days for the females and started 12 days prior to mating. A group of 10 unmated females was also treated 30 days for examination of the oestrus cycle. Compared with controls, water intake was clearly decreased in all dosed groups, and was up to 74% (in the males) or 82% (in the females) at 30 mg/L. In the males, the relative kidney weight was increased at 7.5 mg sodium selenate/L and above. In the females, food intake and terminal body weight were reduced in all dosed groups and in males at 15 and 30 mg sodium selenate/L. The relative testis weight was decreased at 15 and 30 mg/L. In the highest dose group (30 mg/L), animals had an unkempt coat and a hunched posture and, in the males, the organ

weights of liver, *cauda epididymis*, epididymis and spleen were reduced. The sperm parameters were not affected by selenium. In the female rats of the high dose group, significantly fewer corpora lutea and implantations, a slightly reduced number of live foetuses per litter and a slight increase in the number of early resorptions as well as pre- and postimplantation losses were found. The authors attribute the absence of statistical significance to the high standard deviation and the small group size (6 dams), and also consider the greatly reduced water intake by the dams to be responsible for the reproductive toxicity. In the high dose group, the oestrus was shortened and the cycle prolonged by 22% in the unmated females (NTP 1996).

Male fertility

Some publications present the results of a working group that investigated male BALB/c mice by feeding them for eight weeks with low (selenium deficient group: 0.02 mg selenium/kg diet, about 0.0035 mg selenium/kg body weight), normal (control group: 0.2 mg selenium/kg diet, about 0.035 mg selenium/kg body weight) or high selenium concentrations (excess group: 1 mg selenium/kg diet, about 0.175 mg selenium/kg body weight). In the mice of the excess group, the selenium concentration in the testis was significantly increased, sperm motility and sperm count were not affected. The activities of glutathione peroxidase (in liver and testis) and glutathione-S transferase (testis) showed no significant changes compared with controls, the activity of superoxide dismutase (testis) was significantly increased. The levels of luteinizing and follicle-stimulating hormones as well as testosterone in the serum were comparable with control values. Increased DNA fragmentation was observed in the selenium-deficient and selenium-excess groups, which was more pronounced in the selenium-deficient group (Kaur and Bansal 2004 a, b). Morphologically, a decrease in the lumen size of the seminiferous tubules and a displacement of germ cell populations were observed (Kaur and Bansal 2004 c). After eight weeks of treatment, the male animals were each mated with two female mice. The high selenium concentration had no effect on fertility, and litter size was not significantly decreased compared with controls (Kaur and Bansal 2004 b). No effects on germ cell population were observed (Kaur and Bansal 2005). In a further study published by the same working group using the same study design, reduced fertility and reduced litter sizes occurred (Kaushal and Bansal 2009). A high selenium dose produced oxidative damage in the testis, as demonstrated by increased lipid peroxidation and reduced antioxidative status. Due to oxidative stress, gene expression of CDC2 and cyclin B1, which code for two key proteins in cell cycle regulation, was significantly decreased. A decrease in the formation of these proteins results in an arrest of the cell cycle, which leads to apoptosis of the germ cells. In the authors' opinion, a cell cycle arrest can prevent differentiation of the germ cells into mature sperm (Kaushal and Bansal 2007). The mRNA expression and the protein formation of HSP70 were increased, that of HSP70-2 and MSJ-1 decreased.

HSP70-2 is an important constitutive gene product of specific male germ cell stages and plays an important role during the meiotic phase of spermatogenesis. The absence or a mutation of HSP70-2 can produce either an arrest in the maturation of spermatogonia or apoptosis. The chaperone MSJ-1 simultaneously responsible for the correct protein development is necessary for the activity of HSP70-2 (Kaushal and Bansal 2009). Administration of **sodium selenite** (224 µg selenium/kg diet, about 0.017 mg selenium/kg body weight and day) with the diet for 12 to 14 weeks caused hypertrophy of the testis and a significantly reduced body weight in 18 male Wistar rats compared with controls (Turan et al. 1999).

Treatment of male rats (no other details) with 0, 6 or 8 mg **sodium selenite**/kg diet (about 0, 0.2 or 0.28 mg selenium/kg body weight and day) for six or nine weeks produced a dose-dependent and time-dependent decrease in body and testis weights as well as an increase in morphologically abnormal spermatozoa. Histopathological examination of the testis and epididymides revealed a reduction in the tubular diameter and the epithelial height of the seminiferous tubules and the number of spermatogonia. The most sensitive reaction was found in the postmeiotic cells (round spermatids of increased length). The offspring of the treated animals showed retarded growth (Kaur and Kaur 2000).

A significant increase (49%) in testosterone level was found in the serum of male New Zealand rabbits after administration of **sodium selenite** (0.3 mg selenium/kg body weight and day) by gavage once per week for 6 weeks. Compared with controls, the number of spermatozoa without acrosome was not significantly increased. Sperm motility, ejaculate volume, sperm concentration and total spermatogenesis were reduced after the administration of selenium (no details given on statistical significance of these effects) (El-Zarkouny et al. 1999).

