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Assessing the potential of milk iodine intake to mitigate iodine deficiency in pregnant women of the United States via supplementation of *Ascophyllum nodosum* meal to dairy cows: A sensitivity analysis

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ABSTRACT

The brown seaweed *Ascophyllum nodosum* is known to bioaccumulate iodine (I). Previous research showed a linear relationship between *A. nodosum* meal (ASCO) intake and milk I concentration in dairy cows. Thus, improving milk I concentration by supplementation of ASCO to dairy cows may be a compelling strategy to naturally boost I intake in humans. A sensitivity analysis was conducted to gain insights regarding how different milk I intakes affect the I status of pregnant women relative to the United States Institute of Medicine (US IOM) recommended dietary allowance (RDA; 220 μg/d) and the World Health Organization (WHO) recommended nutrient intake (RNI; 250 μg/d) for I. Four studies in which dairy cows received various amounts of ASCO generated the milk I data set used in the sensitivity analysis. The annual per capita consumption of 2% reduced-fat milk in the United States, converted to daily intake (i.e., 0.26 cup; 1 cup = 236.6 mL), was used as the actual milk intake in the simulations. Five additional milk intake scenarios (2, 3, 4, and 5 times the actual per capita milk consumption and the 3 cups-equivalent recommended by the 2015–2020 Dietary Guidelines for American were also included in the sensitivity analysis with varying milk I concentrations (180, 765, and 483 μg/L). The 180, 765, and 483 μg/L values are milk I concentrations derived from cows not receiving ASCO or fed various amounts of ASCO in the diet or a single level (113 g/d) during the grazing season, respectively. With the actual United States milk per capita consumption of 0.26 cup/d and milk I concentrations of 180, 765, and 483 μg/L, 5.09, 21.7, and 13.6% of the RDA for I for pregnant women were met based on the US IOM, respectively. Similarly, 4.48, 19, and 12% of the RNI for I advised by the WHO was achieved with intake of 0.26 cup/d of milk containing I concentrations of 180, 765, and 483 μg/L, respectively. When 3 cups/d was included in the simulations, 58.2, 247, and 156% (US IOM), and 51.2, 217, and 137% (WHO) of the RDA or RNI for I required by gestating women was satisfied with milk I concentrations of 180, 765, and 483 μg/L, respectively. A regression analysis between I intake and milk I concentration revealed that 103 g/d of ASCO in the diet of dairy cows reached the maximum 500 μg/L threshold of I in milk recommended by the European Food Society Authority. Overall, milk from dairy cows fed ASCO can prevent I deficiency in pregnant women, but the amount of ASCO fed to cows needs to be fine-tuned to avoid excess I in milk. Further research is required to better understand the interactions between goitrogenic compounds from forages and concentrates and milk I concentration in cows fed ASCO. Research to evaluate the concentration of I in retail organic milk should be also conducted because of the high prevalence of ASCO fed in organic dairies in the United States.
Key words: dairy food, human health, macroalga, organic agriculture

INTRODUCTION

Farming practices such as the use of iodine (I)-fortified mineral-vitamin premix in dairy cow diets and I-based disinfectants for teat hygiene are major sources of I transferred into milk (Borucki Castro et al., 2011, 2012; Schöne et al., 2017). Milk and dairy products have become significant sources of I in industrialized countries including the United States (Pennington, 1990a; Pearce et al., 2004; van der Reijden et al., 2017). However, the proportion of milk and dairy products to total daily I intake of humans is variable and estimated to range from 25 to 70% (Dahl et al., 2003, 2004; Haldimann et al., 2005; FCN, 2013; Arrizabalaga et al., 2015; Pastorelli et al., 2015; van der Reijden et al., 2017) because of the differences in individual consumption of milk and concentration of I found in dairy foods (van der Reijden et al., 2017). In fact, consumption of milk has declined steadily over the past decades in the United States (USDA-ERS, 2019). Furthermore,

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the growth of plant-based beverages as alternatives to milk is contributing to the decline in milk consumption across many industrialized countries (Ma et al., 2016; Bath et al., 2017; Forgrieve, 2019). It should be noted that plant-based beverages are poor sources of I (Ma et al., 2016; Bath et al., 2017) and can potentially exacerbate the I deficiency in certain population groups such as pregnant women.

