Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ
(PHARMACY & PHARMACOLOGY)

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2025-13-1-45-55

Rationing of iodine content in kelp layers and products based on them. Changing approaches within the framework of a risk-based strategy in drug quality control

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Received 19 May 2023 After peer review 28 Dec 2024 Accepted 11 March 2025

The State Pharmacopoeia of the Russian Federation regulates the lower level of iodine content in Laminaria thalli. However, an excess of iodine is as harmful to the human body as its deficiency.

The aim. To determine the range of permissible iodine content in the medicinal plant raw material “Laminaria thalli” and products based on it within the framework of a risk-oriented strategy in medicine quality control.

Materials and methods. Samples of medicinal herbal preparations, biologically active additives, food products based on Laminaria thalli of various origins, samples of algae collected by the authors on the coast of the White Sea and the Pacific Ocean, as well as literature data on the iodine content in pharmacopoeial species were studied. The iodine content was determined by inductively coupled plasma mass spectrometry after extraction according to GOST EN 15111-2015. The non-carcinogenic risk was calculated in accordance with Guidance R 2.1.10.1920-04.

Results. The average (0.14%) and maximum (0.46%) iodine content in pharmacopoeial species of Laminaria thalli was determined, which correlates with the iodine content norm in Laminaria algae proposed by the U.S. Food and Drug Administration (FDA) — 0.1–0.5%. It was found that at the maximum therapeutic dose and course of treatment with laxative herbal preparations, containing 0.5% of iodine, the level of non-carcinogenic risk falls into the category of maximum permissible. Under similar conditions, treatment, for example, of mastopathy with preparations based on Laminaria thalli with 0.5% of iodine leads to an unacceptable impact of iodine on human health.

Conclusion. The authors recommend, instead of the existing norm of iodine content (not less than 0.1%), to take into account the permissible amount of this element (0.1–0.5%), which corresponds to its real content in pharmacopoeial species of Laminaria thalli.

Keywords: iodine; Laminaria thalli; hazard quotient; risk-oriented strategy; hyperthyroidism; quantitative content

Abbreviations: BAA — biologically active additive; FDA — U.S. Food and Drug Administration; CVD — cardiovascular diseases; MHP — medicinal herbal preparation; MPR — medicinal plant raw material; EPh — European Pharmacopoeia; FCC — Food Chemicals Codex; TMAH — tetramethylammonium hydroxide; HQ — hazard quotient.

Для цитирования: В.М. Щукин, Н.Е. Кузьмина, Е.А. Хорольская, Н.Д. Бунятян. Нормирование содержания йода в слоевищах ламинарии и продуктах на их основе: изменение подходов в рамках риск-ориентированной стратегии в контроле качества лекарственных средств. *Фармация и фармакология.* 2025;13(1):44-55. **DOI:** 10.19163/2307-9266-2025-13-1-44-55

For citation: V.M. Shchukin, N.E. Kuzmina, E.A. Khorolskaya, N.D. Bunyatyan. Rationing of iodine content in kelp layers and products based on them. Changing approaches within the framework of a risk-based strategy in drug quality control. *Pharmacy & Pharmacology.* 2025;13(1):44-55. **DOI:** 10.19163/2307-9266-2025-13-1-44-55

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

Нормирование содержания йода в слоевищах ламинарии и продуктах на их основе: изменение подходов в рамках риск-ориентированной стратегии в контроле качества лекарственных средств

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Получена 19.05.2023 После рецензирования 28.12.2024 Принята к печати 11.03.2025

В государственной фармакопее Российской Федерации нормируется нижний уровень содержания йода в слоевищах ламинарии. Однако переизбыток йода так же вреден для организма человека, как и его дефицит.

Цель. Определить диапазон допустимого содержания йода в лекарственном растительном сырье «Ламинарии слоевища» и продуктах на его основе в рамках риск-ориентированной стратегии в контроле качества лекарственных средств.

Материалы и методы. Были исследованы образцы лекарственных растительных препаратов, биологически активных добавок, пищевой продукции на основе слоевищ ламинарии различного происхождения, образцы водорослей, собранные авторами на побережье Белого моря и Тихого океана, а также литературные данные о содержании йода в фармакопейных видах. Содержание йода определяли методом масс-спектрометрии с индуктивно-связанной плазмой после экстракции по ГОСТ EN 15111-2015. Расчёт неканцерогенного риска проводили в соответствии с Руководством Р 2.1.10.1920-04.

