



Review

Revised reference values for selenium intake



A.P. Kipp^a, D. Strohm^{b,*}, R. Brigelius-Flohé^a, L. Schomburg^c, A. Bechthold^b,
E. Leschik-Bonnet^b, H. Hesecker^d, German Nutrition Society (DGE)

^a German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114-116, D-14558 Nuthetal, Germany

^b German Nutrition Society (DGE), Godesberger Allee 18, D-53175 Bonn, Germany

^c Institute for Experimental Endocrinology, Charité Medical School Berlin, CVK, Suedring 10, D-13353 Berlin, Germany

^d Department of Sports and Health, University of Paderborn, D-33095 Paderborn, Germany

ARTICLE INFO

Article history:

Received 16 April 2015

Received in revised form 7 July 2015

Accepted 8 July 2015

Keywords:

Selenium

Nutrient intake

Dietary reference value

Human nutrition

ABSTRACT

The German, Austrian and Swiss nutrition societies are the joint editors of the 'reference values for nutrient intake'. They have revised the reference values for the intake of selenium and published them in February 2015. The saturation of selenoprotein P (SePP) in plasma is used as a criterion for the derivation of reference values for selenium intake in adults. For persons from selenium-deficient regions (China) SePP saturation was achieved with a daily intake of 49 µg of selenium. When using the reference body weights the D-A-CH reference values are based upon, the resulting estimated value for selenium intake is 70 µg/day for men and 60 µg/day for women. The estimated value for selenium intake for children and adolescents is extrapolated using the estimated value for adults in relation to body weight. For infants aged 0 to under 4 months the estimated value of 10 µg/day was derived from the basis of selenium intake via breast milk. For infants aged 4 to under 12 months this estimated value was used and taking into account the differences regarding body weight an estimated value of 15 µg/day was derived. For lactating women compared to non-lactating women a higher reference value of 75 µg/day is indicated due to the release of selenium with breast milk. The additional selenium requirement for pregnant women is negligible, so that no increased reference value is indicated.

© 2015 The Authors. Published by Elsevier GmbH. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Contents

1. Introduction	196
2. Criteria for the assessment of selenium supply	196
3. Derivation of the reference values for selenium intake	196
3.1. Adults	196
3.2. Children and adolescents	196
3.3. Infants	196
3.4. Pregnancy	197
3.5. Lactation	197
4. Ensuring a sufficient selenium supply	197
5. Preventive aspects	197
6. Conclusion	198
Conflict of interest	198
Acknowledgement	198
References	198

* Corresponding author at: Department of Science, German Nutrition Society
Godesberger Allee 18, D-53175 Bonn, Germany.
E-mail address: strohm@dge.de (D. Strohm).

1. Introduction

The D-A-CH 'reference values for nutrient intake' [1] are jointly issued by the nutrition societies of Germany, Austria and Switzerland [the abbreviation D-A-CH arises from the initial letters of the common country identification for the countries Germany (D), Austria (A) and Switzerland (CH)]. Currently, the 'reference values for nutrient intake' are being revised. Following vitamin D [2], calcium [3] and folate [4] the revised reference values for selenium were published in February 2015.

Selenium is an essential trace element present in a multitude of compounds. It is incorporated into proteins as selenocysteine. It is via these selenoproteins that selenium mainly has its effect. In the human genome, 25 genes for selenoproteins have been identified [5]. Among enzymatically active selenoproteins, selenocysteine is a central component of the active centre and directly involved in redox reactions. Glutathione peroxidases (GPx), thioredoxin reductases and deiodinases are among the group of well-characterised selenoproteins. The five human selenium containing GPx catalyse the reduction of hydroperoxides [6]. Selenoprotein P (SePP) is essential for the distribution and transportation of selenium, in particular to the brain and to the testicles [7].

