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# *Invited review:* Iodine level in dairy products—A feed-to-fork overview

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## ABSTRACT

The theme of iodine in the dairy sector is of particular interest due to the involvement and the interconnection of several stakeholders along the dairy food chain. Iodine plays a fundamental role in animal nutrition and physiology, and in cattle it is an essential micronutrient during lactation and for fetal development and the calf's growth. Its correct use in food supplementation is crucial to guarantee the animal's recommended daily requirement to avoid excess intake and long-term toxicity. Milk iodine is fundamental for public health, being one of the major sources of iodine in Mediterranean and Western diets. Public authorities and the scientific community have made great efforts to address how and to what extent different drivers may affect milk iodine concentration. The scientific literature concurs that the amount of iodine administered through animal feed and mineral supplements is the most important factor affecting its concentration in milk of most common dairy species. Additionally, farming practices related to milking (e.g., use of iodized teat sanitizers), herd management (e.g., pasture vs. confinement), and other environmental factors (e.g., seasonality) have been identified as sources of variation of milk iodine concentration. Overall, the aim of this review is to provide a multilevel overview on the mechanisms that contribute to the iodine concentration of milk and dairy products.
**Key words:** consumer health, dairy industry, farming, iodine, milk

## INTRODUCTION

The milk matrix contains mineral elements of great importance in terms of quality and quantity. Calcium, potassium, magnesium, sodium, and phosphorus are the major minerals, present at relatively high concentration (Cashman, 2006). For decades, these milk components have been studied for their relevance at both nutritional and manufacturing levels. On the other hand, iodine is one of the trace elements of milk and therefore present in low amounts (Cashman, 2006). In addition to iodized salt and seafood, milk and dairy products are the main source of iodine in the human diet (Herrick et al., 2018; Censi et al., 2020). This mineral is fundamental to maintain the functionality of the thyroid gland and to sustain physiologic and metabolic processes regulated by thyroid hormones; thus, iodine intake and availability are important for human health to ensure certain physiological functions. Proper iodine supplementation strategies in dairy species can guarantee animal health, together with the consumer's iodine prophylaxis.

Iodine level in milk is affected by numerous factors along the entire dairy food chain, on a feed-to-fork perspective. The main driver is the level of iodine in the feed administered to lactating animals, which has been demonstrated to be linearly associated with the final milk iodine concentration. Such a relationship is well documented in literature (Moschini et al., 2010; Weiss et al., 2015; Antaya et al., 2019), even if the dose-response effect is far from being standardized due to several hurdles, including high analytical costs for the determination of this mineral in feed and milk, and the presence of iodine antagonists in several ingredients included in the animals' rations (Bath and Rayman, 2016). Some of the factors potentially influencing the milk iodine content, such as season and farming system, can be largely traced back to the effect of diet composition (Nerhus et al., 2018; Stevenson et al., 2018). The adoption of

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iodized teat sanitizers has been identified as a further factor able to increase milk iodine concentration. This happens due to the presence of disinfectant in the teat canal after postdipping and to the local absorption of iodine at the epithelial level, followed by a release of this mineral into the secreted milk (French et al., 2016). The scientific literature demonstrates that milk iodine concentration also has a genetic component in cattle, meaning that there is genetic variability for this trait as the populations diverge in terms of estimated breeding value for milk iodine concentration (Denholm et al., 2019; Costa et al., 2021). Different studies have described the importance of milk and dairy products in respect to iodine prophylaxis in humans (Herrick et al., 2018; Censi et al., 2020).

In this scenario, the aim of this review is to update the scientific community on the latest findings concerning (1) the most recent recommendations in terms of iodine requirements and adequate intake in dairy cows; (2) the major factors affecting the variability of iodine in milk and dairy products—namely, animal feeding, farm management, and processing at the dairy industry level; (3) the key role of iodine in human nutrition and health. The importance of milk and dairy foods as sources of iodine in humans perceived by the scientific community was also investigated through a posteriori analysis of bibliographic data.

## REVIEW METHODOLOGY

Papers included in this review article were retrieved from different databases, including Scopus (www.scopus.com), ISI Web of Science (www.webofknowledge.com), and Google Scholar (www.scholar.google.com), for the period between January 2010 and December 2021. However, previous relevant papers dealing with historical information, pilot research, regulations, and important knowledge related to the topic of the current review were also included. Therefore, the actual proportion of the papers published before 2010 is about the 16% of the total cited articles considered in the present review. Key words used in the literature search were "bovine," "cattle," "cheese," "cheese making," "dairy," "dairy cows," "dairy products," "diet," "farm," "feed," "food," "fortification," "goiter," "health," "integration," "intake," "iodine," "metabolism," "milk," "mineral," "requirement," "salt," "species," "supplementation," and "thyroid." Appropriate combinations of the aforementioned key words were also searched. Table 1 displays the descriptive information of the reviewed literature, such as (1) the country where the trials were conducted; (2) the food, feed, or biological substrates analyzed for iodine concentration; (3) the species (and the breed) of animals involved in the study; (4) the number of herds; and (5) the analytical methods used for quantification. The studies were conducted in 14 countries, with Italy (8 papers) and the United States (6 papers) ranking first in the number of publications. Few studies considered species other than bovine and breeds other than Holstein. The most common analytical method for determination of iodine concentration was the inductively coupled plasma mass spectrometry (24 papers), which is indeed considered the reference method for several minerals including iodine. Only a few papers used alternative analytical approaches (9 papers), including direct quantification methods (ion exchange chromatography), indirect quantification methods (colorimetric assays and enzyme-linked immunosorbent assays), and predictive methods (mid-infrared spectroscopy).

## ANIMAL PHYSIOLOGY AND NUTRITION

### *Iodine in Cattle Physiology*

According to the US National Academies of Sciences, Engineering, and Medicine (NASEM, 2021), iodine is the principal constituent of thyroid hormones, including thyroxine (**T4**) and triiodothyronine (**T3**). Iodine is mostly present in the thyroid gland, which stores about 80% of the total iodine circulating in the organism. Secretion of thyroid hormones is regulated by other hormones: thyrotropin-releasing hormone, formed by the hypothalamus, activates the anterior pituitary gland for the release of thyroid-stimulating hormone, which in turn induces T4 formation from thyroglobulin and T4 release (Meschy, 2010). A negative feedback mechanism is in charge of regulating formation of T4 and T3. In cattle, the main site of absorption of this element is the rumen, from where it is transported in the organism through specific binding with plasma proteins (Meschy, 2010).

The impact of different iodine levels on cows' health and performance and identification of requirements have been investigated by administration of iodine-deficient diets. A compendium of symptoms related to iodine deficiency in dairy cattle has been summarized by Anderson et al. (2007), who monitored 12 farms located in the Manawatu District (New Zealand). High iodine intake also causes goiter, which translates into an augmented production of thyroid-stimulating hormone produced by the pituitary gland. Other than visible goiter formation, clinical signs of deficit include silent estrus, low first service conception rate, and stillbirths, all associated with subphysiological T4 concentrations in blood (<45 nmol/L; Anderson et al., 2007). On the other hand, Iannaccone et al. (2019) reported a better immunological activation in dairy cattle receiving short-term feed iodine administration, as milk SCC