Результаты. Определено среднее (0,14%) и максимальное (0,46%) содержание йода в фармакопейных видах слоевищ ламинарии, которое соотносится нормой содержания йода в ламинариевых водорослях, предложенных Управлением по санитарному надзору за качеством пищевых продуктов и медикаментов США (U.S. Food and Drug Administration) — 0,1–0,5%. Установлено, что при максимальной терапевтической дозе и курсе лечения слабительными фитопрепаратами, при условии содержания йода в них 0,5%, уровень неканцерогенного риска попадает в категорию предельно допустимого. При аналогичных условиях лечение, например, мастопатии препаратами на основе слоевищ ламинарии с содержанием йода 0,5% приводит к недопустимому воздействию йода на здоровье человека.

Заключение. Авторы рекомендуют вместо существующей нормы содержания йода (не менее 0,1%), принимать во внимание допустимое количество этого элемента (0,1–0,5%), которое соответствует его реальному содержанию в фармакопейных видах слоевищ ламинарии.

Ключевые слова: йод; слоевища ламинарии; коэффициент опасности; риск-ориентированная стратегия; гипертиреоз; количественное содержание

Список сокращений: БАД — биологически активная добавка; FDA — Управление по санитарному надзору за качеством пищевых продуктов и медикаментов США (U.S. Food and Drug Administration); ССЗ — сердечно-сосудистые заболевания; ЛРП — лекарственный растительный препарат; ЛРС — лекарственное растительное сырье; EPh — Европейская фармакопея; FCC — Кодекс пищевых химикатов; ЛС — лекарственное средство; ТМАН — тетраметиламмония гидроксид; HQ — коэффициент опасности.

INTRODUCTION

The implementation of salt iodization programs around the world has reduced the incidence of iodine deficiency-related diseases. However, 30% of the world's population is still at risk[1]. Iodine deficiency in the diet is a growing problem in many countries, including industrialized ones, partly due to changes in eating patterns and food production methods [1, 2].

Iodine intake is extremely important for the functioning of the human body, since the production of thyroid hormones directly depends on the amount of this element. Thyroid hormones are acutely necessary for brain development during intrauterine development, as well as during the first years of life [3]. A deficiency of this element has an adverse effect on

[1] American Thyroid Association Iodine Deficiency. Available from: https://www.thyroid.org/iodinedeficiency/

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2025-13-1-45-55

the development of mental and physical retardation in children [4], and is also the most common preventable cause of brain damage and the development of neurological diseases [5].

Iodine deficiency in the areas of Ukraine, Belarus and Russia adjacent to the Chernobyl nuclear power station became a factor in the increased uptake of radioactive iodine by the thyroid gland and, after a few years, led to a multiple increase in the incidence of thyroid cancer not only in adults, but also in children [6]. Optimal iodine intake dramatically reduces the risk of thyroid lesions. In Japan, where there is no iodine deficiency (mainly due to the unique dietary characteristics of the population, in particular the active consumption of brown algae), after the accident at the Fukushima nuclear power station, there was no significant increase in the incidence of thyroid cancer in children, even without emergency iodine prophylaxis immediately after the accident [7]. Efforts to prevent and control these diseases are primarily aimed to ensure iodine intake to maintain normal thyroid function [8] (90 μg/day for children, 150 μg/day for people of both sexes over 12 years of age, and 250 μg/day for pregnant and lactating women)[2, 3]. Adequate iodine intake can be achieved by fortifying food with iodine and/or iodine-containing supplements, such as iodates and iodides [9, 10], added as a potassium salt. It should be noted that iodate is more stable in adverse climatic conditions and at elevated temperatures (in particular, during heat treatment of food).

One of the main ways to iodize food is to enrich table salt with iodine additives. The amount of iodine additive is 20–60 mg/kg[4], which, with the norm of table salt consumption (5.0 g/day), is 100–300 μg/day. However, due to the identified relationship between high sodium content and cardiovascular diseases (CVD) [11, 12], hypertension [12–14], urolithiasis and osteoporosis [13], there has recently been a tendency to reduce salt consumption [14, 15]. Replacing table salt with an alternative mixture, according to the latest research, has confirmed the value of a low-salt diet in the prevention of CVD [11, 14]. The best products for the prevention of iodine deficiency are those that are natural sources of iodine: seafood (fish, brown algae, crustaceans), beans, garlic, beets [10]. Brown algae containing iodine in large quantities, are actively used as medicinal herbal products (MHPs) and dietary supplements (DSs) [16–18], in particular, the U.S. Food and Drug Administration approved the use of dietary supplements based on algae of the Laminaria family as a source of this element[5]. These plants contain a large number of useful components (polysaccharides, including alginic acid salts [19], vitamins, polyunsaturated fatty acids and antioxidants, a wide range of essential elements, and most importantly iodine) [20–22]. The concentration of iodine in brown algae exceeds its content in all other living organisms [23], therefore they are a good natural source of iodine for humans [24, 25].