Female fertility

Female F344 rats were given drinking water containing **sodium selenite** or **sodium selenate** for 13 weeks. At a dose of 0.4 mg selenium/kg body weight and day and above in the form of sodium selenate or 0.9 mg selenium/kg body weight and day in the form of sodium selenite, the dioestrus took longer compared with controls, while prooestrus, oestrus and metoestrus were shortened (NTP 1994). In addition, after receiving **sodium selenite** with the drinking water for 13 weeks, female B6C3F1 mice were found to have an extended oestrus cycle after administration of 1.6 mg selenium/kg body weight and day. **Sodium selenate** (up to 2.6 mg selenium/kg body weight and day) had no effects on the oestrus cycle. The authors regarded these cycle changes as substance-related effects (NTP 1994).

The effects of selenium on the oestrus cycle and ovaries were investigated in rats after daily intraperitoneal injections of 2 or 4 mg **sodium selenite**/kg body weight, or additionally four times during the oestrus cycle or once during prooestrus or

oestrus for 30 days. Selenium administration before mating produced changes in the number of ovulations, implantations and live embryos depending on dose and cycle stage at treatment (Parshad 1999).

The studies on fertility are shown in Table 1.

Table 1 Effect on fertility

Species, strain, number per group	Exposure	Findings	References
mouse, CD, 5 ♂, 5 ♀ per group	**4-generation study**, 0 or 3 mg **sodium selenate**/L drinking water (about 0 or 0.1 mg selenium/kg body weight and day)	**0.1 mg Se/kg body weight and day**: adult F1, F2, F3: mating frequency ↓; adult F3: number of litters ↓ (3, control 23); offspring pups F1, F2: mortality ↑; pups F1, F2, F3: runts ↑	Schroeder and Mitchener 1971
mouse, BALB/c, 8 ♂	**male fertility**,0, 0.02, 0.2 or 1 mg **sodium selenite**/kg feed (about 0; 0.0035, 0.035 or 0.175 mg selenium/kg body weight and day), 8 weeks	**0.175 mg Se/kg body weight and day**: testis: selenium concentration ↑, superoxide dismutase activity ↑, DNA fragmentation ↑, lipid peroxidation ↑, decreased lumen size of seminiferous tubules, detachment of germ cells	Kaur and Bansal 2004 a, b, c
mouse, BALB/c, 8 ♂	**male fertility**, 0, 0.02, 0.2 or 1 mg **sodium selenite**/kg feed (about 0; 0.0035, 0.035 or 0.175 mg selenium/kg body weight and day), 8 weeks	**0.175 mg Se/kg body weight and day**: testis: selenium concentration ↑, free radicals ↑, GSH peroxidase activity ↑, oxidative stress: lipid peroxidation ↑, mRNA expression and protein formation of CDC2, cycline B1, HSP70-2, MSJ-1 ↓, HSP70 ↑, mRNA expression of apoptosis factors (Bcl-2, Bax, caspase-3, caspase-9) ↑, CDC2 kinase activity ↓, sperm motility ↓; fertility ↓, litter size ↓	Kaushal and Bansal 2007, 2009
rat, Wistar, 3 ♂, 5 ♀	**2-generation study**, 0, 1.5, 2.5 or 7.5 mg **potassium selenate**/L drinking water (about 0, 0.15, 0.25 or 0.75 mg selenium/kg body weight and day)	**0.15 mg Se/kg body weight and day**: ♀: NOAELfertility; **0.25 mg Se/kg body weight and day**: adult F1:♀: body weight development ↓; F2 pups: survival of young brought up by dams ↓; **0.75 mg Se/kg body weight and day**: ♂: NOAEL fertility;	Rosenfeld and Beath 1954

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
		adult F0: mortality ↑, ♀: body weight ↓; adult F1: ♂, ♀: body weight development ↓, ♀: sterility; F1 pups: survival of young brought up by dams ↓	
rat, no other details, 12 ♂ (6 per duration of treatment)	**male fertility**, 0, 6 or 8 mg **sodium selenite**/kg feed (0, 0.2 or 0.28 mg selenium/kg body weight and day), 6 or 9 weeks	**at 0.2 mg Se/kg and day and above**: loss of hair, red discoloration of claws (from 6 weeks), body weight ↓, weight of testis and epididymides ↓, abnormal spermatozoa ↑, diameter of seminiferous tubules in testis and epididymis ↓, epithelial thickness of seminiferous tubules ↓, number of spermatogonia ↓, F1 pups: body weight development ↓	Kaur and Kaur 2000
rat, Crl:CDBr, 10 ♂, 10 ♀ per group	**1-generation study** 0; 7.5; 15 or 30 mg **sodium selenate**/L drinking water (♂: 0, 0.4, 0.7 or 1 mg sodium selenate/kg body weight and day; about 0, 0.18, 0.30 or 0.46 mg selenium/kg body weight and day; ♀: 0, 0.5, 0.8 or 1.0 mg sodium selenate/kg body weight and day; about 0, 0.23, 0.37 or 0.46 mg selenium/kg body weight and day), 30 days	**at 0.18/0.23 mg Se/kg and day and above**: ♀: water intake ↓, food intake ↓, terminal body weight ↓, ♂: relative weight of right kidney ↑ **from 0.30 mg Se/kg and day**: ♂: food intake ↓, terminal body weight ↓, relative testis weight ↑ **0.46 mg Se/kg and day**: ♂, ♀: clinical symptoms, ♂: absolute weight of liver, *cauda epididymis*, epididymis, spleen ↓, ♀: number of *corpora lutea* ↓, implantations/litter ↓	NTP 1996
rat, Crl:CDBr, 10 ♀	**female fertility**, 0, 7.5, 15 or 30 mg **sodium selenate**/L drinking water (0, 0.5, 0.8 or 1 mg sodium selenate/kg body weight and day; 0, 0.23, 0.37 or 0.46 mg selenium/kg body weight and day), 30 days	**0.46 mg Se/kg body weight and day**: oestrus duration ↓, cycle duration ↑	NTP 1996

