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Review

Variation in milk-iodine concentration around the world: a systematic review and meta-analysis of the difference between season and dairy-production system

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ABSTRACT

Iodine is essential for thyroid hormone production. Milk and dairy products are important sources of iodine in many countries. We aimed to review systematically the variation in milk-iodine concentration between countries, seasons and farming practice. We searched online food composition tables and published literature for data since 2006. Milk-iodine concentration was available for 34 countries (from 66 sources) and ranged from 5.5 to 49.9 μg/100 g (median 17.3 μg/100 g). Meta-analyses identified that iodine concentration is significantly higher in: (i) winter than summer milk (mean difference 5.97 μg/100 g; $p = 0.001$), and (ii) in conventional than in organic milk (mean difference 6.00 μg/100 g; $p < 0.0001$). Sub-group analysis showed that the difference between organic and conventional milk was only significant in summer ($p = 0.0003$). The seasonal variation in milk-iodine concentration may affect iodine intake and status so should be considered in dietary surveys, and when assessing population iodine status.

1. Introduction

Iodine is vital for thyroid hormone synthesis and its deficiency has effects across the human lifespan (Zimmermann, 2009; Zimmermann & Boelaert, 2015). Severe iodine deficiency in utero leads to an increased risk of congenital iodine deficiency disorders (historically called cretinism) in offspring, while mild-to-moderate iodine deficiency has been associated with reduced verbal IQ, reading accuracy and comprehension (Bath et al., 2013). Iodine deficiency in childhood may cause delayed physical development and impaired cognitive ability, and deficiency in adults is linked with reduced mental function and work productivity (Bath & Rayman, 2015; Zimmermann & Boelaert, 2015). Despite the fact that the number of countries with adequate iodine intake almost doubled from 2003 to 2020, iodine deficiency, especially mild deficiency, continues to affect populations around the world, including in Europe (Iodine Global Network, 2021; Zimmermann & Andersson, 2021).

Milk and dairy products are noted as important sources of iodine worldwide (Lee et al., 2016) and are the primary sources of iodine for adults in multiple countries across Europe, including Denmark (30%), Finland (37%), France (21%), Republic of Ireland (53%), Norway (36%) and the UK (34%) (Bath et al., 2022). However, the use of plant-based milk alternatives is on the rise but only a low proportionare fortified with iodine (20% in a 2020 UK market survey) (Nicol et al., 2023); this is of particular concern in countries that are reliant on cows' milk and dairy products to meet iodine needs.

Milk-iodine concentration can vary according to several factors, and investigations have suggested that the main determinant is the cows' diet (Flachowsky et al., 2014). Increasing iodine concentration in the dry matter of cows' feed may correlate with an increase in milk-iodine concentration (van der Reijden et al., 2019). However, this response may not be linear as the mammary gland may act as a bioregulator at high doses to reduce the transfer rate from feed to milk (Norouzian, 2011). The transfer rate can also be affected by the goitrogen content of the feed (Franke et al., 2009); goitrogens are iodine antagonists that act as a competitive inhibitor of iodine via the sodium iodide transporter (NIS) in the mammary gland (Gaitan, 1990; van der Reijden et al., 2017). Other factors that cause variation in milk-iodine concentration,

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such as season and dairy-production system (i.e. whether organic or conventional), are also linked to differences in cattle diet and goitrogen exposure between seasons and/or farm management (Qin et al., 2021; Stevenson et al., 2018; van der Reijden et al., 2018). Milk-hygiene practices (use of iodine-containing disinfectants for teat dipping) can increase the iodine content of milk, while milk processing (e.g. heat treatment) can reduce milk-iodine concentration (van der Reijden et al., 2018).

Although there is evidence of variation in milk-iodine concentration, differences between countries have not previously been compared using a systematic approach. Understanding differences in milk-iodine concentration by country is important from the perspective of the consumer and in understanding milk as a source of iodine in each country. Therefore, our primary aim was to compare the iodine concentration of milk from countries around the world, to consider consumer exposure to iodine from milk. Based on existing studies, we hypothesised that there would be large differences in milk-iodine concentration between countries (due to differences in dairy-production systems and cows' diets in different parts of the world). Furthermore, our secondary and tertiary aims were to compare the difference in milk-iodine concentration between season (summer vs. winter) and dairy-production system (organic vs. conventional) using data from around the world; we hypothesised that iodine concentration would be: (i) lower in summer than in winter milk (as a result of higher iodine content in winter feed) and (ii) higher in conventional than organic milk (as a result of greater use of fresh forage, with a lower iodine and higher goitrogen content, in organic farming).

2. Methods

To obtain information on milk-iodine concentration around the world, and differences by season and dairy-production system, we systematically searched: (i) online food-composition tables and (ii) the published literature. We combined information from both sources to create an overall global database of milk-iodine concentration in liquid cows' milk from January 2006. That date was selected due to the implementation of EU Regulations in 2005, where the permitted dietary iodine intake of dairy cows was reduced from 10 to 5 mg/kg of feed (European Union, 2005). The date restriction also meant that the results were relevant as they represent recent information on milk-iodine concentration (i.e. within the last 20 years).

The guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used for reporting this systematic review. The systematic review was not eligible for PROSPERO registration as our primary outcome was based on food composition data (i.e. milk-iodine concentration), and not outcomes from human or animal studies.

2.1. Food composition tables: Search strategy and data extraction

Online food composition tables were consulted to collate information on the iodine concentration of milk from countries around the world (full list of sources is available in Online Supplementary Materials B). Firstly, the website of the European Food Information Resource (EuroFIR) was used to compile a list of food composition tables (European Food Information Resource, 2011). This was cross-referenced with a published review that indicated which tables included the iodine content of foods (Ershow et al., 2018) to create a final list of relevant tables. The selected food composition tables were then searched using the term, "milk". Where webpages and/or tables were not in English, automatic translation was conducted, or Google Translate was used to translate individual words and identify relevant data. Food composition tables were first searched in August 2022 and an additional author searched again in November 2022.

The data extracted included exact food names (in both English and the original database language), iodine content (μg/100 g), farming methods (i.e., organic or conventional, where available), fat content, and the sample size. Information was also collected on whether the milk-iodine values originated from the reporting country; as an example, the iodine concentration of milk reported in French food composition tables is based on Danish data (Anses, 2020). If food tables had data on skimmed, semi-skimmed and full-fat milk, iodine concentration of semi-skimmed milk was selected as the primary product. This was to reflect the fact that semi-skimmed milk is commonly consumed and because there is no difference in iodine concentration between whole, semi-skimmed or skimmed milk (Isaac-Olive & Chatt, 2012; O'Kane et al., 2018; Payling et al., 2015; Public Health England, 2020). If semi-skimmed milk was not available, data from whole or skimmed milk was used.

2.2. Systematic review of published literature

2.2.1. Search strategy, study selection and exclusion criteria

Four databases - Embase, PubMed, Scopus and Web of Science – were consulted; all searches were conducted on 19th December 2022. The following search terms were used in each database: "(milk AND iodine) AND (concentration OR content) AND (cow OR bovine)". Results were filtered to include only those available in English and published from 2006 onwards.

Screening of titles and abstracts was carried out for each article retrieved from the four databases. Papers assessed as eligible for full-text screening were then evaluated for their suitability for data extraction.

Studies were included from two different levels of the supply chain: retail outlets or farm bulk tank (or mixed settings). All study types were included (i.e., observational and experimental) at the abstract stage. Experimental studies in animals were reviewed at the full-text stage in case they included comparison of retail/bulk-tank samples; otherwise, experimental studies were excluded because of uncertainty as to whether baseline/control measures were representative of that used for milk that is usually supplied to the consumer.

Studies that were not original research but referenced milk-iodine concentration from other research (including meta-analyses) were excluded; the referenced study was included under "additional methods" if it had not been identified through the database search. Studies analysing infant formula or those that trialled multiple laboratory measurement methods were excluded. Studies were excluded if it was not possible to access full texts, e.g., papers with English abstracts but full text in the original language, retracted articles, or conference proceedings.