In the State Register of Medicines of the Russian Federation, algae of the *Laminariaciae* family (*Laminaria saccharina, Laminaria japonica*) are listed as such plants, so the State Pharmacopoeia of the Russian Federation XIV edition regulates the lower limit of iodine content (at least 0.1%)[6] in pharmacopeial types of *Laminaria thalli*. The European Pharmacopoeia (EPh) regulates the use of representatives of the Fucus family as medicinal plant raw materials (MPRMs). The U.S. Food Chemical Codex (FCC) recommends the use of representatives of a wide range of algae of the Laminaria family. Data on the types of brown algae used, as well as standards for iodine content, are shown in Table 1.

However, studies show that an excess of iodine is also harmful to the human body, as is its deficiency [26–28]. High iodine intake (1–10 mg/day) when taking MHPs or dietary supplements based on brown algae leads to an increased risk of endemic goiter, which in some cases is accompanied by hyperthyroidism or myxedema [29], and also stimulates autoimmune diseases [30, 31]. In this regard, EPh and FDA provide a range of iodine content in brown algae, and not its lower level (see Table 1).

THE AIM. To determine the range of permissible iodine content in medicinal plant raw materials “Laminaria thalli” and products based on it within the

[2] WHO/NUT/96.13. Recommended iodine levels in salt and guidelines for monitoring their adequacy and effectiveness. Geneva, World Health Organization; 1996. Available from: https://www.who.int/publications/i/item/WHO-NUT-96.13

[3] WHO Secretariat; Andersson M., de Benoist B., Delange F., Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr. 2007;10(12A):1606–1611. DOI: 10.1017/S1368980007361004. Erratum in: Public Health Nutr. 2008;11(3):327.

[4] GOST R 51575-2000 Iodized table salt. Methods for the determination of iodine and sodium thiosulfate.

[5] Office of the Federal Register, National Archives and Records Administration. Food additives permitted for direct addition to food for human consumption: subpart C—coatings, films and related substances – kelp, 21 CFR Sect 172.365. Washington (DC): US Government Printing Office; 2015. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-172

[6] M.5.0080.18 Laminaria of the stratum. The State Pharmacopoeia of the Russian Federation XIV edition. Available from: https://docs.rucml.ru/ feml/pharma/v14/vol4/999/

framework of a risk-oriented strategy in quality control of medicines. Previously, a risk-oriented approach was mainly used in relation to food contaminants (which include dietary supplements[7, 8]) and environmental objects[9, 10]. Currently, a trend has emerged to assess the carcinogenic and non-carcinogenic risks of contaminants in medicines for a long-time intake: synthetic painkillers [32], MPRMs and MHPs with various pharmacological effects [33, 34].

MATERIALS AND METHODS

Study methodology

The objects of the study were laxative herbal medicines of Russian manufacturing: "*Laminaria thalli* (sea kale)" produced by JSC "Krasnogorskleksredstva" (I-p), LLC "FITO-BOT" (II-p) and CJSC "ST-Medipharm" (III-p); preparations for the treatment of mastopathy "Mammoklam" produced by CJSC MEGA PHARM (IV-p), "Mammolain" produced by CJSC MEGA PHARM (V-p), samples of dietary supplements: "*Laminaria* (sea kale)" produced by CJSC Evalar, Russia (I-b), and "Laminaria SUPERFOOD" produced by LLC "Kron", Russia (II-b), "*Laminaria* for the thyroid gland" LLC PharmOcean Lab. (TM "Doctor More"), Russia (III-b), "Kelp", NOW Internetional, USA (IV-b), "Nalemarin" LLP Biomar, Russia (V-b), food products: Sea kale Kombu Fresh Sakhalin natural (*Laminaria japonica*), Russia (I-e) Arkhangelsk Algae Combine SUPERFOOD AV1918 (*Laminaria Saccharina*), Russia (II-e), as well as samples collected by the authors: thalli of Japanese laminaria (*Laminaria japonica* (L.)) (I-a), collected in the waters of Peter the Great Bay of the Pacific Ocean, and sugar laminaria (*Laminaria Saccharina* (L.)) (II-a), collected in the area of the Bolshoi Solovetsky Island. Self-collected samples were obtained in August 2020, dried in the sun for 2 days, the species identity of the samples was determined using macro- and microscopic analysis. In addition, we used literature data on the iodine content in the thalli of pharmacopoeial species of laminaria from various places of picking [21].