**Table 1.** Reviewed studies on iodine concentration in animal feed, milk, dairy products, and other biological matrices from 2010 to 2021[1]

| Reference | Country[2] | Matrix | Species (breed)[3] | Herds,[4] n | Analytical method[5] |
|---|---|---|---|---|---|
| Moschini et al. (2010) | ITA | Feed, raw milk, cheese | Cow (HO) | 1 | ICP-MS |
| Borucki Castro et al. (2011) | CA | Feed, raw milk | Cow | 60 | ICP-MS |
| Borucki Castro et al. (2012) | CA | Feed, raw milk | Cow (HO) | 1 | ICP-MS |
| Conneely et al. (2014) | IRE | Feed, raw milk | Cow (HO, CR) | 1 | IE chromatography |
| Antaya et al. (2015) | USA | Feed, raw milk | Cow (JE) | 1 | ICP-MS |
| Nazeri et al. (2015) | IRN | Feed, raw milk | Cow (HO) | 1 | Colorimetric |
| Weiss et al. (2015) | USA | Feed, raw milk, serum | Cow | 1 | Colorimetric |
| Bath and Rayman (2016) | GB | Feed, raw milk | Cow | NA | — |
| Chaves Lopez et al. (2016) | ITA | Feed, raw milk | Cow (HO) | 1 | ICP-MS |
| da Silva et al. (2016) | BRA | Whey protein isolates | Cow | NA | ICP-MS |
| French et al. (2016) | USA | Raw milk | Cow (HO, CR) | 1 | ICP-MS |
| Sorge et al. (2016) | USA | Feed, raw milk, serum, tears | Cow (HO) | 1 | — |
| Nerhus et al. (2018) | NOR | Retail milk, dairy products | Cow and goat | NA | ICP-MS |
| O'Kane et al. (2018) | GB | Retail milk | Cow | NA | ICP-MS |
| Ovadia et al. (2018) | ISR | Raw milk | Goat | 1 | ICP-MS |
| Stevenson et al. (2018) | GB | Retail milk | Cow | NA | ICP-MS |
| van der Reijden et al. (2018) | CH, ITA | Raw milk | Cow (BS, HO, SI, ARP) | 32 | ICP-MS |
| Walther et al. (2018) | CH | Raw milk, retail milk | Cow | NA | ICP-MS |
| Antaya et al. (2019) | USA | Feed, raw milk | Cow (JE) | 1 | ICP-MS |
| Denholm et al. (2019) | GB | Raw milk | Cow (HO) | 1 | ICP-MS |
| Iannaccone et al. (2019) | ITA | Feed, raw milk | Cow (HO) | 22 | ICP-MS |
| Konečný et al. (2019) | CZ | Raw milk | Cow | 78 | ICP-MS |
| Niero et al. (2019) | ITA | Raw milk, retail milk | Buffalo, cow, donkey, goat, sheep | NA | ICP-MS |
| van de Kamp et al. (2019) | NED | Retail milk | Cow | NA | ICP-MS |
| van der Reijden et al. (2019) | CH, ITA | Feed, raw milk, cheeses | Cow (HO, ARP) | 1 | ICP-MS |
| Arrizabalaga et al. (2020) | SP | Retail milk | Cow | NA | HPLC |
| Coneyworth et al. (2020) | GB | Feed, raw milk | Cow | 99 | ICP-MS |
| McKernan et al. (2020) | IRE | Soil, feed, raw milk | Cow | 185 | ICP-MS |
| Miseikiene et al. (2020) | LT | Raw milk | Cow | 5 | ICP-AES |
| Niero et al. (2020) | ITA | Raw milk | Cow (HO) | 4 | ICP-MS |
| Roseland et al. (2020) | USA | Retail milk | Cow | NA | ICP-MS |
| Costa et al. (2021) | ITA | Raw milk | Cow (HO) | 221 | MIRS |
| Rezaei Ahvanooei et al. (2021) | IRN | Feed, raw milk, serum, urine | Cow (HO) | 1 | ELISA |

[1] References are listed by year of publication and, within year, by first author surname.

[2] BRA = Brazil; CA = Canada; CH = Switzerland; CZ = Czech Republic; GB = United Kingdom; IRE = Ireland; IRN = Iran; ISR = Israel; ITA = Italy; LT = Lithuania; NED = the Netherlands; NOR = Norway; SP = Spain; USA = United States of America.

[3] ARP = Aosta Red Pied; BS = Brown Swiss; CR = crossbreed; HO = Holstein; JE = Jersey; SI = Simmental.

[4] NA = not available.

[5] ICP-AES = inductively coupled plasma atomic emission spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; IE = ion exchange; MIRS = mid-infrared spectroscopy.

was significantly lower in iodine than control cows under bacterial infection. Through RNA sequencing, these authors demonstrated that 525 genes related to immune response and oxidative stress were differently expressed in the 2 groups.

There is no consensus on the effect of iodine supplementation on the productivity of dairy cows, and a favorable effect has been defined as "largely anecdotal" (Cook and Green, 2010). In the study of Shand (1952), dietary iodine deficiency was claimed to be the factor responsible for a reduced milk production, whereas Iannaccone et al. (2019) did not find differences in milk yield when administering 2 different iodine doses (20 and 85 mg/d). However, both the tested doses exceeded the minimum recommended intake (Iannaccone et al., 2019), making iodine a nonlimiting factor in this case. At the same time, this suggests that extra supplementations—above the minimum recommended value—do not increase milk production. Similar conclusions were drawn from an older study conducted on grazing cows by Grace and Waghorn (2005). In their trial, feed iodine concentration had a low range of variation, with an average of 0.24 mg/kg DM, and cows subjected to multiple iodine injections at 100-d intervals did not present changes in their productivity. In particular, milk yield did not significantly differ between control (3,976 L/lactation) and iodine-supplemented animals (3,923 L/lactation). On the other hand, injections were able to increase the milk iodine concentration, from the basal level of <20 μg/L before treatment to a concentration 3 to 10 times greater, 98 and 55 d after the treatment, respectively (Grace and Waghorn, 2005).

The review of Hidiroglou (1979) summarized several experiments aimed at evaluating health problems due to deficiency of major and trace minerals in ruminants. As in humans and other mammals, iodine deficiency is reported to negatively affect cows' reproductive performance. In fact, fertility disorders are secondary manifestations of thyroid dysfunctions and include anestrus or irregular estrus, retained placenta, abortion, and stillbirth. The administration of iodine-poor diets to dairy cows results in reversible anovulatory estrus and cystic ovaries, whereas thyroidectomized heifers demonstrate irregular estrus. Due to the impaired fetal thyroid functions, cows deficient in iodine during pregnancy are prone to abort (Hidiroglou, 1979).

With regard to the young stock, the beneficial effect of iodine supplementation in calves has been described by several authors. Guyot et al. (2011) demonstrated that there is a long-term effect of iodine deficiency observable in calves born from dams subjected to different levels of supplementations below the recommended allowance of 0.5 mg/kg DM. In particular, 2 different levels of supplementation, low (0.45 mg/kg iodine and 0.15 mg/kg selenium) and high (5.45 mg/kg iodine and 0.45 mg/kg selenium), were evaluated for a period of 120 d on open cows, pregnant cows, and their calves. In the group receiving the high level of supplementation, the nutritional markers related to either iodine (iodine concentration in plasma, urine, colostrum, and fetal fluids) or selenium (selenium concentration in plasma) improved in both dams and calves.

In a field trial, Gamsjäger et al. (2020) studied the efficacy of the therapeutic oral administration of sodium iodide (20 mg/kg DM) in preventing respiratory disease in preweaned dairy calves. Although such an administration led to a greater concentration of iodine in both serum and nasal fluid of calves, it was not effective in preventing the occurrence of bovine respiratory diseases (Gamsjäger et al., 2020). In calves, goiter (diagnosed as diffuse thyroid hyperplasia and significantly increased thyroid size and weight) was observed in 16% of the 44 stillborn calves retrieved from a pool of New Zealand dairy farms suspected of being iodine deficient (Anderson et al., 2007). In that study, the aim was to define potential and useful indicators to monitor the iodine status at herd level in field conditions. Results demonstrated that calves suffering from iodine deficiency were characterized by thyroid hyperplasia and by suboptimal serum T4 concentrations (80 nmol/L). Adult cows sampled within the study of Anderson et al. (2007) presented an average T4 plasma concentration of 42.8 nmol/L, which is below the physiological threshold of 45 nmol/L (Anderson et al., 2007).

## Iodine in Animal Nutrition

Scant and dated information is available to determine the average iodine requirement of cattle, and adequate intakes rather than actual requirements are usually provided (NASEM, 2021). Given this, the term "adequate intake" is adopted throughout this review for consistency.