2. Criteria for the assessment of selenium supply

The following parameters are used as biomarkers for selenium supply: the concentration of selenium in plasma or serum, the GPx activity in plasma (GPx3), in erythrocytes (GPx1), in thrombocytes (GPx1) or in whole blood (GPx3 and GPx1) and the concentration of SePP in plasma or serum. In principle the measurement of selenoproteins reflects the functional selenium pool bound to selenoproteins, whilst the total selenium content also includes selenomethionine that is unspecifically incorporated in proteins. Given maximum synthesis of selenoprotein, SePP and GPx3 together constitute a concentration of 80 µg to 90 µg of selenium/l of plasma [8].

Most reference values are based on the measurement of GPx activity in plasma. Meanwhile however, SePP concentration in plasma is deemed to be the most conclusive marker for determining the optimum supply of selenium [9–12]. The SePP concentration does not indicate a maximum level until a plasma selenium concentration of 100 µg/l to 120 µg/l is reached whilst GPx activity in plasma reaches its optimum at a lower level of approximately 90 µg/l [13,14]. In addition, nowadays there are improved analysis methods that allow determination of SePP. Based on human intervention studies, it is assumed that any further increase in the supply of selenium above and beyond a plasma selenium concentration of 120 µg/l will not lead to any further increase in selenoprotein expression [15]. However, in humans the data is limited to those selenoproteins ascertainable in blood, because tissue samples of bigger cohorts of healthy subjects are unavailable.

3. Derivation of the reference values for selenium intake

3.1. Adults

The basis for the derivation of reference values for selenium intake in adults is a study published in 2010, in which an adequate intake of selenium was established by means of the saturation of SePP in plasma [14]. In persons from selenium-deficient regions (China) with an average body weight of 58 kg SePP saturation was achieved with a daily intake of 49 µg of selenium [14]. This corresponds to a daily intake of approximately 1 µg of selenium per kg of body weight. Using the reference body weights the D-A-CH reference values are based upon (70.7 kg for men and 60.0 kg for

Table 1
Estimated values for adequate selenium intake.

Age	Selenium [µg/day]		
	m	f	
Infants			
0 to under 4 months		10	
4 to under 12 months		15	
Children and adolescents			
1 to under 4 years		15	
4 to under 7 years		20	
7 to under 10 years		30	
10 to under 13 years		45	
13 to under 15 years		60	
15 to under 19 years	70		60
Adults			
19 to under 25 years	70		60
25 to under 51 years	70		60
51 to under 65 years	70		60
65 years and older	70		60
Pregnant women			60
Lactating women			75

women [1]¹), the resulting estimated values for selenium intake are 70 µg/day for men and 60 µg/day for women (see Table 1). Notably, these reference values are calculated for normal-weight adults.

3.2. Children and adolescents

No data is available regarding the selenium requirement for children and adolescents. Therefore, the reference values for children and adolescents are based on the values compiled for adults and are calculated taking into account differences in body weight and including varying growth factors to take into account requirements for growth (see Table 2). Growth factors were calculated as the proportional increase in protein requirement for growth relative to the maintenance requirement according to WHO [17] at the different ages [1]. When using the age groups and reference body weights the D-A-CH reference values are based upon [1], the resulting estimated values for selenium intake are: for 1 to under 4 year-olds 15 µg/day, for 4 to under 7 year-olds 20 µg/day, for 7 to under 10 year-olds 30 µg/day, for 10 to under 13 year-olds 45 µg/day and for 13 to under 15 year-olds 60 µg/day. For 15 to under 19 year-old boys, the resulting estimated value for selenium intake is 70 µg/day and for girls of the same age, 60 µg/day (see Table 1).

3.3. Infants

The derivation of reference values for selenium intake in infants aged 0 to under 4 months is based on the selenium content of breast milk, which is considered to be the optimal diet for infants [19,20]. Deficiency diseases occurred in China where the selenium content of breast milk was below 0.3 µg/100 ml [21]. In Germany the selenium content of breast milk is approximately 1.5 µg/100 ml [22–24]. Selenium content levels measured in colostrum are twice as high as in mature breast milk [24,25]. Given an average breast milk intake of 750 ml/day [26] a selenium intake of approximately 11 µg/day results. The estimated value for adequate selenium intake for breast-fed infants aged 0 to under 4 months is indicated as 10 µg (see Table 1).