The iodine content in the test samples was determined by inductively coupled plasma mass spectrometry according to GOST EN 15111-2015[11]. Crushed laminaria algae thalli samples, as well as MHPs, were sieved through a sieve with a hole diameter of 1 mm. Then 3 samples of 500 mg each (accurate sample) were taken, followed by iodine extraction with an aqueous solution of tetramethylammonium hydroxide (25% Lot 331635, Sigma-Aldrich, USA, TMAH) according to GOST EN 15111-2015[12]. During the determining of the iodine content in DSs, 20 tablets were crushed, 3 samples of 500 mg each (accurate sample) were taken, then iodine extraction was carried out according to the GOST method. A sample of the test sample was placed in a flask with a capacity of 50 cm^3, 5 cm^3 of water was added and thoroughly mixed. Then 1 cm^3 of 0.5% TMAN solution was added, thoroughly mixed, the tightly closed flask was placed in a drying oven preheated to a temperature of 90±3°C for 3 h. After cooling, the samples were quantitatively transferred to a 25 cm^3 volumetric flask and brought to the mark with water. To remove coarse particles, aliquots were filtered through a membrane filter with a pore diameter of 5 µm. Then the solution of the internal standard of tellurium ions, prepared from a standard sample (SS; R2-TE691015 1000 µg/mL, Inorganic Ventures Lot, USA), was added to the aliquot of the sample extract. Calibration solutions (iodine concentration 5–20–50 µg/dm^3) were prepared by placing the appropriate volume of iodine SS (P2-IOD675953 1000 µg/mL, Inorganic Ventures Lot, USA) and internal standard (tellurium ion solution) in a 50 cm^3 volumetric flask, brought to the mark with 0.5% TMAH solution. A blank sample was prepared similarly to the calibration solution, without adding the SS solution. The iodine content in the test and calibration solutions was determined on an Agilent 7900 instrument (Agilent, USA), the parameters of the experiment are shown in Table 2.

Statistical processing

For each of the tested samples, the average value of measurements obtained from 3 parallel samples in 5 replicates was taken as the measurement result. The measurement results were statistically processed using Microsoft Office Excel 2007. The standard coefficient of variation, confidence interval, and systematic error were determined.

The calculation of non-carcinogenic risk was carried

[7] Technical Regulations of the Customs Union TR CU 021/2011 On Food Safety. Available from: https://docs.cntd.ru/document/902320560. Russian

[8] SanPiN 2.3.2.1078-01, Food raw materials and foodstuffs. Hygienic requirements for food safety and nutritional value; Ministry of Health of the Russian Federation, Moscow; 2002. Available from: https://docs.cntd.ru/document/901806306. Russian

[9] MU 2.3.7.2519-09 Determination of exposure and assessment of the risk of exposure to chemical food contaminants on the population. Methodological guidelines. Moscow: Federal Center of Hygiene and Epidemiology of Rospotrebnadzor; 2010. Russian

[10] R 2.1.10.1920-04 Guidelines for assessing the risk to public health when exposed to chemicals that pollute the environment. Moscow: Federal Center for State Sanitary and Epidemiological Supervision of the Ministry of Health of Russia; 2004. Russian

[11] GOST EN 15111-2015 Food products. Identification of trace elements. Method of iodine determination by inductively coupled plasma mass spectrometry (ICP-MS).

[12] Ibid.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2025-13-1-45-55

out according to R 2.1.10.1920-04. "Guidelines for assessing the risk to public health when exposed to chemicals that pollute the environment".

RESULTS AND DISCUSSION

The iodine content in laminaria thalli and products based on them, according to the recommendations for the implementation of analysis methods R 50.2.060–2008[13], the suitability of the GOST-approved method[14] was confirmed using standard sample of SRM 3530 Iodized Table Salt. The results are presented in Table 3.

The recovery rate was 103.1±5%, which corresponds to the requirements of the Eurasian Economic Union Pharmacopoeia for the correctness of analytical methods (recovery [R]=90–110%)[15], the precision (repeatability) of the method (RSD=4.31%) also meets pharmacopoeial requirements (RSD ≤5%)[16].

To determine the concentrations of iodine in the test samples, the calibration curve was used with prepared calibration solutions. The calibration curve, linear regression equation, correlation coefficient (R ≥0.99), detection limit (DL; DL ≥10DL), and background equivalent level (BEC) obtained using the instrument software (MassHunter 4.5) are shown in Figure 1. The calculated values of R^2 (0.9998) and DL (0.02 μg/L) confirmed the suitability of the method for determining the iodine content in samples[17].

At the first stage of the study was the applicability of the iodine content normalization ranges proposed in foreign regulatory documents (RD) to pharmacopoeial types of laminaria thalli (*Laminaria saccharina* L. and *Laminaria japonica* L.)[18], taking into account our own experimental and literature data on the concentration of the element in this herbal medicinal product (Table 4).