2.2.2. Data extraction

Data were extracted on country, author(s), year of publication, title, median/mean iodine content, and the range (μg/100 g), fat content (g/100 g), heat treatment (UHT, pasteurised), dairy-production method (conventional or organic), season (winter or summer), number of samples, year of sample collection, sample source (farm or retail), laboratory accreditation, certified reference material (CRM) use, and the CRM results. If data from multiple years were available in a single study, results from the most recent year were extracted.

2.2.3. Assessment of data quality – Development of a quality assessment tool

A suitable validated Quality Assessment Tool (QAT) does not exist for evaluating data on milk-iodine concentration from published studies. We therefore developed a QAT (Supplementary Materials A), broadly based on the Newcastle-Ottawa Scale (Wells et al., 2021), to assess the literature. Our QAT scored studies based on three domains: (i) laboratory method, (ii) sampling, and (iii) production. According to the score in each domain, papers could be classified as "Good", "Fair", or "Poor". The laboratory domain included questions on the method of laboratory analysis of milk samples, and the use of certified reference materials (CRMs). The use of CRMs to ensure method accuracy, and therefore the validity of results was deemed the most critical factor in evaluating the quality of iodine analysis; use of a CRM, with reported results, was therefore given greater weighting in the overall score and was mandatory for a paper to be classified as "Good". The sampling domain assessed whether the milk samples were retail or farm, and whether the year of sampling was stated. As the aim of this review was focused on relevance of the findings to consumer iodine intakes, points were scored for studies that measured retail samples, rather than farm milk. Finally, the production domain considered whether the study stated the farming system (conventional or organic) and the season of milk sample collection, as these factors may influence the overall result and how representative the data are for a country.

2.3. Methodology common to searches of both online food-composition tables and published literature

2.3.1. Date exclusion criteria

Food-composition tables and published literature with samples collected prior to January 2006 were excluded. Papers where sample collection commenced before 2006 but continued beyond that date were included.

2.3.2. Volume to mass conversion

If milk-iodine concentration was given by volume (e.g. μg/L), the specific gravity of milk was used to convert to mass (i.e. μg/kg). The specific gravity values for whole, semi-skimmed and skimmed milk were used (1.031, 1.034 and 1.036 g/ml respectively) (Food Standards Agency, 2005) where specified; if not specified, the specific gravity for whole milk was used for farm milk, and the average specific gravity (i.e. 1.034) was used for retail milk.

2.3.3. Dual screening and data extraction

Two authors conducted blind dual screening of abstracts, full texts, and food composition tables, as well as blind dual data selection and extraction. Where discrepancies existed, a third author was consulted, and resolution was achieved through discussion. Data were extracted into a form in Microsoft Excel.

2.4. Summarising results by country

To create an overall global database of milk-iodine concentration, a single value was selected to represent each country, using data from either food composition tables or the literature. Countries were grouped into world regions as described by WHO (World Health Organization, 2023). The preference was to use data based on retail milk (as representative of consumer use), from both summer and winter seasons (to account for seasonal variation), and from conventional milk (to represent the most commonly consumed milk type). However, these preferences were frequently unavailable due to study design and/or reporting. If a study gave both summer and winter values, a weighted mean was calculated to represent the seasonal average. For the purposes of country comparisons, only seasonal-average data were used. If studies included both retail and farm milk, retail data were used, except in cases where the sample size of farm milk was greater, and where the retail milk did not have key information (such as date of sampling or whether organic or conventional) (Rey-Crespo et al., 2013; Sakai et al., 2022). Data from conventional milk from a single season was chosen over data from organic milk (Rey-Crespo et al., 2013). Median values were selected, where available, as nutritional data are often not normally distributed (Tooze et al., 2010).

Where countries had multiple results, (either numerous papers for a single country, or data from both literature and food composition tables), one value was selected based on the following criteria: (i) higher score on the QAT, (ii) most recent date of sampling, (iii) larger sample size, or (iv) where data from food composition tables were better described (e.g. by season/farming system) than a literature source in that country. A worldwide median milk-iodine concentration (μg/100 g) was calculated from the single value chosen for each country.

We evaluated whether milk in each country would be considered as a "source" of iodine by using the threshold milk-iodine concentration that would be required for labelling according to EU legislation (European Parliament, 2011). To be a "source" of iodine, foodstuffs must have a minimum of 15% of the adult nutrient reference value (NRV) of iodine [i.e. 150 μg/d (European Parliament, 2011)], which would mean an iodine concentration of 22.5 μg/100 g (European Parliament, 2011).

2.5. Meta-analysis of differences by season and dairy-production system

To investigate the effect size of differences in milk-iodine concentrations due to season (summer vs. winter) and dairy-production system (organic vs. conventional), meta-analyses were conducted using the software Review Manager 5.4.1 (RevMan), with a random effects model applied. Where there were clear outliers in terms of the Forest Plot pattern, sensitivity analysis was completed. Heterogeneity was assessed using the I^2 statistic.

The difference in milk-iodine concentration by season was explored using data from all relevant studies, and a sub-group analysis was conducted of differences in iodine content by season according to whether milk was organic or conventional. Studies of UHT milk were excluded from the meta-analysis of seasonal variation owing to the "long-life" nature of UHT milk, meaning that it was not possible to determine the season of production based on sample collection dates. Meteorological seasons were used – summer was defined as months June through August, and winter was defined as months December through February for countries in the northern hemisphere (and vice versa for countries in the southern hemisphere, such as New Zealand) (National Centers for Environmental Information, 2016).

The difference in milk-iodine concentration by dairy-production system (organic vs. conventional) was explored using data from all relevant studies. A sub-group analysis examined differences between organic and conventional milk within different seasons, where data were available.

The meta-analysis included mean and standard deviation (SD) values for each country; where papers gave only medians (plus minimum and maximum values and/or interquartile range), values were converted using published formulae (Wan et al., 2014). Some studies reported mean ± standard error (SE); the SE was converted to SD using the formula $SD = SE^* \sqrt{n}$. Where necessary, authors of the published studies were contacted to provide clarification on data and/or additional information. Data from food-composition tables were excluded from the meta-analyses where there was no indication of whether the value was the mean or median, and where there was insufficient information to estimate SD.

3. Results

The number of food composition tables and published studies are shown by each review stage in a PRISMA flow diagram (Fig. 1).

3.1. Food composition tables

A total of 37 food composition tables were identified (Ershow et al., 2018; European Food Information Resource, 2011) but of the 30 that were accessible, only 16 (from 16 countries) had eligible data on milk-iodine concentration (i.e. using samples collected from 2006 onward; Fig. 1; Supplementary Materials B).

3.2. The published literature

The search of the research databases identified a total of 659 articles, of which 358 were duplicates; a further seven articles were identified from reference lists (Fig. 1). Following abstract and full-text screening,