According to the recent guidelines reported in NASEM (2021), for the maintenance purposes of dairy cows, the adequate intake of iodine can be calculated as follows:

$$\text{Adequate intake, mg/d} = (0.216 \times \text{BW}^{0.528}) + (0.1 \times \text{MY}),$$

where BW is the animal body weight (kg) and MY is the daily milk yield (kg/d). The calculation is valid for all categories of cattle (lactating and nonlactating), calves excluded, with MY assuming a value of 0 for nonlactating cows. The adequate intake for calves, as still functionally nonruminating animals, is estimated on the basis of the requirements for human infants as 0.8 mg of iodine per kilogram of DMI (NASEM, 2021).

Even if the diet is apparently balanced in terms of minerals and the intake of iodine seems adequate, the real amount of iodine absorbed may not be. In fact, the amount of iodine absorbed is "overestimated" in the presence of goitrogens such as canola meal. Goitrogens are organic compounds that interfere with the synthesis and secretion of thyroid hormones either by hampering iodine transport across the thyroid cell membrane (and ultimately reducing iodine retention) or by inhibiting thyroperoxidase (and ultimately preventing the biosynthesis of monoiodotyrosine and diiodotyrosine). It has been reported that diets with canola meal decreased transfer of iodine into milk by 50% (NASEM, 2021). Assuming that the synthesis of thyroid hormones is decreased to a similar extent, the adequate intake would be twice that previously estimated (NASEM, 2021). Given a typical dry cow (700 kg BW; 13.5 kg DMI) and lactating cow (650 kg BW; 35 kg/d MY; 21 kg DMI), such cattle categories would need to be fed, respectively, with 0.51 and 0.48 mg of iodine per kg DM in the presence of goitrogen-free diets (NASEM, 2021). Such values become 1.02 and 0.96 mg/kg DM, respectively, if goitrogenic compounds are also included (NASEM, 2021).

**Table 2.** Average iodine concentration of baleage, concentrates, hay, mineral supplements, silages, and TMR (mg/kg of DM)

| Feed ingredient | References | Mean | SD |
|---|---|---|---|
| Baleage | | | |
| Grass | Antaya et al. (2015), Schöne et al. (2017), van der Reijden et al. (2018), Antaya et al. (2019) | 0.29 | 0.15 |
| Legume | Antaya et al. (2015) | 0.20 | — |
| Concentrate | Antaya et al. (2015), Chaves Lopez et al. (2016), van der Reijden et al. (2018), Antaya et al. (2019) | 1.95 | 1.09 |
| Hay | Borucki Castro et al. (2011), van der Reijden et al. (2018) | 0.11 | 0.04 |
| Mineral supplement | | | |
| *Ascophyllum nodosum* meal | Antaya et al. (2015), Sorge et al. (2016), Antaya et al. (2019) | 763.67 | 49.52 |
| Mineral premix | van der Reijden et al. (2018), Rezaei Ahvanooei et al. (2021) | 81.50 | 26.16 |
| Silage | | | |
| Corn | Borucki Castro et al. (2011), Schöne et al. (2017), van der Reijden et al. (2018) | 0.10 | 0.04 |
| Grass | van der Reijden et al. (2018) | 0.10 | — |
| Mixed | Borucki Castro et al. (2011), McKernan et al. (2020) | 0.25 | 0.12 |
| Sugar beet | van der Reijden et al. (2018) | 0.21 | — |
| TMR | Moschini et al. (2010), Conneely et al. (2014), Antaya et al. (2015), Chaves Lopez et al. (2016), French et al. (2016), Sorge et al. (2016), Antaya et al. (2019), Iannaccone et al. (2019), Rezaei Ahvanooei et al. (2021) | 1.27 | 0.64 |

## ANIMAL FEEDING, MANAGEMENT, AND GENETICS

### Iodine Concentration in Animal Feeds

Table 2 summarizes the average iodine concentration of baleage, concentrates, hay, mineral supplements, silages, and TMR based on data retrieved from the literature. As expected, mineral supplements had the greatest iodine concentration, with *Ascophillum nodosum* meal and mineral premix accounting for 763.67 and 81.50 mg of iodine per kilogram of DM, respectively. Concentrates exhibited an average concentration of 1.95 mg of iodine per kilogram of DM. Still, it is worth noting that concentrates were characterized by a relatively high iodine variability, being the standard deviation equal to 1.09 mg of iodine per kilogram of DM and the coefficient of variation 56%. This indicates that we are far from a standardization of this mineral in complex matrixes like concentrates. Iodine concentration in TMR averaged 1.27 mg/kg DM, which is greater than the recommended concentration of about 0.5 mg/kg DM (NASEM, 2021), but far below the upper tolerable limit (5 mg/kg DM; EU, 2005). Similarly, wide standard deviation (0.64 mg/kg DM) and large coefficient of variation (51%) are reported for iodine concentration. Overall, this may be attributed to different types and levels of supplementations, which in turn are related to different nutritional requirements of cattle categories, specific feeding programs, and different farm management practices. Grass and legume baleage were characterized by relatively low iodine concentration, averaging 0.29 and 0.20 mg/kg DM, respectively. Similar iodine concentrations were observed for mixed silages and sugar beet silages, averaging 0.25 and 0.21 mg/kg DM, respectively. Among the considered feed ingredients, hay, corn silage, and grass silage present the lowest iodine concentration per kilogram of DM (Table 2).

### Iodine Supplementation

Iodine content of feed ingredients reflects the passive uptake of crops and vegetables from soil and water. This, however, is generally not sufficient to cover the adequate intake of a dairy cow, and inclusion of iodine supplements in the diet is fundamental to fulfill the adequate intake and support body maintenance, milk production, and fetal development. Type and amount of iodine supplementation in the daily ration is the major source of variation of milk iodine. In fact, the correlation between iodine supplementation and milk iodine concentration portrayed (Figure 1A) is linear and is characterized by different dose-response effects, as demonstrated by the slopes (Figure 1B). Regressions obtained from single studies, together with Figure 1A and 1B, are intended to facilitate the comparison between different trials and to present the response dose effect and the recovery rate of iodine from feed to milk in a synthetic manner. The linear regression obtained using all the data from the considered studies (Figure 1C) allows one to infer milk iodine concentration in the presence of a known feed iodine concentration.

Weiss et al. (2015) studied the effect of 2 levels of iodine supplementation (i.e., 0.59 and 1.34 mg/kg DM) on midlactation Holstein cows by administering ethylenediamine dihydroiodide. Results showed a sharp increase in milk iodine level (from 358 to 733 μg/L) and an average milk iodine recovery of 85%. The linear regression calculated using the data points provided by Weiss et al. (2015) is