Table 1 (Continued)

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, ♀, no other details	**female fertility**, 0, 2 or 4 mg **sodium selenite**/kg body weight (0, 0.9 or 1.8 mg selenium/kg body weight and day), intraperitoneally, 30 days	**from 0.9 mg Se/kg body weight and day and above**: after 2 normal oestrus cycles arrest in dioestrus phase, mortality ↑, cystic follicles, no *corpora lutea* in animals without cysts	Parshad 1999
rat, Wistar, 9♀	**female fertility**, 0, 2 or 4 mg **sodium selenite/kg** body weight (0, 0.9 or 1.8 mg selenium/kg body weight) intraperitoneally,4× during the oestrus cycle, investigation on gestation day 14	**at 0.9 mg Se/kg body weight and day and above**: mortality ↑, number of *corpora lutea* ↓, implantations ↓, live embryos/litter ↓; **1.8 mg Se/kg body weight**: resorptions ↑	Parshad 1999
rat, Wistar, 9♀	**female fertility**, 0, 2 or 4 mg **sodium selenite**/kg body weight (0, 0.9 or 1.8 mg selenium/kg body weight), intraperitoneally, 1× during prooestrus or oestrus, investigation on gestation day 14	prooestrus:**1.8 mg Se/kg body weight**: number of pregnant animals ↓, implantations ↓, live embryos/litter ↓; oestrus: **at 0.9 mg Se/kg body weight and above**: number of pregnant animals ↓; **1.8 mg Se/kg body weight**: implantations ↓, live embryos/litter ↓, resorptions ↑	Parshad 1999

n.s.: not significant

Developmental toxicity

Table 2 shows the results from studies on developmental toxicity.

As already discussed in the Documentation of 1999 (see Documentation "Selenium" 1999, only available in German), the studies with **sodium selenite** and **sodium selenate** show that teratogenic and foetotoxic effects are only to be expected at maternally toxic doses. The studies with **sodium selenite** from which NOAELs of 0.5 mg selenium/kg body weight and day were derived for rats (Juszkiewicz et al. 1993) and of 3.2 mg selenium/kg body weight and day for mice (Hardin et al. 1987) are described again here:

The NOAEL of 3.2 mg selenium/kg body weight and day for developmental toxicity in mice was obtained in a screening teratogenicity test. In this study 50 pregnant CD1 mice per group were given 0, 3.5, 5, 7 or 14 mg **sodium selenite/kg** body weight and day (about 0, 1.6, 2.3, 3.2 or 6.4 mg selenium/kg body weight and day) by gavage from gestation days 6 to 13. Body weight was measured on gestation day 17. The number of live offspring and their body weights were determined 1 or 3 days after birth. Examinations for malformations were not carried out. The highest dose (6.4 mg selenium/kg body weight and day) was found to be maternally toxic (increased mortality, reduced body weight gain) and produced a reduction in the number of viable offspring with lower weights at birth and a delayed postnatal weight gain (Hardin et al. 1987).

The NOAEL for developmental toxicity in rats was obtained from a study in which 16 Wistar rats received subcutaneous injections of 0.5 mg selenium/kg body weight and day in the form of **sodium selenite** from gestation days 6 to 15. The control group of 18 rats received a single injection of the solvent on gestation day 9 (no other details). Under these conditions, selenium caused no maternal toxicity or teratogenicity (Juszkiewicz et al. 1993).