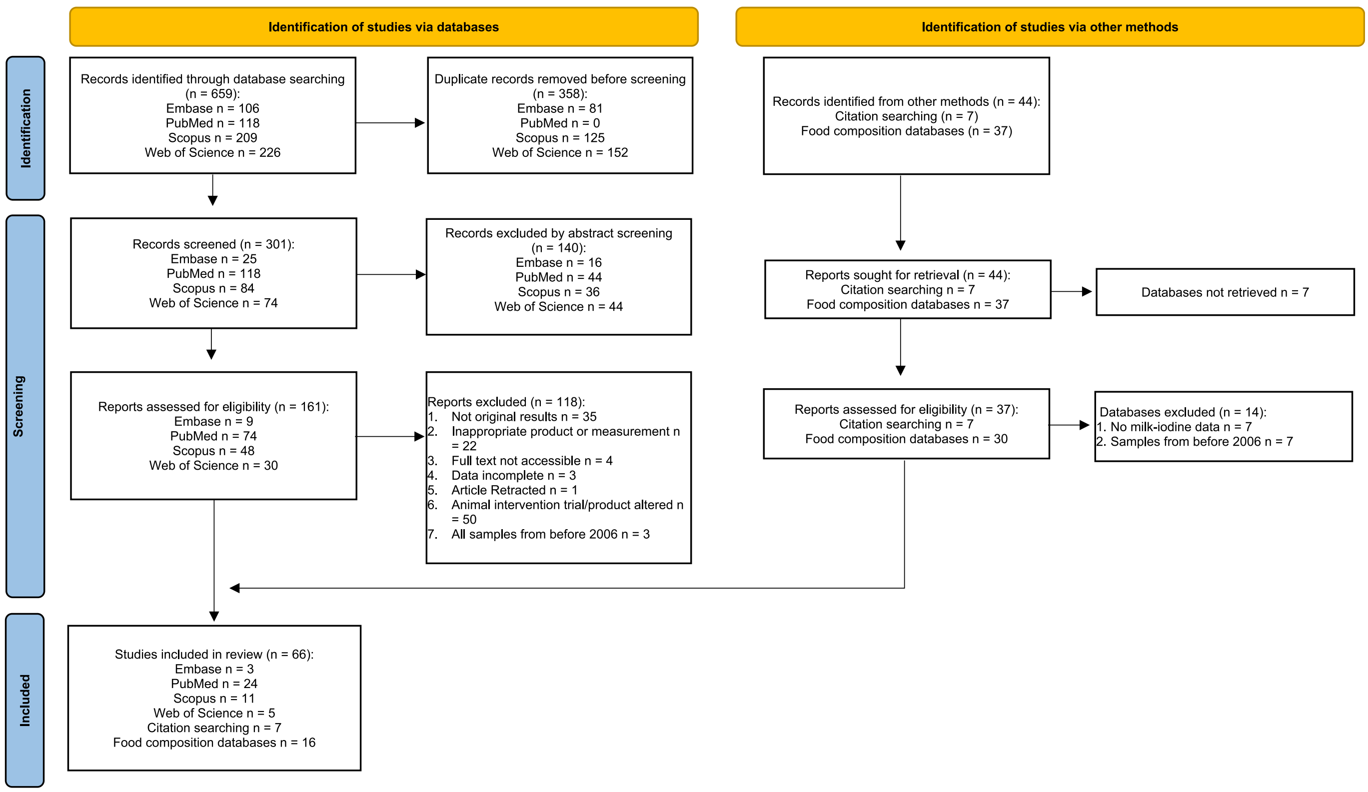

Fig. 1. PRISMA flow diagram of the selection process.

50 articles were eligible for data extraction (Fig. 1), representing 27 countries (Supplementary Materials B).

3.2.1. Quality assessment of papers

Using the QAT designed for this study (Supplementary Materials A), of the 50 publications used for data extraction, 50% ($n = 25$) were scored as poor, 30% ($n = 15$) as fair, and 20% ($n = 10$) as good (Supplementary Materials B). In total, 52% ($n = 26$) of publications (from 15 countries) used CRMs in the laboratory method. A further 12% of studies ($n = 6$) did not specify CRM use but did describe sample analysis being conducted in accredited laboratories, although it was not clear for most if the laboratories were specifically accredited for iodine analysis. Overall, 36% ($n = 18$) of eligible papers did not specify the use of either CRMs or an accredited laboratory.

3.2.2. Characteristics of the included studies for each country

Sixty-six sources were used to identify milk-iodine concentration worldwide ($n = 50$ from literature and $n = 16$ from food composition). Milk-iodine concentration data was available for 34 countries; using our selection criteria, we used data from the literature for 26 countries and values from food-composition tables for eight countries (Table 1).

For seasonal-average milk, sample sizes ranged from four [Republic of Ireland (Paludetti et al., 2019)] to 457 [Slovakia (Paulíková et al., 2008)], while the sample size was not reported for six countries.

Nineteen countries had milk-iodine concentrations based on seasonal-average data (including samples that were from conventional, mixed or unspecified dairy-production system; Table 1). However, just eight (23.5%) countries had seasonal-average data from only conventional milk (i.e. our preferred choice to represent the milk-iodine concentration of each country). Table 1 shows that country milk-iodine concentration values were from only summer milk for three countries (Canada, Italy and Japan) and only from autumn-winter milk for two countries (Belgium and Spain); season was unspecified in studies from 10 countries (Table 1). In 24 countries, the dairy-production system was either unspecified or based on mixed samples of conventional and organic milk. The USA, Italy and South Africa had the most recently collected samples, from 2018. Values for nine countries (26.5%) are based on samples where the year of sample collection was not specified, although all papers were published after 2006. Values for two countries (Belgium and Slovakia) included samples where collection commenced in 2002 although it was continued until 2006 and 2007 respectively (Guyot et al., 2009; Paulíková et al., 2008). Most results were from retail milk (59.9%, $n = 97$), with 34.6% from farm milk ($n = 56$) and nine unknown (5.6%).

3.3. Variation in milk-iodine concentration around the world

Each of the six WHO regions had data from at least one country: Europe ($n = 25$), Western Pacific ($n = 3$), Africa (n = 2), the Americas (n = 2), South-East Asia ($n = 1$), and the Eastern Mediterranean (n = 1). The global median milk-iodine concentration was 17.3 μg/100 g (based on the single value chosen for each country).

The milk-iodine concentration of all countries by season and dairy-production system are presented in Table 1. Fig. 2 shows the value chosen to represent each country, based on the selection criteria to use conventional, seasonal-average, data where possible. Fig. 2 highlights that 25 out of 34 countries have milk-iodine data from studies that reported using a CRM in the laboratory analysis.

When comparing only those countries with seasonal-average data ($n = 19$ as shown in dark blue on Fig. 2), milk-iodine concentration ranged between 5.5 μg/100 g in Slovakia (Paulíková et al., 2008) and 49.9 μg/100 g in Latvia (Neimane et al., 2017).

Fig. 2 shows that 14 of the 34 countries (41%) have a milk-iodine concentration >22.5 μg/100 g, and could therefore be labelled as a "source" of iodine according to EU Legislation (European Parliament, 2011), though data from six of these countries are based on single or unknown seasonal values (Fig. 2). Restricting to those countries with seasonal-average data only, six countries from the European region

Table 1

Selected milk-iodine concentration of all countries by season and dairy-production system. Table is organised according to WHO World Regions (World Health Organization, 2023). Values are median unless otherwise indicated. Values in bold indicate those chosen to represent the countries' milk-iodine concentration.