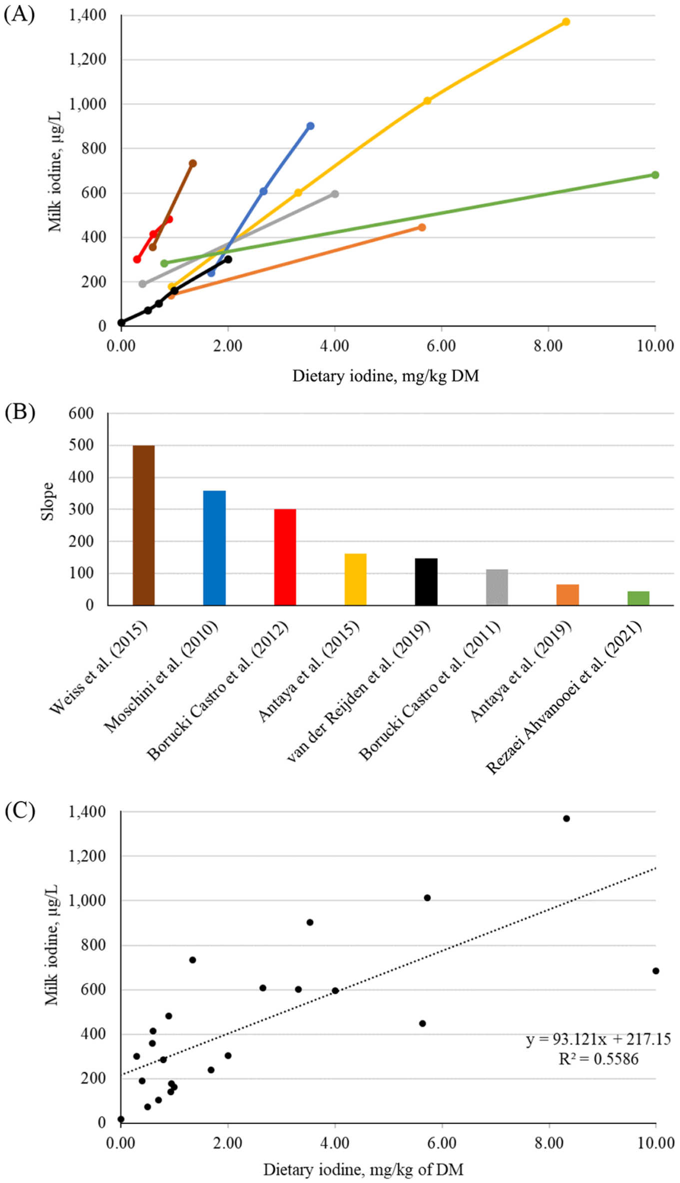

**Figure 1.** (A) Relationship between dietary and milk iodine concentration calculated for the different studies; (B) slope of each line; and (C) overall regression based on all the data points given in panel A. Further details on the iodine sources fed in each study and the iodine levels of the diet are reported in the "Iodine Supplementation" section. Each colored line in panel A corresponds to a published article labeled in panel B. The equation for overall regression is reported together with its coefficient of determination ($R^2$).

$$y = 500x + 63,$$

where y is the iodine concentration in milk (µg/L) and x is the iodine concentration in the diet (mg/kg DM). The slope of the linear regression indicates that an increase in iodine per kilogram of DM (1 mg) is proportional to an increase of 500 µg of iodine per liter of milk. This is the greatest dose-response rate observed in literature; however, the regression was estimated using just 2 test points with a relatively narrow range of variation of iodine concentration in the feed (0.75 mg/kg DM). A similar regression can be calculated using data provided by Moschini et al. (2010):

$$y = 359x - 360.$$

These authors considered 3 levels of feed iodine supplementation (1.69, 2.66, and 3.54 mg/kg DM) administered by adding water fortified with inorganic iodine to the ration. Still, this equation has to be interpreted with caution due to the great intercept of the model and the limited number of animals (n = 4) per treatment. Results reveal a relatively low transfer in milk (23%), which indicates that there is a certain inefficiency when water is used as a carrier. In a controlled study, Borucki Castro et al. (2012) observed an average iodine recovery of 88% in Holstein cows. The same authors reported increasing levels of milk iodine (301, 414, and 482 µg/L) as a direct effect of increased integration of iodine-rich feed (0.3, 0.6, and 0.9 mg/kg DM, respectively) by the introduction of vitamin and mineral mixes. That relationship can be modeled as

$$y = 301x + 218.$$

Considering the very narrow range of supplementation doses (Borucki Castro et al., 2012) and the great intercept of the model, this equation should be used prudently. On the other hand, data provided by Antaya et al. (2015) were obtained on a wide range of iodine supplementation doses (i.e., from 0.95 to 8.33 mg/kg DM), achieved through the addition of *Ascophyllum nodosum* meal. In particular, Antaya et al. (2015) tested different levels of iodine supplementation: 2 below the tolerable limit of 5 mg/kg of DM (0.95 and 3.32 mg/kg DM) and 2 exceeding that limit (5.73 and 8.33 mg/kg DM). Their results can be modeled as

$$y = 162x + 47.$$

Overall, Antaya et al. (2015) observed a very low recovery rate (16%) in terms of the ratio between milk and feed iodine concentration. A similar regression and average recovery rate (23%) can be calculated starting from the data of van der Reijden et al. (2019), who tested 5 levels of iodine supplementation (0, 0.5, 0.7, 1, and 2 mg of iodine/kg DM):

$$y = 145x + 9.$$

Given the relationships just described (Antaya et al., 2015; van der Reijden et al., 2019), it can be estimated that milk iodine can increase by 162 and 145 µg/L per each milligram of iodine present in the DM, respectively. Lower slopes were calculated in regressions obtained from recent data published by Antaya et al. (2019) and Rezaei Ahvanooei et al. (2021):

$$y = 65x + 79 \text{ and } y = 43x + 249.$$

To the authors' knowledge, only Borucki Castro et al. (2011) proposed a regression equation based on an observational longitudinal study, considering the iodine level of feed and bulk milk samples collected in 60 commercial farms. The equation, characterized by a coefficient of determination (**$\mathbf{R^2}$**) of 0.15, looks like

$$y = 113x + 145.$$

The low model accuracy calculated for bulk milk suggests that other factors in addition to feed affect the transfer of iodine at tank level, such as milking practices or animal management.

The equation obtained from the overall regression in Figure 1C is

$$y = 93x + 217 \ (R^2 = 0.56).$$

In general, although the linear relationship between milk and feed iodine concentration has been well documented, there is still the need to (1) explore more thoroughly processes impairing the transfer from feed to milk, (2) validate the association using larger sample sizes, and (3) conduct observational studies to identify on-field practices with a favorable or unfavorable role in iodine recovery.

## Goitrogens and Iodine Antagonists in Animal Feed

Goitrogenic substances, such as glucosinolates (**GLS**), thiocyanates, and nitrates, have been identified and characterized in a variety of plant species, including ones in the cruciferous family (rape, canola, and kale), soybean, beet pulp, millet, linseed, white clover, and sweet potato. Goitrogenic substances and their metabolites can inhibit the sodium iodide symporter, diminishing iodine uptake by the thyroid and mammary gland (Flachowsky et al., 2014). Consequently, feedstuff containing relatively high amounts of GLS leads to a low excretion and thereby reduces milk iodine concentration (Flachowsky et al., 2014). Furthermore, it is worth mentioning that, within the same plant species, goitrogen concentration varies depending on the specific variety, and the technological processes that the crop is subjected to (e.g., extrusion) may alter the antagonistic effect of goitrogens. In the former case, it was observed that fewer strains of red clover contain cyanogenic glycosides compared with white clover, indicating that the red variety has lower goitrogenic potential compared with the other (Bath and Rayman, 2016). Concerning the treatments, instead, Ngwa et al. (2004) reported that ensiling techniques can reduce goitrogens in *Acacia sieberiana*. Speculations, hypotheses, and discussions about the antagonistic activity of goitrogenic compounds in respect to milk iodine content have been presented by several authors, but very few of them have provided direct quantification of goitrogens in animal feed and have successfully correlated goitrogen iodine with milk iodine. Antaya et al. (2019) reported GLS concentration to be maximum in the concentrate blend (80.10 mg/kg DM), followed by TMR (58.70 mg/kg DM), and thereafter mixed grass baleage (32.9 mg/kg DM). The level of GLS in animal feed increased linearly ($r = 0.98$) with the percentage of canola meal in the TMR (Weiss et al., 2015). Diets without canola meal contained on average 3.55 m*M* of GLS per kilogram of DM, whereas diets supplemented with 3.9 and 13.9% of canola contained 3.73 and 5.23 m*M* GLS per kilogram of DM, respectively (Weiss et al., 2015). Indeed, the same authors reported a relatively greater amount of GLS in canola meal averaging 8.50 m*M*/kg DM and observed that milk iodine concentration was negatively associated with the percentage of canola meal included in the feed, and ultimately to feed GLS levels. In particular, cows supplemented with 0.5 mg of iodine per kilogram of DM transferred 358, 289, and 169 µg of iodine per liter of milk for 0, 3.9, and 13.9% canola inclusion in the ration DM, respectively ($r = -0.99$; Weiss et al., 2015). This was confirmed also when cows were exposed to 2.0 mg of iodine per kilogram of DM, which led to milk iodine concentrations of 733, 524, and 408 µg/L for 0, 3.9, and 13.9% canola meal treatments, respectively ($r = -0.93$; Weiss et al., 2015).