In a screening test, 13 pregnant Sprague Dawley rats were given 0, 7.5, 15 or 30 mg **sodium selenate**/L (0, 0.6, 1.0 or 1.0 mg sodium selenate/kg body weight and day; 0, 0.28, 0.46 or 0.46 mg selenium/kg body weight and day) with their drinking water from gestation day 6 up to the birth of the offspring. Dams and offspring were investigated on postnatal day 4. Due to a dose-dependent reduction in drinking water intake by the dams, the substance intake calculated for the intermediate and the high dose groups was the same. Reduced maternal body weight gain was observed in the intermediate and high dose groups. Clear developmental toxicity (increased length of gestation time, reduced number of live births, reduced weight of the offspring) occurred in the high dose group. In the lowest dose group, no effects on the offspring were found (NTP 1996). The NOAEL for developmental toxicity in this screening study, in which no investigation of the foetuses for visceral or skeletal malformations took place, is 0.28 mg selenium/kg body weight and day.

Oral administration of 12 mg **sodium selenite**/kg diet to rats (about 0 or 1.2 mg sodium selenite/kg body weight and day; about 0 or 0.56 mg selenium/kg body weight and day) during the entire gestation period caused an increased offspring mortality at birth (10.5%). Their body weight and the absolute weight of testis, ovaries, liver and kidneys at the day of birth were significantly decreased. On days 61 and 85 after birth, however, these were only slightly reduced.

In addition, the histological changes occurring in the testis at the time of birth (seminiferous tubules with reduced diameter and reduced epithelial height, reduced number of spermatogonia per tubule) were no longer found on days 61 and 85 after birth. The time of vaginal opening and oestrus in the female offspring corresponded to those of the controls (Kaur and Lakshmi 2002). Details on maternal toxicity are lacking.

Table 2 Effect of selenium and its inorganic compounds on the development of offspring

Species, strain, number per group	Exposure	Findings	References
mouse, CD-1, 50 ♀	**gestation day 6–13**, 0, 3.5, 5, 7 or 14 mg **sodium selenite**/kg body weight and day (0, 1.6, 2.3, 3.2 or 6.4 mg selenium/kg body weight and day), orally, investigation until postnatal day 3;	**up to 3.2 mg/kg body weight and day**: NOAEL; **6.4 mg/kg body weight and day**: dams: mortality ↑; offspring: number of live births/litter ↓ (10/25; control 34/38); offspring: weight at birth ↓, postnatal body weight gain retarded	Hardin et al. 1987
rat, Wistar, 14–18 ♀	**gestation day 9**, 0, 0.5, 1 or 2 mg selenium/kg body weight in the form of **sodium selenite**, subcutaneously, investigated on gestation day 21	**up to 2 mg/kg body weight**: NOAEL	Juszkiewicz et al. 1993
rat, Wistar, 16 ♀	**gestation day 6–15**, 0 or 0.5 mg selenium/kg body weight and day in the form of **sodium selenite**, subcutaneously, investigated on gestation day 21	**0.5 mg/kg body weight and day**: NOAEL	Juszkiewicz et al. 1993
rat, Sprague Dawley, 13 ♀	**gestation day 6 to birth**, 0, 7.5, 15 or 30 mg **sodium selenate**/L (0, 0.6, 1.0 or 1.0 mg sodium selenate/kg body weight and day; 0, 0.28, 0.46 or 0.46 mg selenium/kg body weight and day), postnatal investigation	**at 0.28 mg/kg body weight and day and above**: dams: water intake ↓; offspring: NOAEL;**from 0.46 mg/kg body weight and day**: dams: food intake ↓ (statistically significant on gestation day 8 and 12), body weight ↓, bright, small adrenal glands, thickened stomach walls; pup: weight at birth ↓, body weight (postnatal day 3) ↓; **0.46 mg/kg body weight and day**: dams: mortality ↑, spleen size ↑, implantation sites with nodular material, adhesions of the intestinal organs with the stomach, gestation time ↑; offspring: number of live births/litter ↓, live pups in birth ↓, body weight ↓, survival ↓	NTP 1996

Table 2 (Continued)

Species, strain, number per group	Exposure	Findings	References
rat, no other details, 6♀	**gestation day 1 to birth**, 0 or 12 mg **sodium selenite/kg** feed (about 0 or 1.2 mg sodium selenite/kg body weight and day; 0 or 0.56 mg selenium/kg body weight and day), investigation on postnatal days 1, 61 or 85	**0.56 mg/kg body weight and day**: offspring: postnatal day 1: mortality ↑, weight at birth ↓, weight of testis, ovaries, liver, kidneys ↓, seminiferous tubules: diameter, lumen and epithelial height ↓, number of spermatogonia ↓, size of Leydig cells ↓	Kaur and Lakshmi 2002

Genotoxicity

In vitro

The results from in vitro investigations on genotoxicity published since the 1999 Documentation (see Documentation "Selenium" 1999, only available in German) are given in Table 3, and confirm genotoxic effects of inorganic selenium compounds.

Bacteria and yeasts

In the Umu test with Salmonella typhimurium TA1535/pSK1002, DNA damage occurred from 100 µg **sodium selenite**/ml without addition of a metabolic activation system (Yasunaga et al. 2004).

In Saccharomyces cerevisiae, **sodium selenite** produced gene mutations from 0.1 mM without metabolic activation. In the same concentration range, **selenomethionine** had no mutagenic effects (Letavayova et al. 2008).