Country	Year of Sampling	Season	Median milk-iodine concentration (μg/100 g)			Reference
			Organic	Conventional	Mixed or Unspecified	
EUROPE						
Austria	2014	Average	–	–	**40.7 *(n10)***	Sager, 2018
Belgium	2002–2006	Winter	–	–	**14.9 *(n12)***	Guyot et al., 2009
Bosnia and Herzegovina	U	Summer	-	-	5.1[†] *(n40)*	Crnkić et al., 2015
		Winter	-	-	8.4[†] *(n50)*	
		Average	-	-	**6.1[†] *(n139)***	
Croatia	2014–2015	Average	–	–	**27 *(n200)***	Dold et al., 2018
Czechia	U	Average	16.9[†] *(n16)*	**44.9[†] *(n36)***	–	Hanuš et al., 2008
Denmark	2013	Summer	8[†] *(n21)*	12[†] *(n20)*	-	Rasmussen et al., 2014
		Winter	13[†] *(n26)*	13[†] *(n22)*	-	
		Average	11[†] *(n47)*	**12[†] *(n42)***	-	
Estonia	2021	U	–	–	**16[*] *(nU)***	National Institute for Health Development, 2021
Finland	2013	U	18.4[*] *(nU)*	–	**13.8[*] *(nU)***	Finnish Institute for Health and Welfare, 2013a
						Finnish Institute for Health and Welfare, 2013b
France	2008	Average	–	**18.3 *(n11)***	–	Arrizabalaga et al., 2020
Germany	2007–2011	Average	–	–	**12[†] *(n135)***	Kohler et al., 2012
Iceland	U	U	–	–	**11.2[*] *(n2)***	Matís, 2009
Italy	2018	Summer	–	**35.9[†] *(n5)***	–	Niero et al., 2019
Latvia	U	Summer	-	-	45.4[†] *(n11)*	Neimane et al., 2017
		Winter	-	-	54.5[†] *(n11)*	
		Average	-	-	**49.9[†‡] *(n22)***	
Netherlands	2016–2017	Summer	-	-	12.4 *(n16)*	van de Kamp et al., 2019
		Winter	-	-	17.3 *(n16)*	
		Average	15.9 *(n32)*	**16.2 *(n32)***	15.9 *(n64)*	
Norway	2016	Summer	15[†] *(n3)*	13[†] *(n3)*	-	Nerhus et al., 2018
		Winter	20[†] *(n3)*	16[†] *(n3)*	-	
		Average	17.5[†‡] *(n6)*	**14.5[†‡] *(n6)***	-	
Poland	2011–2012	Summer	-	-	14.3[†] *(n96)*	Sliwinski et al., 2015
		Winter	-	-	18.3[†] *(n77)*	
		Average	-	-	**16.1[†‡] *(n173)***	
Portugal	2015–2016	U	–	–	**19.5[†] *(n3)***	Delgado et al., 2019
Republic of Ireland	U	Summer	-	-	13.7[†] *(n2)*	Paludetti et al., 2019
		Winter	-	-	43.4[†] *(n2)*	
		Average	-	-	**28.6[†‡] *(n4)***	
Serbia	U	U	–	–	**14[*] *(nU)***	Institute for Medical Research – Department of Nutritional Research, 2022
Slovakia	2002–2007	Summer	-	-	5.5 *(n288)*	Paulíková et al., 2008
		Winter	-	-	5.5 *(n169)*	
		Average	-	-	**5.5 *(n457)***	
Slovenia	U	U	–	–	**3.3[*] *(nU)***	JSI & Biotechnical faculty Ljubljana, 2006
Spain	2011	Summer	3.4 *(n13)*	-	-	Rey-Crespo et al., 2013
		Winter	7.1 *(n13)*	**15.2 *(n10)***	-	
		Average	5.2 *(n26)*	-	-	
Sweden	2013	U	–	–	**12[*] *(nU)***	Livsmedelsverket (Swedish Food Agency), 2022
Switzerland	2013–2014	Average	6.9[†] *(n55)*	**10.8[†] *(n55)***	–	Walther et al., 2018
UK[§]	2015	Summer	16[†] *(n16)*	37[†] *(n16)*	-	Stevenson et al., 2018
		Winter	34.7[†] *(n8)*	47.1[†] *(n8)*	-	
		Average	23.3[†] *(n48)*	**41.3[†] *(n48)***	-	
AFRICA						
South Africa	2018	Summer	-	-	18.5 *(n109)*	Arns-Glaser et al., 2022
		Winter	-	-	21.7 *(n130)*	
		Average	-	-	**20.2[‡] *(n239)***	
United Republic of Tanzania	2017	Summer	-	-	22.7 *(n70)*	Arns-Glaser et al., 2022
		Winter	-	-	24.3 *(n86)*	
		Average	-	-	**23.6[‡] *(n156)***	
AMERICAS						
Canada	2008	Summer	–	–	**31.3[†] *(n51)***	Borucki Castro et al., 2011
USA	2018	Summer (retail)	24.4 *(n21)*	34.9 *(n21)*	-	Sakai et al., 2022
		Summer				
		Winter	21.9 *(n49)*	45.4 *(n34)*	30.4 *(n83)*	
		Average	29.1 *(n49)*	35.8 *(n34)*	30.9 *(n83)*	
			24.5 *(n98)*	**41.1 *(n68)***	30.6 *(n166)*	
EASTERN MEDITERRANEAN						
Iran	U	U	–	–	**25.2[†] *(n72)***	Rezaei Ahvanooei et al., 2021
SOUTH-EAST ASIA						
Sri Lanka	U	U	–	–	**31.4 *(n3)***	Guruge et al., 2011
WESTERN PACIFIC						
Australia	2008	U	–	–	**25.7[*] *(n20)***	Food Standards Australia & New Zealand, 2021
Japan	2010	Summer	–	–	**30 *(n45)***	Guruge et al., 2011
New Zealand	2013–2014	Spring	-	-	4.5[*] *(nU)*	The New Zealand Institute for Plant and Food Research Limited and the Ministry of Health (New Zealand) 2021a; The New Zealand Institute for Plant and Food Research Limited and the Ministry of Health (New Zealand) 2021b
		Autumn	-	-	14.5[*] *(nU)*	
		Average	-	-	**9.5[‡] *(nU)***	

U: unspecified (i.e. unspecified sample year, season, and/or sample size);
(nx) sample size where *x* is the number of samples;
[*] not specified mean or median;
[†] mean value;
[‡] seasonal average has been calculated by the author using individual summer and winter values;
[§] Summer value is the mean of data from July and August; Winter value is data from December; Average uses data from the months July through December.

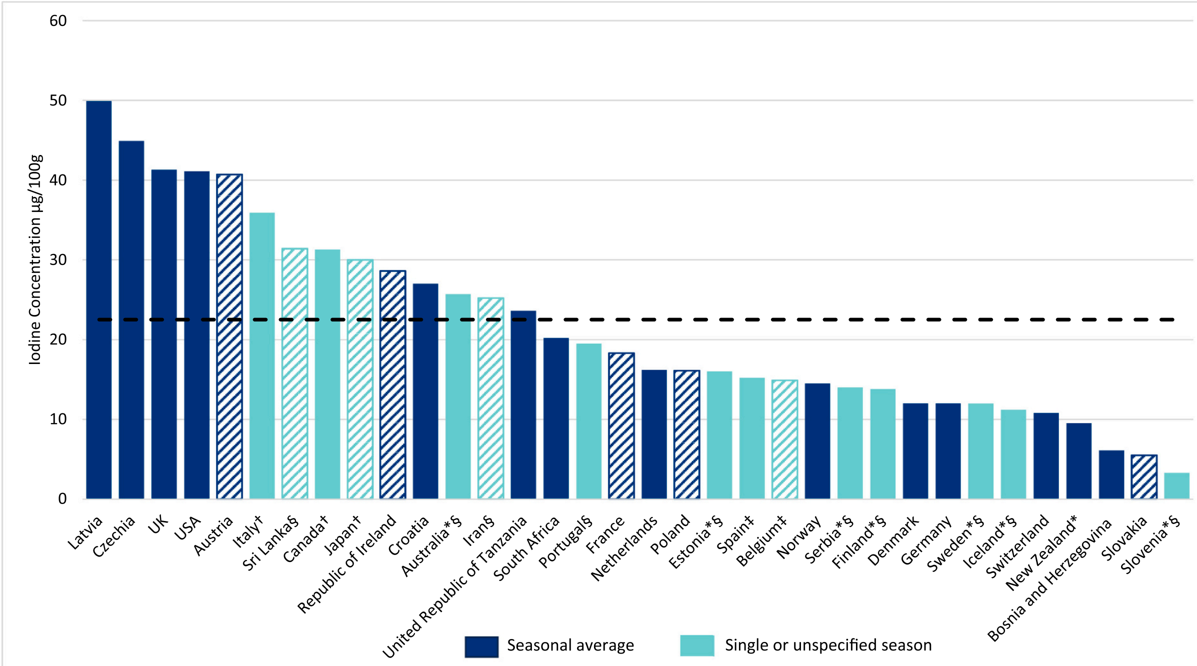

Fig. 2. Milk-iodine concentration for 34 countries worldwide with available data dashed black line at 22.5 μg/100 g represents the minimum iodine concentration of a foodstuff to be labelled a source, according to EU Legislation (European Parliament, 2011); diagonal stripes indicate that the study did not use CRM or accredited laboratories; *data from food composition tables; †summer milk only; ‡winter milk only; §unspecified season.