The brown seaweed *Ascophyllum nodosum* is known to bioaccumulate I through the uptake of iodide (I^-) leached from the Earth's upper crust (Baily and Kelly, 1955; Küpper et al., 1998; Muramatsu and Wedepohl, 1998; Fuge and Johnson, 2015). *Ascophyllum nodosum* also contains a wide spectrum of bioactive compounds such as polysaccharides, PUFA, antioxidants, peptides, and vitamins (Allen et al., 2001; Antaya et al., 2015; Makkar et al., 2016). It is also a rich source of phlorotannins (Connan et al., 2004), which are polyphenolic compounds with antimicrobial (Wang et al., 2009; Belanche et al., 2016; Zhou et al., 2018) and antidiabetic (Lee and Jeon, 2013; Lopes et al., 2016) properties.

Dried and ground *A. nodosum* meal (**ASCO**) is a mineral-based supplement available commercially and used in livestock diets (Allen et al., 2001; Antaya et al., 2015; Makkar et al., 2016). Surveys revealed that 49, 58, and 83% of organic dairies feed ASCO in Wisconsin (Hardie et al., 2014), the northeastern United States (Antaya et al., 2015), and Minnesota (Sorge et al., 2016a), respectively. A dose-response study conducted at the University of New Hampshire (**UNH**; Durham) showed that the concentrations of milk I responded linearly (177, 602, 1,015, and 1,370 μg/L) to incremental amounts of ASCO (0, 57, 113, and 170 g/d) fed to organic-certified dairy cows (Antaya et al., 2015). Therefore, improving the concentration of milk I through ASCO supplementation to dairy cows appears to be a natural way to boost I intake in humans. Iodine deficiency represents a greater public health concern worldwide than I toxicity (Pearce et al., 2013), especially because I is essential for the synthesis of thyroid hormones that are involved in growth, development, and control of metabolic processes in the body. In the United States, pregnant women do not consume enough I based on a median urinary I concentration <150 μg/L (Sullivan et al., 2013), suggesting that milk naturally enriched with I has the potential to mitigate I deficiency in this population group. It is well known that I is particularly important during pregnancy for fetal brain development and cognitive development of newborns (Zimmermann, 2009; Leung et al., 2011). The central objective of this study was to conduct a sensitivity analysis to gain insights into the amount of milk that needs to be consumed to meet the I recommendations for pregnant American women advised by the United States Institute of Medicine (**US IOM**) and the World Health Organization (**WHO**) using milk I data sets built from studies in which lactating dairy cows were fed various amounts of ASCO at the UNH.

MATERIALS AND METHODS

Cows, Experimental Design, Treatments, and Milk Sampling and Iodine Analysis

Four studies conducted at the UNH with pure-bred Jersey cows fed various amounts of ASCO were used to build milk I concentration data sets for developing a sensitivity analysis of milk consumption relative to recommended I intake for pregnant women by the US IOM (IOM, 2001) and WHO (WHO, 2007). Three experiments—study 1 (Antaya et al., 2015), study 2 (Antaya et al., 2019), and study 4 (A. F. Brito, unpublished)—were conducted at the UNH Burley-Demeritt Organic Dairy Research Farm (Lee) using organic-certified Jersey cows; study 3 (A. F. Brito, unpublished) was run at the UNH Fairchild Dairy Teaching and Research Center (Durham) with conventional Jerseys. Care and handling of cows used in the 4 experiments were performed as outlined in the guidelines of the UNH Institutional Animal Care and Use Committee [Protocols no. 111002 (study 1), 120504 (study 2), 140803 (study 3), and 160908 (study 4)]. An I-free, chlorhexidine-based solution was used for pre- and postdipping teat hygiene every milking in all 4 studies.