Mammalian cells

In the comet assay, **sodium selenite** caused no DNA damage in lymphoblastoid TK6 cells in the µM range, however, in human lymphocytes DNA damage was observed from 100 mM. **Selenious acid** caused DNA damage from 3 mM (Cemeli et al. 2003). Without metabolic activation, **sodium selenite** increased the number of chromosome aberrations in human lymphocytes from 0.2 µM (Biswas et al. 2000). No increased number of chromosome aberrations were observed in V79 cells at 0.5 µM **sodium selenite** (Bronzetti et al. 2003). In the absence of metabolic activation, **sodium selenate** produced an increase in the number of chromosome aberrations in human lymphocytes (Biswas et al. 2000).

Table 3 In vitro genotoxicity of selenium and its inorganic compounds

Endpoint	Test system	Substance	Concentration range	Effective concentration	Cyto-toxicity	Results		References
						– m. A.	+ m. A.	
Bacteria								
DNA damage, Umu test	Salmonella typhimurium TA1535/pSK1002	Na_2SeO_3	0– 600 µM	n.d.	600 µM	+	–	Yasunaga et al. 2004
	Salmonella typhimurium TA102	Na_2SeO_4	0, 3.5, 7.0, 10.5, 14, 35 or 70 µM			–	nd	Cemeli et al.2003
	Salmonella typhimurium TA102	Na_2SeO_3	0, 4, 8, 12, 16, 40 or 80 µM			–	nd	
	Salmonella typhimurium TA102	H_2SeO_3	0, 4.6, 9.2, 13.8, 18.4, 46 or 92 µM			–	nd	
Yeasts								
Gene mutation	Saccharomyces cerevisiae SRJ751	Na_2SeO_3	0, 100, 500, 1000, 5000 or 10 000 µM	100 µM	100 µM	+	nd	Letavayova et al. 2008
		Se-Met	0, 100, 500, 1000, 5000 or 10 000 µM			–	nd	
Mammalian cells								
DNA damage, comet assay	Human lymphocytes	Na_2SeO_4	0, 100 000, 300 000, 500 000 or 1 000 000 µM	at 100 000 µM and above		+	nd	Cemeli et al.2003
		Na_2SeO_3	0, 100 000, 300 000, 500 000 or 1 000 000 µM	at 100 000 µM and above		+	nd	
		H_2SeO_3	0, 3000, 6000, 9000, 12 000 or 15 000 µM	at 3000 µM and above		+	nd	

Table 3 (Continued)

Endpoint	Test system	Substance	Concentration range	Effective concentration	Cyto-toxicity	Results		References
						– m. A.	+ m. A.	
	TK6 cells	Na_2SeO_3	0, 1 or 10 µM			–	nd	
SCE	Purified human lymphocytes	Na_2SeO_3	0, 1.6, 7.9, 11.9, 15.8 or 79 µM		lethal at 79 µM	–	nd	Ray and Altenburg 1978
	Human lymphocytes in whole blood	Na_2SeO_3	0, 1.6, 7.9, 15.8 or 79 µM	at 7.9 µM and above	at 15.8 µM and above	+	nd	
		Na_2Se	0, 1.12, 1.6, 4.0, 8.0, 11.2, 16.0 or 40.0 µM	at 11.2 µM and above	n.d.	+	nd	
		SeO_2	0, 1.12, 1.6, 4.0, 8.0, 11.2, 16.0 or 40.0 µM	at 11.2 µM and above	n.d.	+	nd	
		Se	0, 1.6, 4.0, 8.0, 11.2, 16.0 or 48.0 µM	at 8.0 µM and above	n.d.	+	nd	
		Na_2SeO_4	0, 1.12, 1.6, 4.0, 8.0, 11.9, 16.0, 40.0 or 79.9 µM		n.d.	–	nd	
CA	Human lymphocytes	Na_2SeO_3	0, 0.2, 1.2, 2.9, 5.8 or 29.0 µM	at 0.2 µM and above	at 2.9 µM; lethal at 29 µM and above	+	nd	Biswas et al. 2000
		Na_2SeO_4	0, 1.1, 2.7, 5.3, 10.1 or 26.5 µM	at 1.1 µM and above	at 10.1 µM and above; lethal at 26.5 µM	+	nd	
	V79 cells	Na_2SeO_3	0, 0.5 µM		0.7 µM (determined by pretesting)	–	nd	Bronzetti et al. 2003

Table 3 (Continued)