(Austria, Croatia, Czechia, Latvia, Republic of Ireland, UK) and two countries from other regions of the world (United Republic of Tanzania and the USA) have a milk-iodine concentration above the threshold for labelling.

3.4. Seasonal variation

Data on seasonal variation were available for 14 countries but season was not specified in ten. Winter values ranged from 5.5 μg/100 g [in Slovakia (Paulíková et al., 2008)] to 54.5 μg/100 g [in Latvia (Neimane et al., 2017)], while summer values ranged from 3.4 μg/100 g [in organic milk in Spain (Rey-Crespo et al., 2013)] to 45.4 μg/100 g [in Latvia (Neimane et al., 2017)].

Winter milk was higher in iodine than summer milk in all countries, except the USA [where summer milk was 9.6 μg/100 g higher than the winter value (Sakai et al., 2022)] and Slovenia [where iodine content was equal in summer and winter (JSI & Biotechnical faculty Ljubljana, 2006)]. The greatest difference by season was in the Republic of Ireland, where, at 43.4 μg/100 g, winter milk-iodine concentration was over three times higher than the summer milk value, at 13.7 μg/100 g (Paludetti et al., 2019).

3.4.1. Meta-analysis

The meta-analysis examining the effect of season used data from 13 countries (data from one country was excluded as it did not report SD), with a total of 1145 summer and 1350 winter samples (Fig. 3a, Fig. 3b). Overall, there was a significant effect of season, with milk-iodine concentration being 5.97 μg/100 g (95% CI 2.37 to 9.57, $p = 0.001$; $I^2 = 98\%$) greater in winter than summer milk.

The sub-group analysis of the effects of dairy-production system on seasonal differences included 427 conventional and 375 organic samples (Fig. 3b). This analysis showed that iodine concentration was significantly higher in winter than summer milk for both organic and conventional samples, but the difference between winter and summer milk was greater in organic milk, at 7.69 μg/100 g (95% CI 4.48 to 10.89, $p < 0.00001$, $I^2 = 67\%$) vs. 3.54 μg/100 g (95% CI 0.84 to 6.23, $p = 0.01$, $I^2 = 83\%$) in conventional milk (Fig. 3b).

A sensitivity analysis showed that heterogeneity was not affected by the removal of one outlier study (Sakai et al., 2022); the I^2 in sub-group analysis changed by 1% only, but the difference between seasons increased from 5.97 to 6.43 μg/100 g overall (95% CI 2.73 to 10.14, $p = 0.0007$; $I^2 = 98\%$). In the sub-group analysis, the difference between seasons in organic milk decreased from 7.69 to 7.18 μg/100 g (95% CI 3.96 to 10.39, $p < 0.0001$; $I^2 = 68\%$) and increased in conventional milk from 3.54 to 4.11 μg/100 g (95% CI 1.66 to 6.56, $p = 0.001$; $I^2 = 82\%$).

3.5. Dairy-production system variation

Variation in milk-iodine concentration associated with dairy-production system was measured in nine countries. Only Norwegian milk had a lower iodine concentration in conventional than organic milk (Nerhus et al., 2018); in Denmark, during winter, milk-iodine concentration was the same across production systems (Rasmussen et al., 2014). In all other countries, milk-iodine concentration was higher in conventional than organic milk.

3.5.1. Meta-analysis

A meta-analysis used data from nine countries with 629 organic and 742 conventional samples (Fig. 4a, 4b). Overall, there was a significant effect of dairy-production system on milk-iodine concentration; the iodine concentration of conventional milk was 6.00 μg/100 g higher than that of organic milk (95% CI 3.64 to 8.37, $p < 0.00001$, $I^2 = 93\%$; Fig. 4a).

The sub-group analysis with season within the dairy-production system included 665 summer and 409 winter samples. The difference in milk-iodine concentration between organic and conventional milk was only significant in the summer – conventional summer milk was 7.71 μg/100 g higher than organic summer milk (95% CI 3.56 to 11.87, $p = 0.003$, $I^2 = 92\%$); there was no significant difference between organic and conventional milk in the winter ($p = 0.10$).

A sensitivity analysis where outliers were removed (Rey-Crespo et al., 2013; Sakai et al., 2022) did not substantially change the findings. The overall difference between conventional and organic milk-iodine concentrations reduced slightly from 6.00 to 5.65 μg/100 g (95% CI 3.26

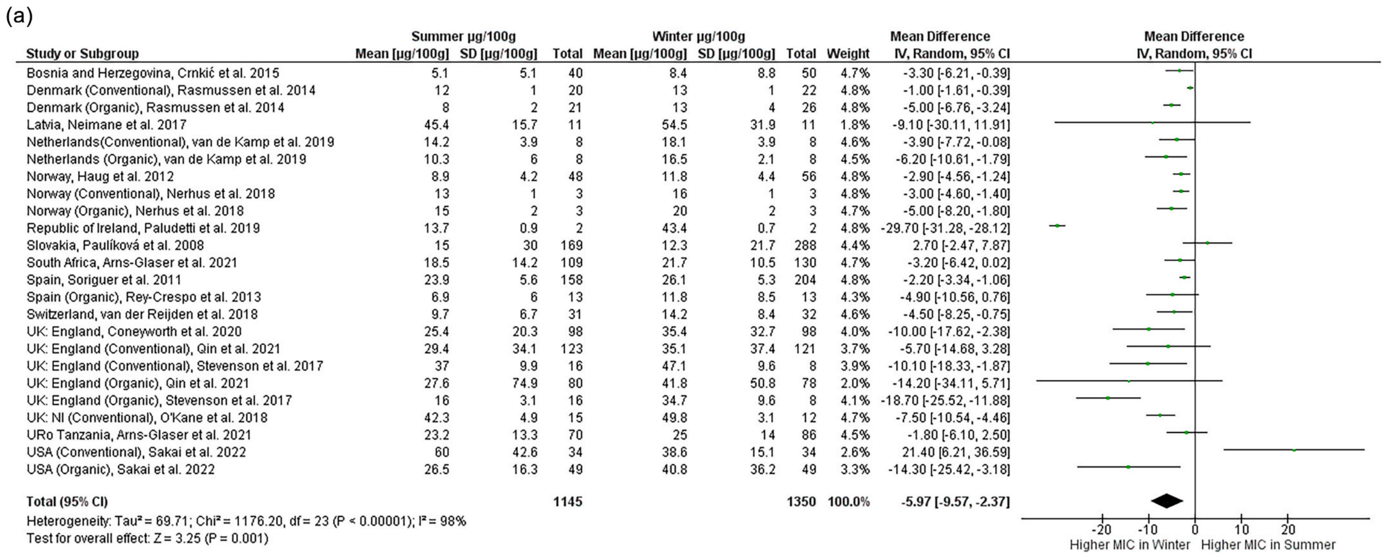

Fig. 3a. Meta-analysis Forest Plot comparing the effect of season (summer vs. winter) on milk-iodine concentration.