In this scenario, there is room to (1) specifically characterize goitrogen content and goitrogenic potential of crops and strains included as feed ingredients and (2) assess the relationship between these dietary antagonists and final milk iodine concentration.

## Milking Practices

The use of iodinated sanitizers for udder hygiene has been recognized as an important factor affecting the concentration of this mineral in individual—and thus bulk—milk. How composition of sanitizers (e.g., iodized vs. noniodized, concentration of iodine) and their application (e.g., predipping vs. postdipping, immersion vs. spraying) influence iodine concentration of milk has been explored in the literature. Although not significant, the application of iodized sanitizer in the premilking phase resulted in 16% more milk iodine (121.1 μg/L) compared with control animals (104.4 μg/L; Rezaei Ahvanooei et al., 2021). A significantly greater carryover was observed when postdipping sanitizers were applied after milking (334.2 μg/L, +220%). Due to dermal absorption, an increase in iodine was observed even in serum and urine of those animals (Rezaei Ahvanooei et al., 2021).

Borucki Castro et al. (2012) observed that the application of 1% iodized sanitizer through dipping and spraying increased milk iodine concentration of about +20 and +166%, respectively, compared with the application of noniodized disinfectants. Borucki Castro et al. (2012) also observed that teats dipped in 0.5% iodized sanitizer presented +54% of milk iodine concentration compared with not predipped teats. A smaller increase was observed when predipping was performed with 0.5 and 1% iodine sanitizers followed by complete drying before milking (+15 and +33%, respectively). Similar increases were reported by McKernan et al. (2020), who compared postmilking iodine-based teat dips or sprays with non-iodine-based teat treatments, whereas French et al. (2016) discovered that milk iodine concentrations increased from 6 to 20% when using iodine-based teat disinfectants compared with products free of iodine. Notably, milk iodine increased gradually and consistently along the experimental period (French et al., 2016), suggesting again that iodine transfer is subjected to a carryover effect due to skin permeability. This has also been demonstrated by Conrad and Hemken (1978), who observed that one way to increase milk iodine is through skin absorption. Accordingly, Borucki Castro et al. (2010) reported that in-line or hand spraying (which covers a large part of the mammary gland with iodine) was the application resulting in the greatest level of iodine in milk. These findings have been—at least partially—confirmed in goat milk. As an example, Ovadia et al. (2018) reported an increase of 15% iodine in milk collected from goats treated with iodized sanitizer compared with animals subjected to an iodine-free disinfectant. However, such an increase was not significant, likely due to the limited sample size, which reduced the statistical power of the study.

### Genetic Variation of Milk Iodine

Breeding objectives for dairy cattle breeds have changed in the last century, moving the emphasis from productive traits to fitness and health performances, such as functional morphology, reproductive characteristics, longevity, and resistance to diseases (Miglior et al., 2017). In addition, milk technological traits have been proposed in some countries where cheese production is important (Cassandro et al., 2016). However, desired characteristics that are not presently considered in dairy breeding objectives are potentially numerous—for example, fine milk quality attributes, including protein composition and mineral fractions. Although such attributes manifest exploitable genetic variation (Visentin et al., 2017, 2019) and are important for the dairy stakeholders (Henchion et al., 2016), the difficulty of large-scale and cost-effective data collection on fine composition traits is still a limiting factor to be considered when designing ad hoc breeding schemes. For this reason, for instance, genetic parameters of milk minerals have been estimated by few authors (Sanchez et al., 2018; Denholm et al., 2019; Visentin et al., 2019; Zaalberg et al., 2021). In Denholm et al. (2019), genetic parameters of milk iodine concentration, quantified through inductively coupled plasma mass spectrometry, were estimated using a linear mixed repeatability animal model in 267 Scottish Holstein dairy cows. In the aforementioned research, heritability (0.22 ± 0.12) and repeatability (0.24 ± 0.08) estimates were characterized by relatively large standard errors due to the relatively small sample size. This is a typical characteristic of genetic studies based on data generated from reference (gold-standard) laboratory methodologies that are generally costly and time consuming. Such limitations can be overcome by employing large-scale and cost-effective assessment techniques such as prediction via mid-infrared spectroscopy. Prediction of milk minerals and their fractions is still challenging, and the prediction accuracy at the moment is not sufficient for punctual determination. Mid-infrared predicted minerals of milk can be used for screening and discrimination; thus, equations are not commercially available yet. Through the prediction model developed by Niero et al. (2020) that was characterized by a moderate accuracy ($R^2$ in calibration, cross-validation, and external validation of 0.69, 0.60, and 0.57, respectively), Costa et al. (2021) attempted to estimate genetic parameters of predicted iodine concentration using milk data of 4,072 Italian Holsteins. Their results indicated that iodine concentration is lowly heritable (0.025 ± 0.005) and characterized by an extremely low coefficient of genetic variation (1.72%). These estimates suggest that directly improving iodine concentration in milk through selective breeding is far from being feasible and convenient. However, it is worth highlighting that

**Table 3.** Average iodine concentration in dairy products

| Reference | Matrix (dairy species) | Samples, n | Mean | Minimum | Maximum |
|---|---|---|---|---|---|
| Milk, µg/kg | | | | | |
| Nerhus et al. (2018) | Semiskimmed pasteurized milk (cow) | 54 | 149 | 117 | 200 |
| O'Kane et al. (2018) | Whole pasteurized milk (cow) | 24 | 470 | 467 | 473 |
| O'Kane et al. (2018) | Semiskimmed UHT milk (cow) | 12 | 489 | — | — |
| Stevenson et al. (2018) | Whole pasteurized milk (cow) | 96 | 334[1] | 198[1] | 522[1] |
| Stevenson et al. (2018) | Whole UHT milk (cow) | 48 | 314[1] | 280[1] | 343[1] |
| Walther et al. (2018) | Whole UHT milk (cow) | 220 | 91[1] | 35[1] | 151[1] |
| van de Kamp et al. (2019) | Semiskimmed pasteurized milk (cow) | 64 | 159 | 38 | 358 |
| Niero et al. (2019) | Whole pasteurized milk (cow) | 5 | 254 | — | — |
| Niero et al. (2019) | Semiskimmed pasteurized milk (cow) | 5 | 359 | — | — |
| Niero et al. (2019) | Whole UHT milk (cow) | 5 | 305 | — | — |
| Niero et al. (2019) | Semiskimmed UHT milk (cow) | 5 | 267 | — | — |
| Arrizabalaga et al. (2020) | Whole UHT milk (cow) | 489 | 190[1] | 106[1] | 272[1] |
| Cheese, µg/kg | | | | | |
| Nerhus et al. (2018) | Solid cheese (cow) | 9 | 157 | 140 | 190 |
| Nerhus et al. (2018) | Soft cheese (cow) | 6 | 155 | 130 | 180 |
| Nerhus et al. (2018) | Soft cheese (goat) | 6 | 300 | 140 | 460 |
| Nerhus et al. (2018) | Whey cheese (cow) | 6 | 1,200 | 1,000 | 1,400 |
| Nerhus et al. (2018) | Whey cheese (goat) | 3 | 4,500 | — | — |
| van der Reijden et al. (2019) | Solid cheese (cow) | 32 | 186 | 0 | 522 |
| van der Reijden et al. (2019) | Soft cheese (cow) | 12 | 78 | 0 | 195 |
| Yogurt, µg/kg | | | | | |
| Nerhus et al. (2018) | Yogurt (cow) | 6 | 155 | 130 | 180 |
| van der Reijden et al. (2019) | Yogurt (cow) | 4 | 72 | 4 | 174 |
| Protein concentrate | | | | | |
| da Silva et al. (2016) | Casein concentrates (cow) | 1 | 371 | — | — |
| da Silva et al. (2016) | Whey protein concentrates (cow) | 4 | 4,348 | 2,530 | 8,040 |
| Milk whey, µg/kg | | | | | |
| van der Reijden et al. (2019) | Milk whey (cow) | 44 | 75 | 0 | 197 |

[1] Data expressed as micrograms per liter.

mid-infrared predictions carry a certain prediction error, depending on the accuracy of the developed model. Such a prediction error contributes to increase the residual variance in the animal model and, at the same time, to decrease the amount of variance attributable to additive genetic effect. This explains why the heritability of mid-infrared predicted traits tends to be generally lower than that of reference traits measured using gold-standard analyses (McParland et al., 2015). This is clearly evident for milk iodine, if one compares the heritability found by Costa et al. (2021; 0.025) and Denholm et al. (2019; 0.22). Further genetic investigations about milk iodine are advisable and should rely on more accurate phenotypes.