Endpoint	Test system	Substance	Concentration range	Effective concentration	Cyto-toxicity	Results		References
						– m. A.	+ m. A.	
Micro-nucleus	Human lymphocytes in whole blood	Na_2SeO_3	0, 0.1 or 1 µM		–	–	nd	Cemeli et al. 2006
		Na_2SeO_4	0, 5 or 50 µM		–	–	nd	
		H_2SeO_3	0, 0.5 or 5 µM		5 µM	–	nd	
	TK6 cells	Na_2SeO_3	0, 1 or 10 µM	1 µM	–	+	nd	
		Na_2SeO_4	0, 10 or 100 µM	100 µM	–	+	nd	
		H_2SeO_3	0, 1 or 10 µM	1 µM	–	+	nd	
Gene mutation $TK^{+/-}$ test	Mouse lymphoma cells	SeS	– m.A.:0, 1.13, 2.25, 4.5, 6.75; 9 or 18 µM	– m.A.: 1.13 µM	– m.A.: 6, 75 µM	+	–	NTP 2009
			+ m.A.: 0, 4.5, 6.75, 9, 18, 36 or 54 µM		+ m.A.: not toxic			

m.A.: metabolic activation, nd: not done, Se-Met: selenomethionine

In human lymphocytes, **sodium selenite** at 1 μM or **sodium selenate** at 50 produced no micronuclei (Cemeli et al. 2006). After cultivation of lymphoblastoid TK6 cells in cytotoxic concentrations of **sodium selenite** (1 μM) or **sodium selenate** (100 μM), micronuclei were formed to an increased extent (Cemeli et al. 2006). **Selenious acid** produced a higher number of micronuclei in human lymphocytes and in lymphoblastoid TK6 cells at cytotoxic concentrations (Cemeli et al. 2006).

In the absence of metabolic activation, a dose-dependent and significant increase in gene mutations was found after incubation of mouse lymphoma cells with **selenium sulfide** (at 0.125 μg/ml and above). Cytotoxicity occurred at 0.75 μg/ml and above, and the selenium sulfide precipitated at 4 μg/ml and above (NTP 2009).

In vivo

Drosophila melanogaster

In the wing spot test, **sodium selenite**, **selenious acid** and **sodium selenate** did not increase somatic mutations and recombinations (Rizki et al. 2001).

Somatic cells

Since the Documentation of 1999 (see Documentation "Selenium" 1999, only available in German), no further animal studies on genotoxicity in somatic cells have been published. After two oral administrations of **selenium sulfide,** increased DNA damage from 16.2 mg selenium/kg body weight was demonstrable in the rat liver. The LD_{50} was 27 mg selenium/kg body weight (Kitchin and Brown 1994).

Single intraperitoneal injection of **sodium selenite** increased the number of sister chromatid exchanges in the bone marrow of Chinese hamsters from 3 mg selenium/kg body weight, but not in NMRI mice at 0.8 mg selenium/kg body weight (Norppa et al. 1980 a, c).

In two independent studies, **selenium sulfide** produced no increase in micronuclei in the bone marrow of B6C3F1 mice after one or three intraperitoneal injections (within 24 hours) of 2.7 to 14.2 mg selenium/kg body weight. Cytotoxicity occurred at 14.2 mg selenium/kg body weight (NTP 2009; Shelby and Witt 1995). After two intraperitoneal injections of **sodium selenite** within 24 hours (up to 10.7 mg selenium/kg body weight), no increased frequency of micronuclei in the bone marrow of mice was observed. In a parallel study, **selenious acid** in doses up to 1.5 mg selenium/kg body weight produced no increase in micronucleus frequency, though an increase in micronuclei and cytotoxicity occurred from 3.0 mg selenium/kg body weight (Itoh and Shimada 1996).

After two intramuscular injections of **sodium selenite** within 24 hours, the micronucleus frequency had increased in female BALB/c mice from the lowest dose (0.2 mg selenium/kg body weight) 24 hours after the last treatment. In an earlier study, the authors observed no induction of chromosome aberrations and no change in the mitosis index at the same dose (Rusov et al. 1996). Only contradictory data on the dose can be found in the description of this study, as the administered

substance was supposed to be selenium in one case and sodium selenite in the other. No information was given on the mitosis index or other signs of cytotoxicity, the origin and purity of the sodium selenite or individual data on the investigated mice. Due to the insufficient and contradictory study description, this publication cannot be used in assessing the genotoxic effect of selenium and its inorganic compounds.

After oral administration of **selenium sulfide** to rats a simultaneous occurrence of cytotoxicity with an increase in micronuclei was observed from 35.5 mg selenium/kg body weight in the bone marrow, but not in the spleen. In these animals, death occurred at 53.3 mg selenium/kg body weight and above (Moore et al. 1996).

After nasogastric intubation of **L-selenomethionine** for 14 or 19 days, a significant increase in the number of micronuclei in one female crab eating macaque (Macaca fascicularis) at 0.24 mg selenium/kg body weight. In another female monkey, body weight was reduced from 0.12 mg selenium/kg body weight (Choy et al. 1989). As only one animal per dose was treated, the results have no impact on the assessment and can only be regarded as indication for a genotoxic effect.