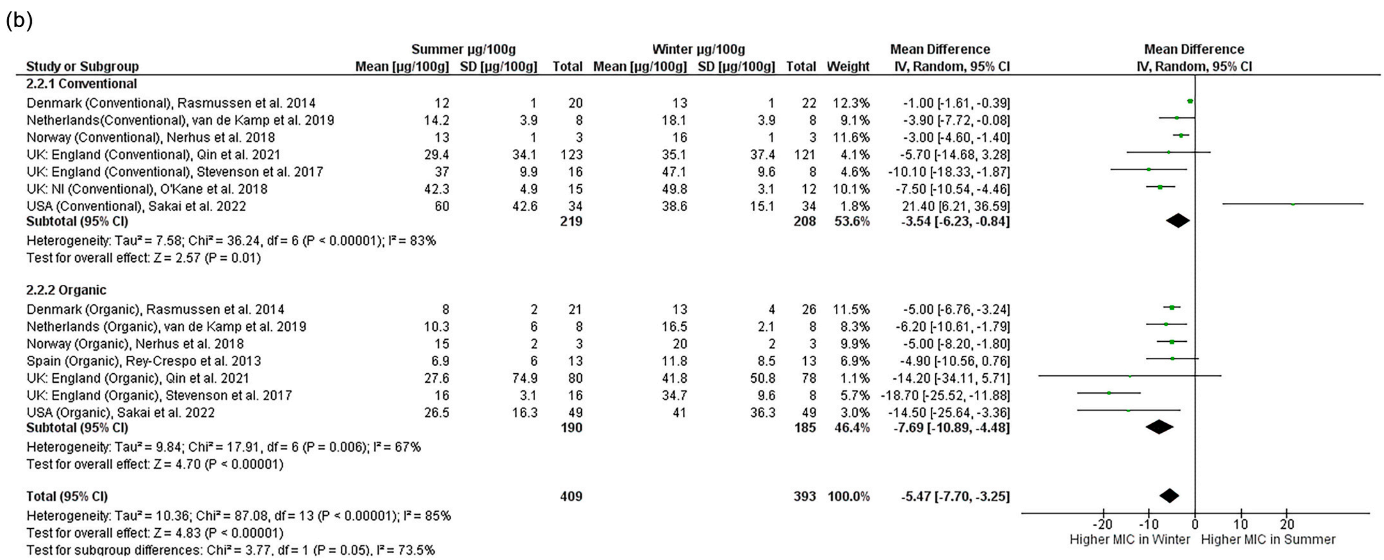

Fig. 3b. Meta-analysis Forest Plot comparing the effect of system of dairy production (organic vs. conventional) within season (summer vs. winter) on milk-iodine concentration.

to 8.04, $p < 0.00001$; $I^2 = 93\%$); in summer, the difference reduced from 7.71 to 6.48 μg/100 g (95% CI 2.24 to 10.72, $p = 0.003$; $I^2 = 93\%$), whilst in winter, the difference increased slightly, from 3.75 to 4.07 μg/100 g (95% CI 0.55 to 8.69, $p = 0.08$; $I^2 = 90\%$), but remained non-significant.

4. Discussion

4.1. Summary of main findings

The findings of this review are discussed in more detail below, but can be summarised as: i) milk-iodine concentration varies around the world – the three countries with the highest seasonal-average milk-iodine concentration were Latvia, Czechia and the UK; ii) winter milk has a significantly higher iodine concentration than summer milk; iii) organic milk has greater seasonal variation in milk-iodine concentration than conventional milk; (iv) the difference between organic and conventional milk-iodine concentration (and therefore the effect of the dairy-production system) is only significant during summer. Although we have data for 34 countries, the ability to compare milk-iodine concentration around the world was limited by the quality of the studies. Indeed, only a fifth of papers were classified as being of "good" quality by our Quality Assessment Tool (QAT) and half the studies were classified as "poor". The use of CRMs, or accredited laboratories, was not reported in 36% of papers, meaning that we were unable to judge the validity of results.

4.2. Variability around the world

Milk-iodine concentration varies around the world, from 5.5 to 49.9 μg/100 g (using seasonal-average values). The amount of iodine provided by a glass (200 g) of milk would vary between 7% and 69% of the adult recommended iodine intake (150 μg/day) (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2014).

The reason for the differences in milk-iodine concentration between countries could not easily be determined from the data collected in this review but there are several possible explanations. It is unlikely that the differences relate to variation in the regulations on the permitted iodine

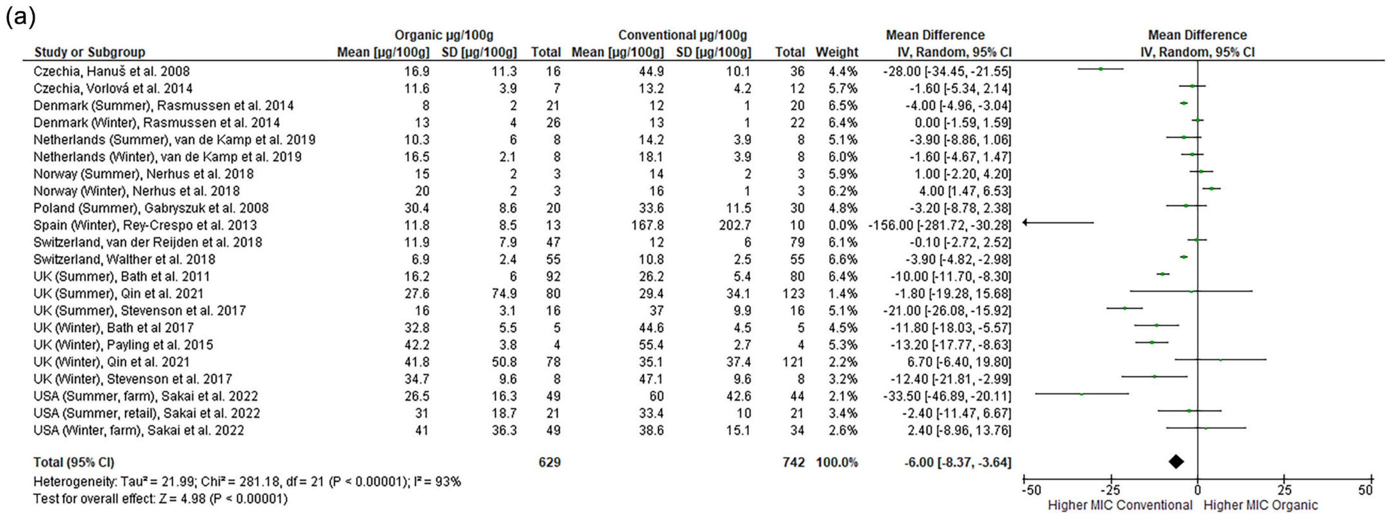

Fig. 4a. Meta-analysis Forest Plot comparing the effect of dairy-production system (organic vs. conventional) on milk-iodine concentration.

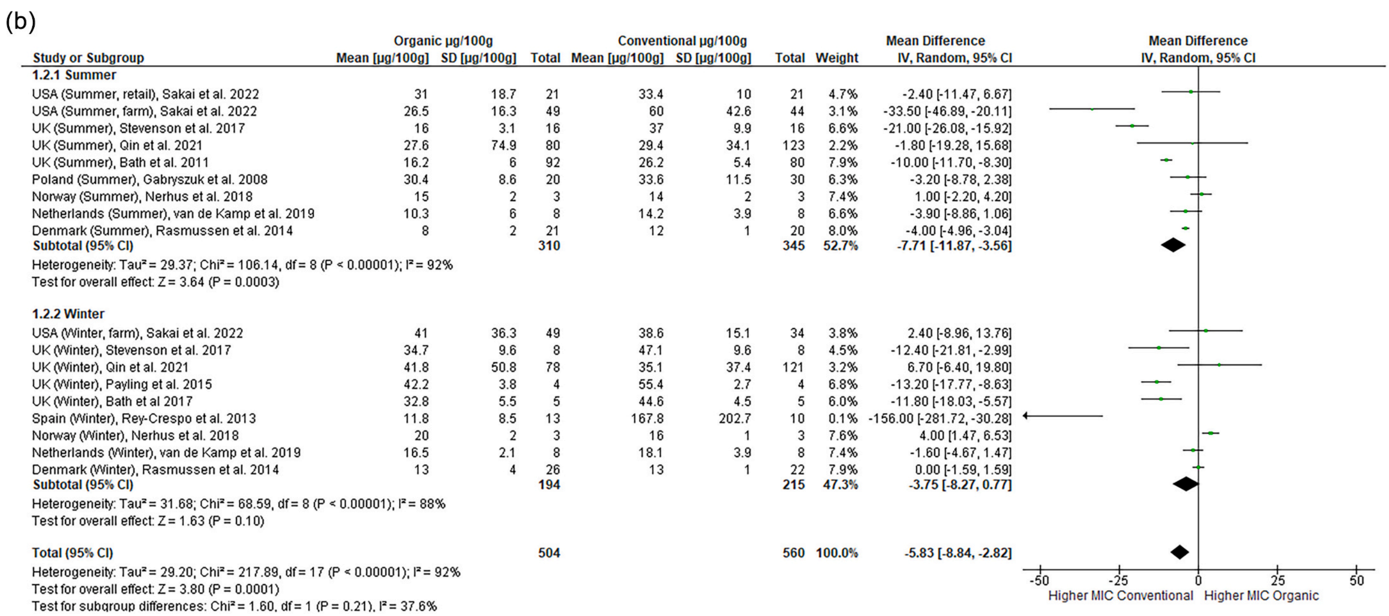

Fig. 4b. Meta-analysis Forest Plot comparing the effect of season (summer vs. winter) within dairy-production system (organic vs. conventional) on milk-iodine concentration.