In addition to the heritability, Costa et al. (2021) estimated the genetic correlations of milk iodine with other traits of interest, including milk composition. Infrared-predicted iodine concentration was negatively correlated with fat (−0.405) and protein content (−0.169) and positively with milk yield (0.379), whereas the association with both lactose (0.140) and SCS (−0.057) was weak. Whether there will be interest in increasing milk iodine even through breeding, an indirect selection through genetically correlated traits can be an effective solution.

## IODINE IN DAIRY PRODUCTS

### Iodine Concentration in Dairy Products

Table 3 summarizes average iodine concentration in dairy products, including retail milk, different types of cheese, yogurt, protein concentrates, and whey. To date, iodine content has been well profiled in retail milk samples, addressing the effect of heat treatment (i.e., pasteurization and UHT), fat content (i.e., whole, semiskimmed, and skim milk), month and season of sampling, and farming system (i.e., conventional and organic). Iodine concentration in retail milk is not subjected to standardization and is thus extremely variable, from 91 µg/L (Walther et al., 2018) to 489 µg/kg (O'Kane et al., 2018). The recommended daily iodine intake in adult women and men has been established at 150 µg/d (WHO, 2007). Considering the minimum and maximum milk iodine level retrieved from literature, a glass of milk (125 mL) can provide from 11 to 61 µg of iodine, which translates into 7 to 41% of the recommended daily intake of adults, respectively. This review puts in evidence that a more stable iodine concentration in drink milk can be achieved through different strategies within the dairy chain (Coneyworth et al., 2020)—for example, by monitoring iodine intake in lactating animals (Arrizabalaga et al., 2020). In fact, the high variability of this mineral in retail milk has implications for the adequacy of iodine intake in consumers, which could result in more serious consequences for vulnerable groups such as newborns, children, and pregnant women (van de Kamp et al., 2019).

Fewer data are available for commercial dairy products other than milk. Van der Reijden et al. (2019) reported average iodine concentration in cow cheese varying from 78 μg/kg (Tomino) to 186 μg/kg (Fontina), meaning that 30 g of cheese provides between 2.3 and 5.6 μg of iodine (i.e., from 1.5 to 3.7% of the recommended daily intake for adults). Similar concentrations have been reported for yogurt by both Nerhus et al. (2018) and van der Reijden et al. (2019), with average iodine concentrations of 155 and 72 μg/kg, respectively. Drastically greater iodine concentrations were measured in cow whey cheeses (1,200 μg/kg) and goat whey cheeses (4,500 μg/kg), suggesting that a portion of 30 g contributes 24 and 90% of the recommended daily intake, respectively. High iodine concentrations were also obtained for different kinds of whey protein isolates and concentrates, with an average iodine concentration of 4,348 μg/kg (da Silva et al., 2016). Such results suggest that iodine is likely embedded in whey proteins, but specific and dedicated studies are recommended to confirm this empirical speculation. More efforts should be made to define analytical protocols for iodine concentration, with particular regard to processed dairy foods. It will be useful to have a comprehensive overview of iodine concentration variability in a broader range of products, including more industrial-scale products in addition to laboratory or experimental-scale products.

### Effect of Heating and Skimming on Retail Milk Iodine Concentration

The effects of heat and skim treatments on milk iodine concentration have been extensively investigated. However, most of the studies focused on retail milk samples where no corresponding samples of the same batch of milk were analyzed before and after the technological treatment. A simple comparison of differently treated commercial samples is not optimal for studying the influence of processing, because several other factors are likely to interfere with the iodine level. Therefore, it is advisable to evaluate the effect of processing on iodine concentration along the processing line. This would permit researchers to follow the same batch of milk along the different processing stages (Walther at al., 2018).

As regards heat treatment, significant differences in iodine concentration were not detected between pasteurized and UHT retail milk (van de Kamp et al., 2019), nor between unpasteurized and pasteurized retail milk (O'Kane et al., 2018). However, authors of both studies acknowledged that the limited sample size considered could skew the results in relation to temperatures used during treatment. To investigate the influence of heating on milk iodine concentration, Walther et al. (2018) analyzed the same milk samples before and after the UHT treatment. Iodine concentration of untreated milk averaged 95 ± 23 μg/L, whereas the same samples averaged 95 ± 25 μg of iodine per liter after UHT treatment, indicating that this treatment had no influence on milk iodine concentration. These conclusions were likely expected due to the fact that iodine is a mineral element (i.e., inorganic compound) and therefore is not subject to deterioration through heating. Moreover, at dairy plant level, milk sterilization is commonly performed as a continuous process, without contact with the external environment, and for a very short period. Given this, any arising differences between iodine concentration in raw and heat-treated milk can be due to an artifact. In a study aimed at validating a chromatographic method for iodine quantification in raw and processed milk, Niero et al. (2019) concluded that the variation in iodine concentration of commercial milk was more related to the milk chemical composition than to heat treatments such as pasteurization or UHT. Moreover, Arrizabalaga et al. (2020) observed a similar concentration of iodine along the fat gradient found in whole, semiskimmed, and skimmed UHT milk available in the Spanish (187, 189, and 189 μg/L, respectively) and French (201, 189, and 215 μg/L, respectively) markets. Similar conclusions were reported by O'Kane et al. (2018), who observed similar iodine concentrations in whole (488.5 μg/kg), semiskimmed (466.5 μg/kg), and skim milk (472.6 μg/kg). Due to the solubility of iodine compounds, O'Kane et al. (2018) hypothesized that milk iodine is likely to increase in low-fat milk, which indeed contains a greater soluble fraction compared with other milk as a result of the skimming process (Niero et al., 2019). Nevertheless, although this idea sounds reliable and is in line with the aforementioned study, it is fair to point out that this is a mere speculation inferred from a small sample size that lacks robust statistical support.

### Effect of Season and Farming System on Retail Milk Iodine Concentration

Scientific literature agrees on the seasonal variation of iodine concentration in bovine milk. In general, greater concentrations are usually found in winter milk compared with summer milk (O'Kane et al., 2018; van de Kamp et al., 2019; Arrizabalaga et al., 2020). Greater iodine supplementation and fewer iodine antagonists in winter feed are among the main direct explanatory factors of these differences. Also, differences in milk iodine concentrations across years and seasons can be indirectly related to climatic conditions of specific geographical areas, which regulate the beginning and end of the grazing period, and to the adoption of calving patterns, which lead to synchronous administration of mineral supplements at different levels depending on cattle physiological status and needs (Arrizabalaga et al., 2020). Such factors may hide or overlap the proper effect of season. In addition, assessing seasonal variations in iodine concentration of retail milk is even more difficult in the case of UHT milk. Indeed, there may be a wide variation in the time span between the treatment date and the purchase date, which ultimately creates challenges to date back to the actual milking season (Arrizabalaga et al., 2020).

Most studies also agree that conventionally produced milk is characterized by greater iodine concentration compared with milk produced under organic systems (Bath et al., 2012; Stevenson et al., 2018; Walther et al., 2018). Frequent administration of fresh forages with relatively great goitrogenic content and the reduced use of iodine supplements coupled with less frequent teat dipping are likely to reduce iodine concentration in organically produced milk (Flachowsky et al., 2014). Lower iodine concentrations in organic milk compared with conventional milk have been confirmed by Nerhus et al. (2018), although with a less evident trend in comparison to the previously cited literature. In contrast, the study conducted by van de Kamp et al. (2019) in the Netherlands resulted in no differences in iodine concentration between conventional and organic milk; similar results were reported by Qin et al. (2021) in conventional and organic milk produced in southern England.