In the bone marrow of crab eating macaque foetuses, whose dams had received 0, 0.15 or 0.3 mg **L-selenomethionine**/kg body weight (0.01, 0.06 or 0.12 mg selenium/kg body weight) by nasogastric intubation from gestation days 20 to 50, no induction of micronuclei was observed on gestation day 100. Maternal and foetal toxicity were reported (no other details) from 0.06 mg selenium/kg body weight (Choy et al. 1993). After administration of **sodium selenite**, no increase in the incidence of chromosome aberrations was found in the bone marrow of mice up to 2.3 mg selenium/kg body weight (Biswas et al. 1999 b; Norppa et al. 1980 c). Chromosome aberrations in the bone marrow of mice were dose-dependently increased after oral administration of **sodium selenite** and **sodium selenate** from 3.2 and 5.9 mg selenium/kg body weight, respectively. Cytotoxicity started from 3.2 and 2.9 mg selenium/kg body weight, respectively (Biswas et al. 1997, 1999 a). At 7.1 mg selenium/kg body weight and above, intraperitoneal injections of **selenium sulfide** induced frequent chromosome aberrations in mice. Investigation was performed 36 hours after treatment (Shelby and Witt 1995).

After single intraperitoneal injection of **sodium selenite**, the incidence of chromosome aberrations was increased in the bone marrow of Chinese hamsters at doses of 3 mg selenium/kg body weight and above (Norppa et al. 1980 a).

An increase in chromosome aberrations was found in the bone marrow of rats after intravenous **sodium selenite** injection from 2.3 mg selenium/kg body weight (Newton and Lilly 1986).

In rats, single oral administration of **selenium sulfide** up to 35.5 mg selenium/kg body weight in rats caused no increase in the frequency of chromosome aberrations in bone marrow and spleen after 24, 36 or 48 hours (Moore et al. 1996). No increased frequency in chromosome aberrations up to 2.8 mg selenium/kg body

weight was found in the peripheral lymphocytes of rats after **sodium selenite** administration (Newton and Lilly 1986).

Germ cells

In spermatocytes of mice, the number of chromosome aberrations after single intraperitoneal administration of 0.8 mg selenium/kg body weight (corresponding to 1/5 the LD_{50}) was not increased by **sodium selenite**. Investigation took place after 24 hours (Norppa et al. 1980 c).

Summary

In vitro, selenium and its inorganic compounds are genotoxic. Animal studies showed positive results in the micronucleus test and in testing for chromosome aberrations at doses close to the LD_{50}. With regard to germ cell mutagenicity, a study on chromosome aberrations in spermatocytes yielded a negative result. The clastogenic potential observed in vitro does not take effect in vivo until high doses are reached. In valid studies, no genotoxic effects were observed in vivo up to 1.5 mg selenium/kg body weight (Itoh and Shimada 1996; Norppa et al. 1980 a, c).

Carcinogenicity

In humans, the reflux of gastric and duodenal content into the oesophagus is a risk factor that may result in adenocarcinomas developing in the oesophagus. In order to mimic this condition in an animal model, the duodenum was surgically connected with the oesophagus (oesophagoduodenostomy) in male Sprague Dawley rats. The animals were subsequently given **sodium selenate** with their diet (1.7 mg selenium/kg diet, about 0.13 mg selenium/kg body weight and day) for 40 weeks, as well as iron supplementation to avoid anaemia. The incidence of adenocarcinomas in the oesophagus was significantly increased by the selenium dose (90.3% compared with 67.9% in controls) and the tumour volume was also increased. In the authors' opinion, in this animal model, oxidative stress plays a decisive role in the development of adenocarcinomas in the oesophagus and is further increased by a high selenium dose (Chen et al. 2000). However, due to its unconventional design, this study cannot be used to assess the carcinogenic effect of selenium and its inorganic compounds.

Manifesto (MAK value, classification)

MAK value. Previously, as an upper safe dose for daily selenium intake, values between 300 and 500 µg were postulated, even though some authors suspected that initial adverse effects also occurred below a daily intake of 300 µg. Based on a

NOAEL of 4 µg selenium/kg body weight, a value of 400 µg/day was given as upper safe dose by the WHO/FAO (Food and Agriculture Organization of the United Nations). The values of 300 µg selenium/day cited by the SCF (Scientific Committee on Food of the EU) and of 400 µg selenium/day by the FNB (Food and Nutrition Board of the US National Academy of Sciences) were also within a similar magnitude. A dose of 15 µg selenium/kg body weight per day was derived by the US-EPA as NOAEL for the symptomatic picture of selenosis. Assuming a retention of 100%, the previous MAK value of 0.05 mg selenium/m³ I corresponds to a daily intake of about 490 µg (7 µg selenium/kg body weight and day). The prolongation of the prothrombin time observed above a daily intake of 12 µg/kg body weight (850 µg) (Yang et al. 1989) occurring in volunteers from areas with high selenium concentrations in soil and vegetation was used as the critical toxic effect for derivation of this value (see Documentation "Selenium" 1999, not available in English). Due to the fact that, as a number of more recent epidemiological studies indicate at relatively high initial plasma levels of >121.6 µg selenium/L, the additional intake of 200 µg selenium per day poses a probably slight, though not negligible, risk of diabetes mellitus, a chronic selenium exposure at the level of the present MAK value is therefore no longer acceptable. According to the study by Stranges et al. (2007), daily supplementation with 200 µg selenium leads to an increase in the plasma selenium concentration by about 75 µg selenium/L (corresponding to an increase in the selenium level by about 67%). With a mean selenium level of 75 µg selenium/L in the general population of Germany, an increase of 75 µg selenium/L results in a selenium concentration within the range of the selenium level (up to 147 µg selenium/L) at which, according to the study of Laclaustra et al. (2009) no increased prevalence of diabetes occurred. The MAK value for selenium and its inorganic compounds is therefore provisionally reduced to 0.02 mg selenium/m³ I. As a result, the additional selenium intake at the workplace is limited to about 200 µg selenium/day. For hydrogen selenide, the MAK value is correspondingly reduced to 0.006 ml/m³ ≙ 0.020 mg selenium/m³. As Peak Limitation for selenium and its inorganic compounds, Category II has been retained and the excursion factor increased to 8. On account of its systemic effects, hydrogen selenide has also been assigned to Peak Limitation Category II, and the excursion factor increased to 8 in view of the low MAK value. No irritant effect is to be expected under this classification.