Table 4 demonstrates that the average (0.14%) and maximum (0.46%) iodine content in pharmacopoeial types of laminaria thalli correlates with the range of normalization values proposed by the FDA (0.1–0.5%). The lower level of permissible iodine content proposed by EPh (0.03–0.2%) is obviously due to the fact that fucus algae, which are a pharmacopoeial family in European countries, accumulate this element in smaller quantities compared to laminaria algae [42, 43].

At the next stage, the range of iodine content (0.1–0.5%) was evaluated from the point of view of the non-carcinogenic risk of its exposure during oral intake into the body along with the therapeutic dose of MHPs and dietary supplements based on laminaria thalli. Non-carcinogenic risk is understood as an indicator of the expected increase in the incidence of the population due to the toxic properties of chemical substances in the studied objects. When assessing non-carcinogenic risk, it is assumed that there is a threshold of harmful effect, below which toxic effects do not develop. The main quantitative indicator of non-carcinogenic risk is the hazard quotient (HQ), which is equal to the ratio of the average daily dose of consumption of the elemental impurity (ADD) to its safe (reference) exposure level[19, 20]:

$$HQ = \frac{ADD}{RfD},$$

where *RfD* is the reference dose of iodine (0.01 mg/kg[21]).

The value of ADD was calculated using the formula[22]:

$$ADD = \frac{C \times IR \times EF \times ED}{BW \times AT},$$

where C is the concentration of the studied elemental impurity in laminaria thalli, mg/kg; IR is the therapeutic dose of laminaria thalli, kg/day; EF is the frequency of exposure during the year, days; ED is the duration of exposure, years; BW is the average value of human body weight (70 kg[23]) AT is the averaging time of exposure, days.

Information on the values of IR, EF, ED was taken from the instructions for the preparations presented in the State Register of Medicines. The value of AT was equated to the expected human life expectancy (70 years)[24].

[13] R 50.2.060-2008. The state system of ensuring the uniformity of measurements. Implementation of standardized methods of quantitative chemical analysis in the laboratory. Confirmation of compliance with the established requirements (approved and put into effect by Order No. 320-st of the Federal Agency for Technical Regulation and Metrology dated November 25, 2008). Available from: https://docs.cntd.ru/document/1200069291

[14] GOST EN 15111-2015 Food products. Identification of trace elements. Method of iodine determination by inductively coupled plasma mass spectrometry (ICP-MS).

[15] GPhM.2.1.2.55. Inductively coupled plasma mass spectrometry. Pharmacopoeia of the EAEU. Vol. 1, Part 2. Moscow: Publishing House of the Eurasian Economic Commission; 2023. P. 48–50. Russian

[16] Ibid.

[17] Ibid.

[18] PhM 2.5.0080.18 Laminaria of the stratum (sea cabbage). The State Pharmacopoeia of the Russian Federation XIV ed.

[19] R 2.1.10.1920-04 Guidelines for assessing the risk to public health when exposed to chemicals that pollute the environment, 2004.

[20] Q3D(R2) Guideline for Elemental Impurities. International Council for Harmonisation; 2022. Available from: https://database.ich.org/sites/default/files/Q3D-R2_Guideline_ Step4_2022_0308.pdf

[21] Regional Screening Level (RSL) Summary Table. United States Environmental Protection Agency (USEPA); 2022. Available from: https://semspub.epa.gov/work/ HQ/404057.pdf

[22] United States. Environmental Protection Agency. Office of Emergency, Remedial Response. Risk Assessment Guidance for Superfund: pt. A. Human health evaluation manual. Available from: https://www.epa.gov/sites/default/files/2015-09/ documents/rags_a.pdf

[23] MU 2.3.7.2519-09 Determination of exposure and assessment of the risk of exposure to chemical food contaminants on the population. Methodological guidelines, 2009.

[24] R 2.1.10.1920-04 Guidelines for assessing the risk to public health when exposed to chemicals that pollute the environment, 2004.

Table 1 — Regulation of iodine content in brown algae in some regulatory documents

Regulatory document	Family	Types	Regulated iodine content
SP RF XIV ed.[25]	*Laminariaceae*	*Laminaria saccharina* L. *Laminaria japonica* Aresch.	Not less than 0.1%
EPh ed. 11.3[26]	*Fucaceae*	*Fucus vesiculosus* L. *Fucus serratus* L. *Ascophyllum nodosum* Le Jolis	0.03–0.2%
FCC ed. 9[27]	*Laminariaceae*	*Macrocystis pyrifera* L. *Laminaria digitata* Huds. *Laminaria cloustoni* Edm. *Laminaria saccharina* L.	0.1–0.5%

Note: SP RF — State Pharmacopoeia of the Russian Federation; EPh — European Pharmacopoeia; FCC — Food Chemical Codex.