### *Effects of Milk Processing on Iodine Concentration of Dairy Products*

So far, the effect of cheese-making protocols on iodine concentration in curd, cheese, and whey have been poorly investigated. Studies often show several limitations—for example, limited sample size, laboratory-scale products, or restricted geographical areas.

Van der Reijden et al. (2019) observed a linear relationship between milk iodine concentration and cheese iodine concentration, with $R^2$ from 0.95 (semi-hard cheeses) to 1.00 (fresh cheeses). Such results were confirmed regardless of the cheese-making process and related cheese products; greater iodine concentration of milk was consistently coupled with higher iodine concentration of the manufactured cheese. Van der Reijden et al. (2019) reported that cheese ripening had a negligible to null effect on cheese iodine concentration. The most recent literature agrees that, during cheese manufacturing, milk iodine is mainly found in the whey (75 to 84% of milk iodine; van der Reijden et al., 2019) rather than in the curd where it has become incorporated (below 25% of milk iodine; van der Reijden et al., 2019). Such findings harmonize with the relatively low cheese iodine concentration (Nerhus et al., 2018; van der Reijden et al., 2019), and the extremely high iodine concentration of whey cheeses and protein concentrates (da Silva et al., 2016; Nerhus et al., 2018). This is also in agreement with recent findings of Niero et al. (2020), who reported a positive correlation ($r = 0.22$; $P < 0.01$) between iodine and lactose concentration in milk likely due to the solubility of both compounds. According to the current knowledge, it is not possible to understand the ratio between inorganic iodine (i.e., soluble or free iodine) and organic iodine (i.e., iodine associated with organic compounds such as caseins or whey protein) of cow milk. Based on the considerations mentioned here, we can speculate that most of the milk iodine is in solution or, at the most, in association with whey proteins.

## IODINE IN HUMAN HEALTH AND NUTRITION

The function of the thyroid gland is to produce T4 and T3 thyroid hormones. These are characterized by the presence of 4 and 3 iodine atoms within their molecules, representing 65 and 59% of their molecular weight, respectively. Thus, in humans the production of an adequate quantity of thyroid hormones depends on an adequate intake of iodine, the rate-limiting element for the synthesis of thyroid hormones. Iodine can be obtained exclusively through the diet or through iodine supplements and cannot be replaced by any other nutrient (Velasco et al., 2018). Following the current guidelines of the World Health Organization (WHO, 2007), recommended daily iodine intake is as follows: 150 μg/d in adults (above 12 yr old); 250 μg/d in pregnant and lactating women, due to the increased thyroid hormone synthesis by the mother and initiation of thyroid hormone production at wk 16 to 18 by the fetus, as well as the mother-to-newborn transfer of iodine occurring during breastfeeding; 90 μg/d in preschool children (0 to 59 mo old); and 120 μg/d in schoolchildren (6 to 12 yr old). Iodine deficiency causes a wide range of health side effects. Overall, diseases associated with inadequate thyroid hormone production are collectively referred to as iodine deficiency disorders. The consequences observed after enduring iodine deficiency depend on its duration and severity. Thyroid hormones are indeed fundamental for appropriate neurological development, and the period between conception and the first 2 yr of life (known as the "first 1,000 d") is fundamental in the long-term brain development of the child (Mattei and Pietrobelli, 2019). Thus, severe iodine deficiency endured during fetal life creates higher risks of "cretinism," miscarriage, and infant mortality (Laurberg et al., 2010). The same deficiency in adult life causes hypothyroidism and goiter (Laurberg et al., 2010). However, moderate iodine deficiency can also have consequences for human health, especially during pregnancy. Although data are still weak, because they come from observational studies, a growing body of studies have documented how the offspring of mothers who experienced mild to moderate iodine deficiency during pregnancy are more likely to show learning disabilities and poorer verbal intelligence quotient scores (Levie et al., 2019), and even more conflicting data exist on a possible association with autism (Velasco et al., 2018; Levie et al., 2020).

However, excessive iodine intake should also be discouraged. Indeed, iodine intake and thyroid functions are subject to hormesis, so their relationship follows a relationship-inverted pattern: not only inadequate intake but also excessive iodine availability are harmful to correct thyroid function, leading to goiter, thyroid autoimmunity, hypothyroidism, or hyperthyroidism (Laurberg et al., 2009). The quite small range for adequate iodine intake was clearly pointed out by a Danish population study, set to prospectively monitor the iodine fortification program. The study showed profound effects of even small differences in iodine intake on the prevalence of goiter, nodules, and thyroid dysfunction, with several environmental factors influencing the epidemiology of thyroid disorders, some factors acting via an interaction with iodine intake and others independent of iodine (Laurberg et al., 2006). The relatively narrow range between deficiency and a more-than-adequate intake is particularly evident during infancy: school-age children are great milk consumers and are more prone to an excessive iodine intake (Farebrother et al., 2018; Bath et al., 2022). Thus, many societies recommend a lower iodine intake in young children than that of 90 μg/d recommended by WHO (Committee on Medical Aspects of Food Policy, 1991). Although many data showed that even excessive iodine intakes in children seem to be well tolerated, at least judging based on the absence of short-term thyroid dysfunctions (Farebrother et al., 2018), it should nevertheless be avoided, because data on possible long-term consequences are still lacking. Also, pregnant women and their developing fetus, as well as breastfed infants, may be vulnerable to iodine in excess, although the implications of iodine excess are still poorly understood and data are conflicting (WHO, 2007; Lee and Pearce, 2015; Pearce et al., 2016). Recognizing the importance of iodine deficiency prevention, in 1991 the WHO established the goal to eliminate iodine deficiency, and 2 yr later the United Nations Children's Fund recommended Universal Salt Iodization as the principal strategy to guarantee an adequate iodine intake, based on the iodization of the salt used, including that derived from food industrial processing. Since the 1990s, great improvements have been made in the elimination of iodine deficiency–related diseases: according to WHO data, the number of iodine-deficient countries decreased by half, from 110 countries in 1993 to 54 in 2003 (UNICEF, 2008). From 2003 to 2017, the number of iodine-deficient countries in the world further fell by 64.8%, from 54 countries to 19 (Gizak et al., 2017). Although data demonstrate that improvements were achieved through specific campaigns in the past decades, it is still a long road to reach iodine adequacy and iodized salt coverage, even in developed countries and particularly in childbearing-age women (Gizak et al., 2017). Alternative valid sources of iodine are represented by milk and dairy products due to supplementation of iodine in cattle feed (Herrick et al., 2018; Walther et al., 2018). In numerous published reports, dairy products have demonstrated a significant role in contributing to the total iodine intake, especially in children (Censi et al., 2020; Bath et al., 2022). Cow milk consumption decreases during the lifespan, from childhood to adolescence and adulthood, paralleling the frequency of adequate iodine intake, which falls accordingly, demonstrating the importance of cow milk and dairy products as central contributors to iodine adequacy (Witard et al., 2022).

## INTEREST AND AWARENESS OF SCIENTIFIC COMMUNITY

It is inarguable that milk and its derived products play a key role in facing iodine deficiency, especially in populations with scarce access to seafood or iodized salt (WHO, 2007). Therefore, in some circumstances, the inclusion in the diet of dairy foods naturally rich in iodine becomes of primary importance to reduce the risk of thyroidal dysfunctions and guarantee physiological hormone synthesis (Watutantrige Fernando et al., 2013, 2016). Unfortunately, awareness of the importance of iodine intake is still low among the general population, but also among health care professionals (Combet et al., 2015; Kayes et al., 2022), as is the knowledge of how to achieve adequate iodine intake. In particular, the fact that dairy products are a great source of iodine is largely neglected (Combet et al., 2015; O'Kane et al., 2016). Because a close relationship exists between

**Table 4.** Criteria used to explore the interest in milk iodine in Scopus (https://www.scopus.com/)

| Key word combination | Location | Time period | Output |
|---|---|---|---|
| "Iodine," "milk"<br>"Iodine," "milk," "human health"<br>"Iodine," "milk," "dairy" | Title, abstract, or indexed key words | 2010 to 2021 | Total documents, review articles, or original articles |

the knowledge of iodine's role and its proper dietary intake (O'Kane et al., 2016), efforts should be made to promote a greater awareness in populations.