content of dairy-cattle feed, as our results show that milk-iodine concentration varies even between countries under the same regulations (such as countries under European Commission regulations). Therefore, other farming factors are more likely to explain differences in milk-iodine concentration between countries. This may include between-country differences in the total iodine intake of dairy cows (including the iodine content of soil, water and mineral concentrates), goitrogen consumption, use of iodine-based teat disinfectants, cattle breed and milk yield (Niero et al., 2023; van der Reijden et al., 2018). However, it is also possible that a proportion of the differences in milk-iodine concentration between countries could be explained by the use of different laboratory methods (including inconsistent use of CRMs and therefore questions over method validity), meaning that differences could be an artefact of methodological variability, rather than true differences.

Whether a low iodine concentration in milk may lead to increased risk of iodine deficiency in the population, and therefore be of public-health concern, is a country-specific issue; the impact of low milk-iodine concentration on total iodine intake will depend on the quantity of milk and dairy products consumed, as well as whether there is a salt iodisation policy or other key dietary sources of iodine in a country. For example, although some countries have comparatively low milk-iodine concentration, this does not necessarily correlate with low iodine status. New Zealand is classified as having an adequate iodine status (Iodine Global Network, 2021) although milk-iodine concentration ranks 31st of 34 countries in our review, at a concentration of 9.5 µg/100 g (55% of the worldwide median value of 17.3 µg/100 g). In New Zealand, milk and dairy products contribute only 15–20% of iodine intake (from age 5 years), compared to 40–55% from bread (Ministry for Primary Industries, 2018). This is because since 2009 there has been mandatory fortification of all bread (except organic bread, non-yeast leavened bread and bread mixes) with iodine (Food Standards Australia New Zealand, 2008; Ministry for Primary Industries, 2012) and so milk-iodine concentration is less crucial to iodine status. By contrast, other countries are very reliant on milk and dairy products, especially if iodine-fortification programmes are weak or absent. As an example, in the UK milk and dairy products contribute 32–51% of UK iodine intake for adults and children (Public Health England, 2020) and there is no salt iodisation programme (Bath et al., 2014); UK milk was ranked as 3rd of the 34 countries in this review, and this highlights the reliance on cows' milk for iodine intake and the vulnerability of the UK population iodine status to any changes in milk-iodine concentration.

Of the countries in this systematic review, four are classified as deficient (based on population assessment using urinary iodine concentration): Estonia, Finland, Germany and Norway (Iodine Global Network, 2021). Interestingly, at 12 to 16 μg/100 g, all four of these countries have milk-iodine concentrations below the worldwide median of 17.3 μg/100 g, and considerably below the 22.5 μg/100 g threshold to be considered as a "source" of iodine (European Parliament, 2011). Furthermore, Finland, Germany and Norway have voluntary salt iodisation policies in place (Bath et al., 2022). The three countries with the overall lowest milk-iodine concentration (Slovenia, Slovakia and Bosnia and Herzegovina) have mandatory salt iodisation legislation and are all classified as having adequate iodine status (Iodine Global Network, 2021). Some of these countries are also geographically close together, potentially indicating a locality effect on milk-iodine concentration, such that farming practices and animal feeds may be similar.

4.3. Effect of season

In the meta-analysis we found that the iodine concentration of milk is almost 6 μg/100 g higher in milk produced in winter than in summer; translating this into consumer portions, a glass of winter milk (200 g), would have 12 μg more iodine than a glass of summer milk, which is 8% of the adult recommend intake of iodine (at 150 μg/day) (EFSA Panel on Dietetic Products, Nutrition & Allergies, 2014). The higher iodine in winter milk can be explained by greater use of mineral-supplemented concentrates when dairy cows are housed indoors than in the summer when they graze on pasture (Flachowsky et al., 2014). Pasture grazing is negatively correlated with milk-iodine concentration (Qin et al., 2021; Stergiadis et al., 2021), probably as a result of reduced intakes of concentrate feed alongside the higher exposure of cows to goitrogen-containing fresh forage [such as millet and rape (Borucki Castro et al., 2011)]. A negative correlation has also been noted between milk-iodine concentration and milk yield, with the greatest yield in May and lowest in November; this may indicate that a dilution effect may give a lower concentration of milk-iodine concentration in the summer (Coneyworth et al., 2020).

We found that the seasonal difference was lower in conventional than organic milk (3.54 vs. 7.69 μg/100 g respectively). This is probably a result of a more consistent intake of mineral-fortified concentrates across seasons in conventional farming as some farms may operate year-round indoor housing. Dairy cows on organic farms would also be indoors in the winter but in contrast to conventional farms, would be more likely to be on pasture in the summer months (to align with organic regulations), and would therefore have a greater difference in iodine intake through the year.

Studies in consumers have shown that there are changes in iodine status (as assessed by urinary iodine concentration) by season, with population iodine status found to be lower in summer than winter (McNulty et al., 2017; Vanderpump et al., 2011) and with greater effects seen in individuals consuming larger volumes of cows' milk (Bath et al., 2015). The seasonal difference in consumers' iodine intake could be reduced with more consistent iodine supplementation of grazing cows throughout the year by an adjustment of farming policy.

4.4. Effect of dairy-production system

The meta-analysis showed that overall iodine concentration was higher in conventional milk than in organic milk (by 6 μg/100 g). This may be explained by: (i) the higher pasture intake in organic dairy farms which has variable iodine concentration (Jensen et al., 2019) and is negatively correlated with milk-iodine concentration (Qin et al., 2021; Stergiadis et al., 2021), and (ii) the greater use of white clover in the sward in organic farms for its nitrogen-fixing properties (Bath & Rayman, 2016); some varieties of white clover (*Trifolium repens L.*) are potentially goitrogenic as they contain cyanogenic glucosides that are metabolised to thiocyanate, a competitive inhibitor of iodine for transport into the mammary gland (Crush & Caradus, 1995). Cows' iodine requirements double in the presence of goitrogens, but in practice, farmers may not increase supplementation (Niero et al., 2023).

We found that the effect of dairy-production system was only significant in the summer – in winter there is no significant difference between organic and conventional milk-iodine concentration. This is probably explained by the fact that dairy-farming practices may be similar between organic and conventional farms in the winter i.e., cows are housed indoors and receive conserved forage (silage) and concentrates (Qin et al., 2021). Conserved forage is more likely to contain red clover, fewer varieties of which have goitrogenic properties (Muzashvili et al., 2014), rather than white clover. Even if white clover is used in conserved forage, the goitrogenic effects may be reduced during the ensiling process (Ngwa et al., 2004). In summer, by contrast, organic dairy cows graze on fresh pasture (including clover) that has a higher goitrogenic potential, and any iodine supplementation given to the cows may not be able to overcome the effect of goitrogens in the feed, reducing carry-over of iodine to milk.