Table 2 — HPLC analysis conditions

Parameter	Value
High-frequency plasma generator power	1500 W
Plasma gas flow (argon)	15 l/min
Nebulizer gas flow (argon)	1.0 l/min
Signal integration time	0,1 s
Determined isotope (iodine)	127 amu
Internal isotope	125 amu

Table 3 — Evaluation of the suitability of the analysis method

No.	Iodine content, % of nominal value	Metrology
1	107.98	Average value ($\bar{Z}i$) — 103.10%, Systematic error (δ) — 3.1%, Standard deviation (SD) — 4.44 %, Coefficient of variation (RSD) — 4.31%, Confidence interval (P=95%, α=0.05) is ±4,65%
2	102.32	
3	99.09	
4	105.50	
5	96.90	
6	106.82	

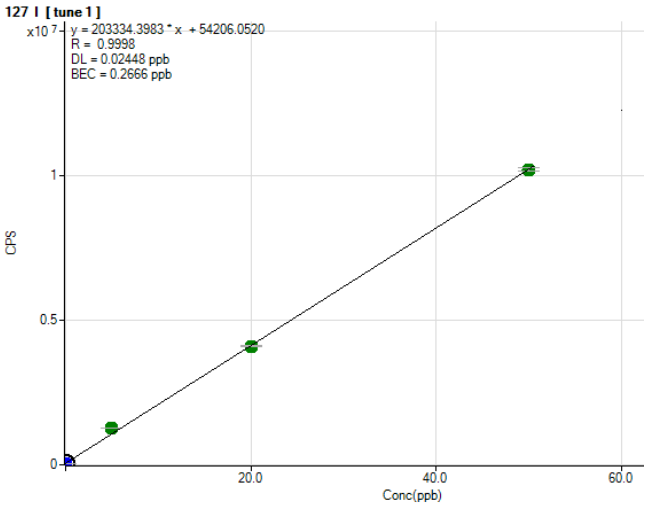

Figure 1 — Calibration curve, characterizing the suitability of the analytical method

[25] Ibid.

[26] Monograph 01/2008:1426 Kelp, in: European Pharmacopoeia, 11.3th ed., European Department for the Quality of Medicines & Health Care, Strasbourg; 2022. Available from: https://pheur.edqm.eu/app/11-3/content/11-3/1426E. htm?highlight=on&terms=kelp

[27] U.S. Pharmacopeia (USP). Food chemicals codex. 9 ed. Baltimore: United Book Press Inc; 2014. 1785p.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2025-13-1-45-55

Table 4 — Iodine content in pharmacopoeial types of laminaria thalli

No.	Concentration, mg/kg	
	Laminaria japonica L.	*Laminaria saccharina* L.
Literary data		
1.	2110 [35]	238 [35]
2.	3040 [36]	957 [38]
3.	3400 [37]	1340 [39]
4.	–	2630 [40]
5.	–	3124 [41]
6.	–	4600 [42]
Experimental data (Median — 1791 mg/kg, max — 4600 mg/kg)		
1.	1216.74±31.05 (I-m)	716.98±16.94(II-s)*
2.	2390.57±27.22 (II-p)	292.53±10.91 (II-a)*
3.	1473.65±25.96 (III-p)	–
4.	899.30±61.73 (I-e)	–
5.	3700±108.9 (I-a)	–

Table 5 — Value of iodine hazard quotients during oral administration of therapeutic doses of herbal medicines based on laminaria thalli

Herbal medicines	Course of administration	IR, kg	EF, days	C_{med}, 3000 mg/kg		$C_{95\%}$, 5000 mg/kg	
				ADD, mg/kg×day	HQ	ADD, mg/kg×day	HQ
I-m, II-m, III-m	Minimum	0,0015	15	$2,6\times10^{-3}$	0,26	$4,4\times10^{-3}$	0,44
	Maximum	0,003	30	0,01	1,0	0,0176	1,76
IV-m, V-m	Minimum	0,0002	90	$2,1\times10^{-3}$	0,21	$3,5\times10^{-3}$	0,35
	Maximum	0,0006	270	0,02	2,0	0,0317	3,2

Note: the average concentration of the range 0.1–0.5% (0.3% or 3000 mg/kg) was taken as the value of Cmed, and the maximum concentration of the specified range (5000 mg/kg) was taken as C95%. IR — therapeutic dose of laminaria thalli, kg/day; EF — frequency of exposure during the year, days; ED — duration of exposure, years; AT — averaging time of exposure, days; HQ — hazard quotient.