Promoting the consumption of animal foodstuff has become more challenging in the current era, even with the proven and documented beneficial properties that come with animal consumption (Henchion et al., 2021). The consumption of animal products rich in saturated fatty acids has been speciously linked to human diseases. According to Nicklas (2003), this was mainly due to the misconception that meat and dairy introduced into the diet, even in small amounts, increases the risk of cardiovascular disease and weight gain. The public should bear in mind that multifactorial disorders and pathologies such as strokes and hypertension are the result of combined actions—that is, genetic predisposition and lifestyle. In addition, it is important to remark that foods of animal origin are essential to humans, as they are providers of essential nutrients such as minerals, fatty acids, amino acids, and vitamins (Niero et al., 2019). Lastly, the dairy chain is currently facing hardship on grounds other than health-related issues, and the whole livestock sector is associated with issues relating to food-animal welfare and to greenhouse gas emissions (FAO, 2018).

Nevertheless, stakeholders along the whole chain of various livestock production systems should identify the most appropriate and effective strategies to valorize their products at best. In the case of milk and dairy, efforts should specifically aim to increase the audience's recognition and awareness of nutritional deficiencies in humans. Proper advertisement, attractive and informative labeling, and awareness campaigns are the best tools to spread knowledge on deficiency-related disorders. These are also useful ways to stimulate—or keep constant—the purchase frequency of dairy (Wesana et al., 2020). Milk is the primary source of iodine in the United Kingdom, but the popularity of plant-based beverages is constantly increasing to such an extent that they have become milk substitutes, especially in adults (Dineva et al., 2021). Although most plant-based drinks are fortified in specific nutrients, the concentration of iodine is lower compared with bovine milk; this inevitably means a reduction in the daily iodine intake in consumers who choose to totally or partly replace bovine milk (Dineva et al., 2021).

The interest in milk iodine within and across different scientific communities has been explored. For this purpose, target key word combinations were input following methodologies and criteria summarized in Table 4. In particular, time trends for the period from 2010 to 2021 were obtained by restricting the time window of the research, and the final output consisted in number of items traced back for each year (Figure 2). Both the key word combinations selected show a positive trend in the same direction and demonstrate that milk iodine is a popular subject of debate. In detail, the number of documents where "milk" and "iodine" are present in the most informative locations—namely, title, abstract, and Scopus indexed key words—progressively increased across years following a linear trend (Figure 2).

## FINAL REMARKS

This review provides a wide-ranging overview of factors that contribute to iodine concentration in milk and dairy products and is primarily intended to make the scientific community aware of the importance of this mineral in animal and human nutrition. Several studies have demonstrated that milk iodine concentration is closely associated with its respective concentration in the feed. The correlation between the iodine concentration in feed and milk is linear and characterized by different dose-response effects according to the feed and presence of supplementation. Goitrogenic substances found in certain forage species are antagonists of iodine, and their specific effects on the concentration of iodine in milk remain to be further elucidated in cattle. From the present literature review, we also conclude that the iodine concentration in bovine milk can be affected by milking practices and industrial processing. In particular, the use of iodine-based products for teat cleaning is responsible for a notable artificial increase in the concentration of iodine in dairy cows. The effect of milk technological treatments had a minor impact on iodine concentration. Being strictly management dependent, the milk iodine concentration is expected to be scarcely heritable. Moreover, collection of accurate phenotypes on a large scale is rather difficult, as the predictive performance of mid-infrared spectroscopy is far from considered reliable enough to be implemented on the pool of traits routinely measured, representing an issue,

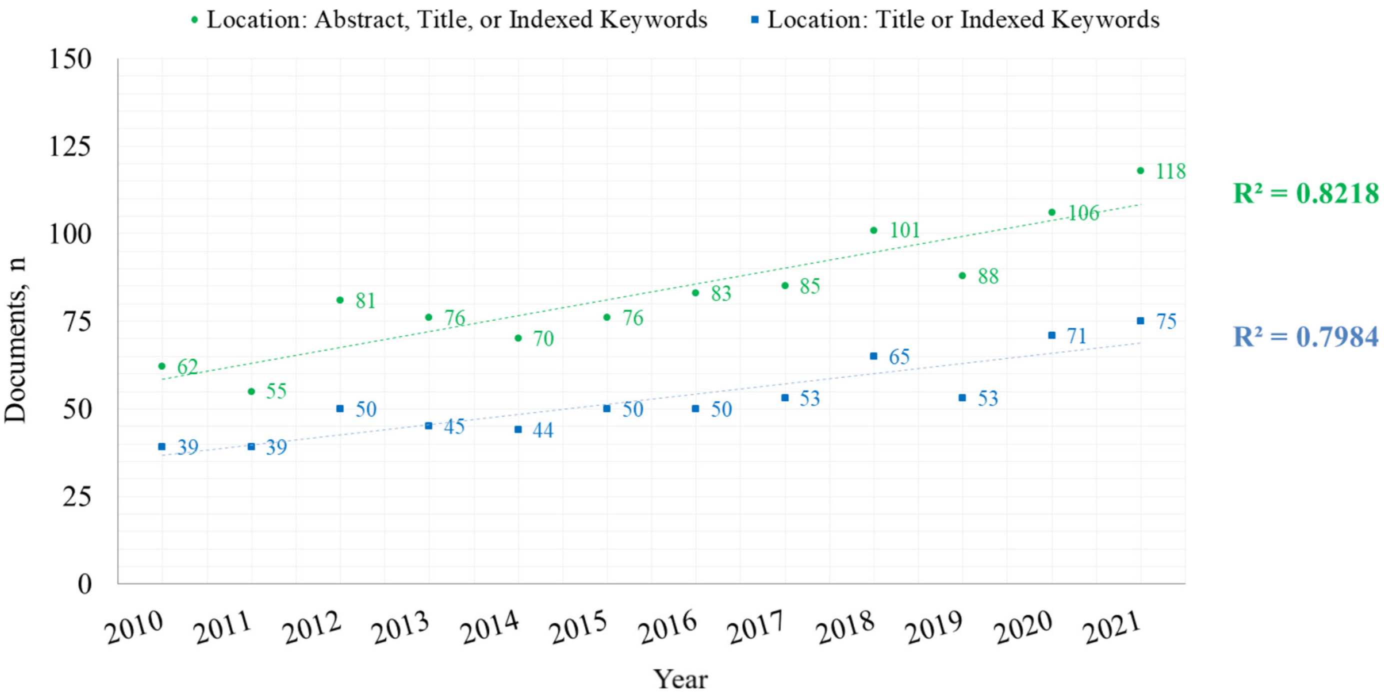

**Figure 2.** Overview of publications including the key words "milk" and "iodine" in various locations across years (source: Scopus, https://www.scopus.com/). The coefficient of determination ($R^2$) is reported for the tendency lines.

for example, when attempting the implementation of animal breeding programs. The investigation of novel and closed mineral-related technologies (e.g., X-ray) should be considered in further research to improve the accuracies of mid-infrared tools. Consumers need to be informed of the importance of dietary iodine and deficit implications, as the human recommended daily allowance could be reached through dietary intake of milk or other dairy products. In recent years, interest in the contribution of milk and dairy to daily iodine consumption has increased, not just within the scientific community but also in various countries. Therefore, we expect milk iodine to remain an important topic in the future that deserves consumer education and attention in food science through scientific research and economic funding.

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