¹ The reference measurements for height correspond to the median of the height measurements from the German Health Interview and Examination Survey for Adults (DEGS1) [16]. Body weight was calculated using the height measurements based on an assumed BMI of 22 kg/m².

Table 2

Calculation of the estimated values for selenium intake for children and adolescents taking differences in average body weight and growth factors into account.

Age [years]	Gender	Reference body weight [kg] ^a [1]	Growth factor ^b [1]	Selenium intake taking reference body weights into account [$\mu\text{g}/\text{day}$] ^c	Estimated value for selenium intake (rounded) [$\mu\text{g}/\text{day}$]
1 to under 4	male	13.9	0.25	17.2	15
	female	13.2	0.25	16.5	
4 to under 7	male	20.2	0.06	21.2	20
	female	20.1	0.06	21.3	
7 to under 10	male	29.3	0.13	32.8	30
	female	28.7	0.13	32.5	
10 to under 13	male	41.0	0.13	45.9	45
	female	42.1	0.11	46.8	
13 to under 15	male	55.5	0.10	60.4	60
	female	54.0	0.07	57.7	
15 to under 19	male	69.2	0.07	73.2	70
	female	59.5	0.02	60.9	

^a The reference measurements each correspond to the 50th percentile of the anthropometrical measurements used in the German Health Interview and Examination Survey for Children and Adolescents in Germany (KiGGS; 2003–2006) [18]. In each case the values stated are for the mid-point of the respective age range.

^b Growth factors were calculated as the proportional increase in protein requirement for growth relative to the maintenance requirement according to WHO [17] at the different ages [1].

^c Calculated from: estimated value_{adults} \times (reference body weight_{children/adolescents}/reference body weight_{adults}) \times (1 + growth factor).

Estimated value_{adults}: men 70 μg , women 60 μg (see Table 1). Reference body weight_{adults}: age group 25 to under 51 years: men 70.7 kg, women 60.0 kg [1].

Along with the introduction of solid foods the consumption of breast milk declines. Since no data is available from Germany with regard to selenium intake via solid foods, the estimated value for infants aged 0 to under 4 months is used to derive the reference value for infants over 4 months of age (see Table 3). Taking into account the differences regarding average body weight an estimated value of 15 $\mu\text{g}/\text{day}$ for infants aged 4 to under 12 months was derived (see Tables 1 and 3).

3.4. Pregnancy

During pregnancy there is a slightly increased requirement for pregnant women to cover the selenium requirement of the fetus. On average this amounts to 2 $\mu\text{g}/\text{day}$ [28–30]. Since the additional requirement however is negligible, an estimated value for selenium intake during pregnancy of 60 $\mu\text{g}/\text{day}$ is indicated (see Table 1).

3.5. Lactation

The selenium requirement in women is increased during lactation due to the amount of selenium that is secreted with breast milk while feeding the infant. Approximately 11 μg of selenium/day is secreted with breast milk (cf. derivation for infants). Taking a bioavailability of 70% [12] into account, an additional 16 $\mu\text{g}/\text{day}$ is required during lactation. The estimated value for selenium intake for lactating women amounts to 75 $\mu\text{g}/\text{day}$ (see Table 1).

4. Ensuring a sufficient selenium supply

Ensuring a sufficient supply of selenium is possible via a balanced wholesome diet. Cruciferous vegetables (such as broccoli and

white cabbage) and bulb vegetables (such as garlic and onions) as well as mushrooms, asparagus and legumes such as lentils all may have a high selenium content, depending on the quality of the agricultural soil on which they were grown. In particular, vegetable foods produced in Germany have a relatively low selenium content since the soil is low in selenium. In Germany, therefore, foods of animal origin such as meat and eggs as well as fish are a more reliable source of selenium. In vegetarian diets particular attention should be paid to include selenium-rich nuts (such as Brazil nuts) and mushrooms [31].