It is important to note that although our results show that overall conventional milk has a higher iodine concentration than organic milk, this does not necessarily apply to all countries and may change over time. A more recent UK study (published after the searches for this systematic review) found no overall difference in milk-iodine concentration between organic and conventional retail milk in 2019 (Newton et al., 2023), and the same has been observed from milk collected at farm-level in the same year (Qin et al., 2021). This aligns with information from a press release from the UK Organic Milk Suppliers Cooperative highlighting their project to increase the iodine content of organic milk (therefore reducing the difference with conventional milk) by working with feed mills and dairy farmers from 2014 (Organic Milk Suppliers Cooperative, 2017). As both UK studies using 2019 milk (Newton et al., 2023; Qin et al., 2021) found that the largest difference between organic and conventional milk-iodine concentration was in the summer months (supporting the results of our meta-analysis), further work is needed to understand the influence of season on dairy-production system.

4.5. Milk-iodine concentration to be labelled as a "source" of iodine

In our review, eight countries (with seasonal-average values only) have milk-iodine concentration of at least 22.5 μg/100 g and therefore meet the threshold to be labelled as a "source" of iodine (European Parliament, 2011); those countries are Austria, Croatia, Czechia, Latvia, Republic of Ireland, UK, United Republic of Tanzania and the USA (Arns-Glaser et al., 2022; Dold et al., 2018; Hanuš et al., 2008; Neimane et al., 2017; Sager, 2018; Sakai et al., 2022; Stevenson et al., 2018). There are a further three countries with milk-iodine concentration in summer milk that is above 22.5 μg/100 g [Italy, Canada and Japan (Borucki Castro et al., 2011; Guruge et al., 2011; Niero et al., 2019)], and therefore it is likely that seasonal-average milk in those countries would also be above the threshold to be labelled as a "source" (as our meta-analysis suggests that summer values would be the lowest). It is important to note that the threshold for labelling is based on the adult requirement for iodine, and therefore milk may still be an important source of iodine for children in countries where milk-iodine concentration does not meet the labelling threshold.

Both seasonal variation and dairy-production system can affect whether milk-iodine concentration meets the threshold of 22.5 μg/100 g. Our results show that there are some regions in which winter milk could be labelled as a "source" of iodine, but summer milk could not, as seen in the Republic of Ireland where milk-iodine concentration was

43.4 μg/100 g in winter and 13.7 μg/100 g in summer (European Parliament, 2011; Paludetti et al., 2019). Considering dairy-production system, results from Czechia indicate that conventional milk exceeds the 22.5 μg/100 g threshold whilst organic milk does not, at 44.9 and 16.9 μg/100 g, respectively (Hanuš et al., 2008).

The labelling threshold is also relevant in the context of the iodine content of plant-based milk alternatives. Unfortified milk alternatives are naturally low in iodine (median 0.73 μg/100 g) (Bath et al., 2017) and studies show that if these products are fortified, it is mostly at a concentration of 22.5 μg/100 g, i.e. the labelling threshold (European Parliament, 2011; Nicol et al., 2023). However, the proportion of plant-based milk alternatives which are iodine-fortified has been found to be relatively low [e.g. 20% in the UK in 2020 (Nicol et al., 2023)]. Our results show that for some countries, including the UK, Czechia and Latvia, iodine-fortified milk-alternatives (at 22.5 μg/100 g) would provide less iodine than the cows' milk in those countries; hence replacing cows' milk with these products might result in lower iodine intake and a potentially increased risk of deficiency, especially in countries where a high proportion of iodine intake is from milk. Conversely, in countries such as France, Denmark and Germany, plant-based milk alternatives fortified at 22.5 μg/100 g would provide a richer source of iodine than the countries' cows' milk.

4.6. Limitations

Some information, such as laboratory method (and CRM use), sample-collection year, dairy-production method and season was not available or varied between studies, such that results may not be directly comparable. Where sample collection year was unspecified, the studies were included although this reduced their quality assessment score and so were less likely to be selected as a final value. This does, however, mean that some values based on samples collected earlier than 2006 might still have been included. In addition, retrieved papers were filtered to include those only published in English; papers that potentially contained useful data in other languages were therefore excluded. Furthermore, some food composition tables reported milk-iodine data from other countries; for example the value in the Estonian food composition table is based on data from Finland, and therefore it is unknown if the value is representative of milk consumed in Estonia. Finally, although single values have been selected to represent a country, the number of areas sampled varies between studies. It could therefore be argued that the value is only relevant to the specific area(s) sampled; for example, the paper representing the USA took samples from two Northeast dairies (Sakai et al., 2022), whilst samples from 14 jurisdictions were analysed in the paper representing Japan (Guruge et al., 2011).

4.7. Implications for future research and policy

Currently, there is no programme in place to routinely monitor milk-iodine concentrations around the world hence there were differences in the methodologies and age of the samples in the studies used in this review. Ideally, uniform studies with consistent use of CRMs should take place around the world at regular intervals (e.g., every five years), to monitor milk-iodine concentration in organic and conventional milk across seasons, particularly in countries that rely on milk as an important iodine source.

This systematic review has shown that there is seasonal variation in milk-iodine concentration, and this may translate to seasonal variation in iodine intake and therefore status (i.e. urinary-iodine concentration). When assessing dietary intake of iodine (e.g. from food diaries), season-specific values for milk-iodine concentration should be used. It is also important to consider seasonal variation when planning national monitoring programmes to ensure either year-round urine sampling or appropriate interpretation if urinary iodine measurements are based on a single season.

Farming practice could be modified to increase milk-iodine concentration in production systems (i.e. organic) and during seasons (i.e. summer) where milk iodine content is known to be lower; this may increase iodine status, where necessary, and reduce the risk of iodine deficiency disorders at a population level. For example, increasing iodine supplementation of the dairy-cow diet during the grazing periods may help to standardise milk-iodine concentration through the year, especially in organic-milk production where seasonal variation was found to be greatest. Appropriate supplementation levels are required to counteract the potential increased goitrogen intake of dairy cows e.g. from white clover, though further research on the goitrogenic potential of feed is required. Any change in farming practice would require customisation on a country-by-country basis and would need to take into account other iodine food-fortification policies, and other sources of iodine in the diet (e.g. fish and eggs).

In addition, given the emphasis of global and national dietary guidance on reducing intake of milk and dairy products for reasons of environmental sustainability (Committee on Climate Change, 2020; Willett et al., 2019), policymakers need to consider the effect on population iodine intake and status, especially in countries where milk-iodine concentration is high (Nicol et al., 2024). Given the rising popularity of plant-based alternatives, information collated in this systematic review could be used by industry to help guide bespoke, country-specific, fortification of plant-based milk alternatives, enabling such products to mirror the iodine concentration of cows' milk from that country; this may help to minimise the risk of reduced iodine intake in consumers who switch to plant-based alternatives from cows' milk.

5. Conclusions

This review has identified a high variation in milk-iodine concentration due to geographical location (country-based differences), production system (with conventional milk containing more iodine in most, but not all, countries when compared with organic milk) and season (with winter milk containing more iodine than summer milk). Most of these differences are probably due to different farming practices, and in particular to variation in the cows' diet, including pasture intake, forage-to-concentrate ratio, and consumption of goitrogenic components in feeds (fresh white clover, rapeseed cake). Variation in milk-iodine content can have implications for iodine intake and status of consumers, especially those at higher risk of iodine deficiency (female adolescents, pregnant women, nursing mothers). Furthermore, good-quality data on milk-iodine concentration is required in many countries around the world.

CRediT authorship contribution statement

Joanne K. Tattersall: Formal analysis, Writing – original draft, Methodology. **Manishka S. Peiris:** Methodology. **Maika Arai:** Methodology. **Katherine McCully:** Methodology. **Neeve Pearce:** Methodology. **Margaret P. Rayman:** Writing – review & editing. **Sokratis Stergiadis:** Writing – review & editing, Supervision, Methodology. **Sarah C. Bath:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Joanne K. Tattersall reports financial support was provided by Biotechnology and Biological Sciences Research Council (BBSRC). Sarah C. Bath reports a relationship with Oatly that includes: speaking and lecture fees. Sarah C. Bath reports a relationship with Dairy UK that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodchem.2024.140388.

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