Table 6 – Hazard quotient values for iodine in oral dietary supplements

Supplement	Course of administration	C, mg/kg	IR, kg	EF, days	ADD, mg/kg×day	HQ
I-s	Minimum	1000	0.0002	180	0.0014	0.14
	Maximum			360	0.003	0.28
II-s	Minimum	1000	0.0002	180	0.0014	0.14
	Maximum			360	0.003	0.28
III-s	Minimum	2000	0.0005	30	0.001	0.12
	Maximum					
IV-s	Minimum	100	0.0045	30	0.0005	0.05
	Maximum					
V-s	Minimum*	1200	0.001	30	0.0014	0.14
	Maximum*			60	0.003	0.28
	Minimum**	600	0.0005	30	0.0003	0.04
	Maximum**			60	0.0007	0.07

Notes: * course of administration for adults; ** course of administration for children. Supplement — dietary supplement; C — concentration of the studied elemental impurity in kelp thalli, mg/kg; IR — therapeutic dose of kelp thalli, kg/day; EF — exposure frequency during the year, days; AT — exposure averaging time, days; HQ — hazard quotient.

Table 7 – Iodine content in samples of dietary supplements I-s and II-s

No.	Iodine content, mg/kg	
	I-s	**II-s**
1	3021	3348
2	3094	3407
3	3189	3443
Average	3101 ± 209.1 (2.7)	3399 ± 119.1 (1.4)

The HQ value was calculated at two concentration levels (median and 95th percentile[28]. It should be noted that there are no criteria in Russian and foreign regulatory documents for assessing HQ values from the point of view of the admissibility of the negative impact of a single elemental toxicant. They are presented only for the total hazard index (HI), which is defined as the sum of the hazard quotients of all analyzed contaminants. It is generally accepted that at HI_{med} >1, there is an unacceptable impact of elemental contaminants on human health, requiring appropriate safety measures. The combination of HI_{med} <1 and $HI_{95\%}$ <1 indicate no risk to human health from the action of contaminants. In a situation where HI_{med} ≤1, but $HI_{95\%}$ >1, it is necessary to strengthen control over the content of contaminants with the greatest contribution to exposure. Taking into account the fact that the iodine content in laminaria thalli is significantly higher than the content of heavy metals and inorganic arsenic in them, these criteria were used to assessing HQ values for iodine.

In Russia, MHPs based on laminaria thalli are used to treat chronic atonic constipation (phytopreparation "*Laminaria thalli*, sea kale"), which is crushed and dried pieces of laminaria thalli from various manufacturers (I-m, II-m and III-m) with the same course of administration and dosage) and for the treatment of mastopathy (tablets "Mammoklam" (IV-m) and "Mammolain" (V-m) based on iodine-lipid complex from laminaria thalli with the same course of administration and dosage). In accordance with the instructions for use, the minimum iodine content in all these preparations is 0.1%, which is the same as in the original herbal medicinal product. The values of IR and EF were determined based on the method of administration and therapeutic doses of herbal medicinal products, and ED — by the difference from the average life expectancy (70 years)[29] and the age of starting the medicine:

- I-m, II-m and III-m: half or 1 teaspoon (or 1.5–3 g) for 15–30 days at the age of 12 years[30] (IR=0.0015–0.003 kg; EF=15–30 days, ED=58 years, AT=365×ED);
- IV-m and V-m: 2–6 tablets of 100 mg from 1 to 3 months with a break of 2 weeks to 3 months from 18 years[31] (IR=0.0002–0.0006 kg, EF=90–270 days, ED=52 years, AT=365×ED)

The results of the assessment of non-carcinogenic risk associated with the toxic effect of iodine during oral administration of therapeutic doses of various herbal medicines are presented in Table 5.

HQ was calculated for oral administration of dietary supplements based on laminaria thalli (Table 6). Data on the content, courses of administration (minimum and maximum) of iodine were taken from the information on the packaging or instructions for use of the supplement.

For supplements I-s and II-s, the actual iodine content in the samples was determined according to GOST EN 15111-2015[32]. The results of determining the iodine content in these samples are presented in Table 7.

As a result of the studies, it was found that the iodine content in supplement I-s was 3101±209 mg/kg, and for supplement II-s — 3399±119 mg/kg.