5. Preventive aspects

In the following, the current available data on selenium in association with some health-related aspects is briefly described by citing recent studies including systematic reviews and meta-analysis, but without performing an evidence judgment based on a systematic literature research. Dietary reference values are aimed for healthy individuals, thus requirements of patients are not being addressed.

In epidemiological studies it has been possible to observe an inverse association between serum selenium concentration and mortality risk [32,33]. In an evaluation of the NHANES study, this inverse association was found only to exist in subjects with serum selenium concentrations of up to 130 $\mu\text{g}/\text{l}$ whereas for serum concentrations of selenium of over 150 $\mu\text{g}/\text{l}$ a slight increase in mortality risk was observed [34].

It is being discussed whether selenium may reduce the risk of cancer, especially bowel, lung and prostate cancer. This is indicated by an intervention study with 1312 participants from the USA (NPC study) with a history of non-melanoma skin cancer (NMSC)

Table 3

Calculation of the estimated value for selenium intake for infants aged 4 to under 12 months.

Age [in months]	Gender	Reference body weight [kg] ^a [1]	Selenium intake taking reference body weights into account [$\mu\text{g}/\text{day}$] ^b	Estimated value for selenium intake (rounded) [$\mu\text{g}/\text{day}$]
4 to under 12	male	8.6	15.4	15
	female	7.9	15.5	

^a The reference measurements correspond to the 50th percentile of the WHO child growth standards [27] for the age of 8 months.

^b Calculated from: estimated value_{0–4months} \times (reference body weight_{4–12months}/reference body weight_{0–4months}).

Estimated value 0–4 months: 10 μg (see Table 1). Reference body weight 0–4 months: male 5.6 kg; female 5.1 kg [1].

[35]. Even though the primary endpoint (recurrence of NMSC) was unaffected, a supplement of 200 µg of selenium-enriched yeast reduced total cancer mortality and total cancer incidence. The clearest effects were seen amongst those participants who had the lowest basal plasma selenium concentration at a level of <106 µg/l [36]. Another large-scale intervention study (SELECT) revealed that a supplement of 200 µg selenomethionine per day in men with a basal plasma selenium concentration of >120 µg/l had no cancer preventive effects [37]. This was observed for the primary endpoint prostate cancer but also for secondary endpoints like lung, colorectal, and overall primary cancer. Based on that, the study was already stopped after 5.5 years instead of running for 7 years. A Cochrane Review of prospective cohort studies and randomised controlled intervention studies described a significant inverse association between selenium supply and cancer risk for the prospective cohort studies [38]. The significant association could not be observed consistently when analysing the controlled intervention studies [38]. This is not surprising since this analysis failed to take into account the selenium supply of the participants at the beginning of the studies. In a cohort study published after the Cochrane Review an inverse association between selenium supply and the risk of bowel cancer was observed [39].

An inverse relationship between selenium supply and the risk of cardiovascular diseases has been assumed since the 1970s and is mostly based on observational studies. It has not been possible to consistently confirm the inverse relationship in intervention studies [15]. Current systematic reviews also demonstrate that there is no consistent correlation between selenium supplementation and the prevention of cardiovascular diseases [40,41].

There are conflicting results regarding the relationship between selenium supply and the risk of type 2 diabetes mellitus [15]. In the SELECT study supplementation with 200 µg of selenium/day had no significant effect on the risk [37]. In the aforementioned NPC intervention study with 1312 participants and comparable selenium supplementation [35] the risk was significantly increased by selenium supplementation amongst those participants who already had plasma selenium concentrations of >120 µg/l at the beginning of the study [42]. The risk of developing type 2 diabetes mellitus was not the primary outcome in either of the studies.