Carcinogenicity. In 1999, selenium and its inorganic compounds were classified into Carcinogen Category 3B. The main reason for this classification were the studies on **selenium sulfide** , which found a weak clastogenic activity in vivo and, at high doses, hepatocellular carcinomas in rats and mice and bronchioalveolar adenomas and carcinomas in female mice. The classification is additionally based on the data for **sodium selenate**, which is weakly genotoxic in vivo, and for which indications of a weakly carcinogenic potential have been found in a study in rats with limited usefulness. Since selenium and all other inorganic selenium compounds have effects similar to sodium selenate and selenium sulfide, and as sodium

selenate is reductively metabolized, it can be assumed that these compounds and selenium itself also have a carcinogenic potential. Studies on genotoxicity revealed a clastogenic potential for inorganic selenium compounds at high doses. Since no more recent valid studies on carcinogenicity are available, classification in Carcinogen Category 3B has been retained.

Germ cell mutagenicity. A study on chromosome aberrations in spermatocytes yielded negative results. Since no further studies on germ cell mutagenic effects are available, selenium and its inorganic compounds have not been classified in any of the categories for germ cell mutagens.

Prenatal toxicity. In 1999, selenium and its inorganic compounds were classified in Pregnancy Risk Group C, as embryotoxic effects were found at maternally toxic doses only and the NOAELs obtained with rats and mice (rats: 0.5 mg selenium/kg body weight and day; mice: 3.2 mg selenium/kg body weight and day) were far above the amount of selenium absorbed when the MAK value of 0.05 mg/m^3 I valid at that time was observed. Based on a screening study (NTP 1996), the NOAEL for developmental toxicity in the rat is now 0.28 mg selenium/kg body weight and day. The LOAEL based on slightly reduced body weights in the offspring at maternal toxicity was 0.46 mg selenium/kg body weight and day. Beginning with a NOAEL of 0.28 mg selenium/kg body weight and day after oral administration, and taking into account the species-specific compensation value between rats and humans of 1:4 (in regard to toxicokinetic differences) and additionally assuming oral absorption of 100% in rats, one arrives at a calculated NOAEC at the workplace of 0.49 mg selenium/m^3 for a human weighing 70 kg with a respiratory volume of 10 m^3 in an eight-hour work-shift and assuming 100% absorption. Since the difference to the reduced MAK value at the level of 0.02 mg selenium/m^3 is sufficiently large, selenium and its inorganic compounds remain assigned to Pregnancy Risk Group C.

Absorption through the skin. The available case reports and one animal study show that inorganic selenium compounds can induce systemic effects after skin contact. In addition, the quantities estimated from model calculations that penetrate the skin after contact with selenium or selenious acid are clearly higher than the quantities which can be absorbed through inhalation when the MAK value is observed. Selenium and its inorganic compounds, with the exception of hydrogen selenide, are therefore designated with an "H". In the case of hydrogen selenide, it is possible to calculate from the Henry's law constant (0.00974; SRC 2010) that the water solubility of gaseous hydrogen selenide is 5×10^{-8} g/L when the MAK value is observed. Using the formula of Fiserova-Bergerova et al. (1990) and a calculated log K_{OW} of 0.24 (SRC 2010) an absorption of 3.8×10^{-5} mg selenium can be estimated for an eight-hour exposure of a body surface area of 1.7 m^2. Compared with an absorption of 0.2 mg selenium after inhalation, the contribution of skin absorption is negligible. Hydrogen selenide is therefore not designated with an "H".

Sensitization. Two casuistic reports for a possible contact allergenic effect of inorganic selenium compounds are available. Their findings, however, are not sufficient to indicate a sensitizing effect, as they permit no differentiation from nonspecific or toxic effects. No animal studies are available. Also no studies have been published on immunological effects on the airways. Thus, in spite of a suspected contact allergenic effect, selenium and its inorganic compounds are not designated with "Sa" or "Sh".

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