Table 4 demonstrates that with the minimum therapeutic dose and course of treatment of MHPs I-m, II-m and III-m, there is no risk of negative effects of iodine on the human body and control over its content is not required. At the maximum therapeutic dose and course of treatment, the risk level falls into the category of the maximum permissible, which entails the need to control the iodine content in this drug. The intake of MHPs IV-m and V-m, its minimum therapeutic dose and duration of administration are also not associated with a risk to human health. Taking the maximum therapeutic dose during such a course of treatment, as provided for in the instructions for use, leads to unacceptable exposure to iodine on human health. This requires appropriate security measures. As such a measure, we recommend reducing the maximum frequency of drug administration to 140 days per year. In this case, the HQ value at an iodine concentration of 0.5% in MHPs IV-m and V-m and a therapeutic dose of 6 tablets per day will not exceed 1. It is important to note that information on contraindications of taking medicines for the treatment of mastopathy associated with thyroid dysfunction is given in the instructions for these medicines. Both doctors and patients need to carefully assess the risks of using these medicines.

Separately, it is worth focusing on supplements based on kelp thalli. It should be noted that the market for supplements made from algae is developing with unprecedented dynamics [44–46] and they are increasingly being chosen as an easy way to enrich the daily diet with vitamins and minerals. At the same time, the consumer is often mistaken believing that supplements are controlled for the content of contaminants and active substances similarly to medicines due to the similarity of finished forms

[28] United States. Environmental Protection Agency. Office of Emergency, Remedial Response. Risk Assessment Guidance for Superfund: pt. A. Human health evaluation manual.

[29] MU 2.3.7.2519-09 Determination of exposure and assessment of the risk of exposure to chemical food contaminants on the population. Methodological guidelines; 2009.

[30] The State Register of Medicines of Russian Federation. Laminaria of the stratum (sea cabbage). Available from: https://grls.rosminzdrav.ru/Grls_View_ v2.aspx?routingGuid=28e7b04d-2b7f-47e4-8f9f-d83e42c12d97

[31] The State Register of Medicines of Russian Federation. Mammoline. Available from: https:// grls.rosminzdrav.ru/Grls_View_ v2.aspx?routingGuid=54f29d82-60f5- 4a67-b770-fd134b96bdb7

[32] GOST EN 15111-2015 Food products. Identification of trace elements. Method of iodine determination by inductively coupled plasma mass spectrometry (ICP-MS).

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2025-13-1-45-55

(tablets, capsules, drops, liquid or powder) and the general place of sale (pharmacy). Despite the fact that the norms for the iodine content in supplements based on kelp thalli are indicated on the packaging, state control of the concentration of this element during quality examination in finished products is not carried out, unlike LRP. This is due to the fact that supplements do not have a proven pharmacological effect and information about their exact composition is missing [47].

According to the data obtained (see Table 5), if supplements are taken in accordance with the manufacturer's recommendations, in no case will the HQ exceed 1, provided that their composition corresponds to that indicated on the packaging. It should be noted that the iodine content in tablets of supplements I-s and II-s on the packaging corresponds to its content in 0.1%, while the actual content of this element, determined according to GOST, is more than 3 times higher than the indicated value. The HQ for the real value with daily intake for 1 year is almost equal to one — the value after which the risk becomes unacceptable. It follows from this that the iodine content in supplements based on kelp thalli also needs to be controlled.

CONCLUSION

Medicines based on thalli kelp in Russia are used to treat diseases not directly related to iodine deficiency in the human body. Therefore, with high contents of this element in the initial raw materials, prolonged use of such drugs in the maximum permissible therapeutic doses leads to the risk of developing hyperthyroidism in such patients. Warnings about the possible appearance of hyperthyroidism in the instructions are not enough; it is necessary to change the principle of rationing the iodine content in the pharmacopoeial article "*Laminaria thalli* (sea kale)". It is recommended, to give the range of permissible content of this element (0.1–0.5%), instead of the existing iodine content norm (not less than 0.1%), which corresponds to its real content in pharmacopoeial types of kelp thalli. People with thyroid dysfunction should use supplements based on brown algae with caution due to the high variability of iodine content, as well as the possible difference between the real and theoretical content of this element in supplements.

FUNDING

The work was performed within the framework of the Scientific Centre for Expert Evaluation of Medicinal Products No. 056-00052-23-00 for applied scientific research (state registration number NIR 121022400083-1).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Victor M. Shchukin — development of research aims and objectives, synthesis of data set out in regulatory documents, collection and processing of primary data, draft writing; Nataliya E. Kuzmina, Natalya D. Bunyatyan — the idea, planning, organization and control of research at stages, processing the results, draft editing; Elena A. Khorolskaya — information and analytical search on the research aim, sample preparation and experiment, draft editing. All the authors confirm their authorship compliance with the ICMJE international criteria (all authors made a significant contribution to the development of the concept, conducting research and preparing the article, read and approved the final version before publication).

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