Furthermore, anti-inflammatory, antirheumatic and antiviral effects of selenium are under discussion [15]. In addition a positive association between selenium supply and bone density was observed in one cohort study [43]. Some clinical studies have demonstrated that selenium-deficient patients with autoimmune thyroid disease benefit from selenium supplementation, although the data are conflicting and many parameters must still be defined [44].

6. Conclusion

SePP concentration in plasma is deemed to be the most conclusive marker for determining the optimum supply of selenium. Taking reference body weights for adults living in Germany into account SePP saturation can be achieved with a daily selenium intake of 60 µg for women and 70 µg for men. European data [12] shows that Europeans and certainly many inhabitants of areas with similarly low soil selenium concentrations are sub-optimally supplied with selenium and therefore selenium intake should be increased. The integration of selenium-rich food items into a balanced wholesome diet constitutes a meaningful measure to avoid an insufficient supply and deficiency. Supplemental intake beyond the amounts needed for the full expression of selenoproteins is potentially increasing health risks and is therefore not recommended.

Conflict of interest

None declared.

Acknowledgement

The authors thank Professor Dr. Gabriele I. Stangl for the valuable suggestions and the contribution to the preparation of the revised reference values for selenium intake.

A.P. Kipp received a honorarium from the German Nutrition Society (DGE) for developing the first draft of the dietary reference values for selenium intake.

References

- [1] Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährung, editors. Referenzwerte für die Nährstoffzufuhr, 2nd ed. Bonn: 2015.
- [2] German Nutrition Society, New reference values for vitamin D, *Ann. Nutr. Metab.* 60 (2012) 241–246.
- [3] German Nutrition Society, New reference values for calcium, *Ann. Nutr. Metab.* 63 (2013) 186–192.
- [4] M.B. Krawinkel, D. Strohm, A. Weissenborn, B. Watzl, M. Eichholzer, K. Bärlocher, et al., Revised D-A-CH intake recommendations for folate: how much is needed, *Eur. J. Clin. Nutr.* 68 (2014) 719–723.
- [5] G.V. Kryukov, S. Castellano, S.V. Novoselov, A.V. Lobanov, O. Zehtab, R. Guigó, et al., Characterization of mammalian selenoproteomes, *Science* 300 (2003) 1439–1443.
- [6] R. Brigelius-Flohé, M. Maiorino, F. Ursino, L. Flohé, Selenium: an antioxidant? in: E. Cadenas, L. Packer (Eds.), *Handbook of Antioxidants*, 2nd rev. ed., Marcel Dekker, New York, 2001, pp. 633–664.
- [7] K.E. Hill, J. Zhou, W.J. McMahan, A.K. Motley, J.F. Atkins, R.F. Gesteland, R.F. Burk, Deletion of selenoprotein P alters distribution of selenium in the mouse, *J. Biol. Chem.* 278 (2003) 13640–13646.
- [8] R.F. Burk, K.E. Hill, A.K. Motley, Plasma selenium in specific and non-specific forms, *Biofactors* 14 (2001) 107–114.
- [9] R. Hurst, R. Collings, L.J. Harvey, M. King, L. Hooper, J. Bouwman, M. Gurinovic, et al., EURRECA-estimating selenium requirements for deriving dietary reference values, *Crit. Rev. Food Sci. Nutr.* 53 (2013) 1077–1096.
- [10] K. Ashton, L. Hooper, L.J. Harvey, R. Hurst, A. Casgrain, S.J. Fairweather-Tait, Methods of assessment of selenium status in humans: a systematic review, *Am. J. Clin. Nutr.* 89 (Suppl) (2009) 2025S–2039S.
- [11] Nordic Council of Ministers, editors: *Nordic Nutrition Recommendations 2012*, 5. ed. Nordic Council of Ministers, Copenhagen, 2014.
- [12] EFSA (European Food Safety Authority), *Scientific opinion on dietary reference values for selenium*, *EFSA J.* 12 (2014) 3846.
- [13] Y. Xia, K.E. Hill, D.W. Byrne, J. Xu, R.F. Burk, Effectiveness of selenium supplements in a low-selenium area of China, *Am. J. Clin. Nutr.* 81 (2005) 829–834.
- [14] Y. Xia, K.E. Hill, P. Li, J. Xu, D. Zhou, A.K. Motley, et al., Optimization of selenoprotein P and other plasma selenium biomarkers for the assessment of the selenium nutritional requirement: a placebo-controlled, double-blind study of selenomethionine supplementation in selenium-deficient Chinese subjects, *Am. J. Clin. Nutr.* 92 (2010) 525–531.
- [15] M.P. Rayman, Selenium and human health, *Lancet* 379 (2012) 1256–1268.
- [16] G.B.M. Mensink, A. Schienkiewitz, M. Haftenberger, T. Lampert, T. Ziese, C. Scheidt-Nave, Übergewicht und Adipositas in Deutschland, *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 56 (2013) 786–794.
- [17] WHO (World Health Organization), *Protein and amino acid requirements in human nutrition: Report of a joint WHO/FAO/UNU expert consultation*, vol 935, Genf: World Health Organization, 2007.
- [18] RKI (Robert Koch-Institut), *Referenzperzentile für anthropometrische Maßzahlen und Blutdruck aus der Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (KiGGS) 2003–2006*, Gesundheitsberichterstattung des Bundes, Berlin, 2011.
- [19] C. Bührer, O. Genzel-Boroviczény, F. Jochum, T. Kauth, M. Kersting, B. Koletzko, et al., Ernährung gesunder Säuglinge, *Monatsschr. Kinderheilkd.* 162 (2014) 527–538.
- [20] Butte NF, Lopez-Alarcon MG, Garza C, Nutrient adequacy of exclusive breastfeeding for the term infant during the first six months of life, WHO (World Health Organization), 2002, www.who.int/nutrition/publications/infantfeeding/nut_adequacy_of_exc_bfeeding_eng.pdf (accessed 25.06.13).
- [21] RKI (Robert Koch-Institut), *Selen in der Umweltmedizin*, *Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz* 49 (2006) 88–101.
- [22] A. Loui, A. Raab, P. Braetter, M. Obladen, V.N. de Braetter, Selenium status in term and preterm infants during the first months of life, *Eur. J. Clin. Nutr.* 62 (2008) 349–355.
- [23] F. Jochum, A. Fuchs, H. Menzel, I. Lombeck, Selenium in German infants fed breast milk or different formulas, *Acta Paediatr.* 84 (1995) 859–862.

- [24] J. Höflich, Die Bedeutung von Selen in der vegetarischen Ernährung und in der Muttermilch, in: Dissertation zur Erlangung des akademischen Grades Doctor medicinae, Berlin, 2010.
- [25] W. Wasowicz, J. Gromadzinska, K. Szram, K. Rydzynski, J. Cieslak, Z. Pietrzak, Selenium, zinc, and copper concentrations in the blood and milk of lactating women, *Biol. Trace Elem. Res.* 79 (2001) 221–233.
- [26] M.C. Neville, R. Keller, J. Seacat, V. Lutes, M. Neifert, C. Casey, et al., Studies in human lactation: milk volumes in lactating women during the onset of lactation and full lactation, *Am. J. Clin. Nutr.* 48 (1988) 1375–1386.
- [27] WHO (World Health Organization) (Ed.), WHO Child Growth Standards – Length/height-for-age, Weight-for-age, Weight-for-length, Weight-for-height and Body Mass Index-for Age, World Health Organization, Geneva, 2006.
- [28] C.E. Casey, B.E. Guthrie, G.M. Friend, M.F. Robinson, Selenium in human tissues from New Zealand, *Arch. Environ. Health* 37 (1982) 133–135.
- [29] O. Oster, G. Schmiedel, W. Prellwitz, The organ distribution of selenium in German adults, *Biol. Trace Elem. Res.* 15 (1988) 23–45.
- [30] B.A. Zachara, H. Pawluk, E. Bloch-Boguslawska, K.M. Sliwka, J. Korenkiewicz, Z. Skok, et al., Tissue level, distribution, and total body selenium content in healthy and diseased humans in Poland, *Arch. Environ. Health* 56 (2001) 461–466.
- [31] M. Anke, C. Drobner, B. Röhrig, U. Schäfer, R. Müller, Der Selenbestand der Flora und der Selengehalt pflanzlicher und tierischer Lebensmittel Deutschlands, *Ernährungsforschung* 47 (2002) 67–79.
- [32] N.T. Akbaraly, J. Arnaud, I. Hininger-Favier, V. Gourlet, A. Rousset, C. Berr, Selenium and mortality in the elderly: results from the EVA study, *Clin. Chem.* 51 (2005) 2117–2123.
- [33] A.L. Ray, R.D. Semba, J. Walston, L. Ferrucci, A.R. Cappola, M.O. Ricks, et al., Low serum selenium and total carotenoids predict mortality among older women living in the community: the women's health and aging studies, *J. Nutr.* 136 (2006) 172–176.
- [34] J. Bleyss, A. Navas-Acien, E. Guallar, Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults, *Arch. Intern. Med.* 168 (2008) 404–410.
- [35] L.C. Clark, G.F. Combs, B.W. Turnbull, E.H. Slate, D.K. Chalker, J. Chow, et al., Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional prevention of cancer study group, *JAMA* 276 (1996) 1957–1963.
- [36] A.J. Duffield-Lillico, B.L. Dalkin, M.E. Reid, B.W. Turnbull, E.H. Slate, E.T. Jacobs, et al., Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the nutritional prevention of cancer trial, *BJU Int.* 91 (2003) 608–612.
- [37] S.M. Lippman, E.A. Klein, P.J. Goodman, M.S. Lucia, I.M. Thompson, L.G. Ford, et al., Effect of selenium and vitamin E on risk of prostate cancer and other cancers the selenium and vitamin E cancer prevention trial (SELECT), *JAMA* 301 (2009) 39–51.
- [38] M. Vinceti, G. Dennert, C.M. Crespi, M. Zwahlen, M. Brinkman, M.P. Zeegers, et al., Selenium for preventing cancer, *Cochrane Database Syst. Rev.* 3 (2014) CD005195.
- [39] D.J. Hughes, V. Fedirko, M. Jenab, L. Schomburg, C. Méplan, H. Freisling, et al., Selenium status is associated with colorectal cancer risk in the European prospective investigation of cancer and nutrition cohort, *Int. J. Cancer* 136 (2014) 1149–1161.
- [40] K. Rees, L. Hartley, C. Day, N. Flowers, A. Clarke, S. Stranges, Selenium supplementation for the primary prevention of cardiovascular disease, *Cochrane Database Syst. Rev.* 1 (2013) CD009671.
- [41] SACN (Scientific Advisory Committee on Nutrition), SACN Position statement on selenium and health, London, 2013.
- [42] S. Stranges, J.R. Marshall, R. Natarajan, R.P. Donahue, M. Trevisan, G.F. Combs, et al., Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial, *Ann. Intern. Med.* 147 (2007) 217–223.
- [43] A. Hoeg, A. Gogakos, E. Murphy, S. Mueller, J. Köhrle, D.M. Reid, et al., Bone turnover and bone mineral density are independently related to selenium status in healthy euthyroid postmenopausal women, *J. Clin. Endocrinol. Metab.* 97 (2012) 4061–4070.
- [44] L. Schomburg, Selenium, selenoproteins and the thyroid gland: interactions in health and disease, *Nat. Rev. Endocrinol.* 8 (2012) 160–171.