A detailed description of the ingredients and nutritional composition of the diets, feeding and management of cows, sampling protocols, and results (e.g., milk yield and composition, apparent total-tract nutrient digestibility, blood metabolites) of study 1 are reported in Antaya et al. (2015). In brief, 12 multiparous organic-certified Jersey cows averaging (mean ± SD) 40 ± 21 DIM and 464 ± 35 kg of BW and 4 primiparous organic-certified Jersey cows averaging 75 ± 37 DIM and 384 ± 17 kg of BW at the beginning of the experiment were randomly assigned to treatment sequences in a replicated 4 × 4 Latin square design with 21-d periods (14 d for diet adaptation and 7 d for data and sample collection). A basal diet consisting of (DM basis) 31.8% mixed, mostly grass baleage, 32.4% mixed, mostly legume baleage, and 35.8% of a ground corn-barley-soybean meal-based concentrate blend was fed twice daily as a TMR and supplemented with incremental amounts of ASCO (Thorvin Inc., New Castle, VA): 0, 57, 113, and 170 g/d. The mineral-vitamin premix, which was part of the concentrate blend, provided 790 mg/kg of I. Milk samples for I analysis were collected from individual cows during 2 consecutive milkings (afternoon and next morning) in each experimental period, composited proportionally by milk weight, and stored at −20°C until shipped to Michigan State University Veterinary Diagnostic Laboratory (Lansing). Milk samples were analyzed for I by inductively coupled plasma mass spectrometry (Agilent 7500 series; Agilent Technologies Inc., Tokyo, Japan).

A detailed description of the ingredient and nutritional composition of the diets, feeding and grazing management, sampling protocols, and results (e.g., milk yield and composition, apparent total-tract nutrient digestibility, blood metabolites) of study 2 were published recently (Antaya et al., 2019). Briefly, 8 multiparous organic-certified Jersey cows averaging (mean ± SD) 175 ± 60 DIM and 441 ± 30 kg of BW, and 12 primiparous organic-certified Jersey cows averaging 142 ± 47 DIM and 389 ± 33 kg of BW at the beginning of the study were used in a randomized complete block design. Cows were blocked in pairs (n = 10 pairs) according to DIM or milk yield and, within pairs, randomly assigned to 1 of 2 treatments: 0 or 113 g/d of ASCO (Thorvin Inc.). Each experimental period (n = 3) lasted 28 d, with data and sample collection taking place during the last 7 d of each period. Animals had approximately 16.5 h of access to pasture daily. Diets were formulated to yield a 70:30 forage-to-concentrate ratio and consisted of (DM basis) 48% cool-season perennial herbage and 52% partial TMR. The partial TMR contained (DM basis) 42.1% mixed, mostly grass baleage, 56% ground corn-barley-based concentrate blend, and 1.9% sugarcane liquid molasses. The mineral-vitamin mix fed as a component of the concentrate blend provided 790 mg/kg of I. Milk samples for I analysis were collected monthly throughout the experiment and analyzed as reported in study 1 (Antaya et al., 2015).

Except for the milk I concentration reported herein, animal production, nutrient digestibility, and blood metabolites data of study 3 have not been published. Briefly, 5 ruminally cannulated, multiparous conventional Jersey cows averaging (mean ± SD) 102 ± 15 DIM and 450 ± 33 kg of BW at the beginning of the experiment were randomly assigned to treatment sequences in a 5 × 5 Latin square design with 28-d periods (21 d for diet adaptation and 7 d for data and sample collection). A basal diet consisting of (DM basis) 25.5% corn silage, 40.7% mixed, mostly grass haylage, 21% ground corn, 7.5% soybean meal, 3.5% roasted soybean, and 1.8% mineral-vitamin premix was fed twice daily as a TMR. The following treatments were offered: 0, 57, 113, and 170 g/d of ASCO (Tasco; Acadian Seaplants Ltd., Dartmouth, NS, Canada), and a pelleted feed containing 300 mg/d of the ionophore monensin sodium (Rumensin; Elanco Animal Health, Indianapolis, IN). Both ASCO and the monensin-containing pellet were introduced directly into the rumen via the cannula of each cow once daily. The mineral-vitamin premix and the monensin-containing pellet provided 14.3 and 18.3 mg/kg of I, respectively. Milk samples for I analysis were collected during 2 consecutive milkings in each experimental period, with morning and afternoon samples analyzed separately (no composites were made) at Dartmouth College Trace Element Laboratory (Hanover, NH) by inductively coupled plasma mass spectrometry.

Apart from milk I concentration used in the present data sets, animal production, nutrient digestibility, and blood metabolite data of study 4 are not published. Briefly, 16 multiparous organic-certified Jersey cows averaging (mean ± SD) 93 ± 58 DIM and 461 ± 63 kg of BW at the beginning of the experiment were randomly assigned to treatment sequences in a replicated 4 × 4 Latin square design with a 2 × 2 factorial arrangement of treatments. Each experimental period lasted 21 d with 14 d for diet adaptation and 7 d for data and sample collection. Dietary treatments were 2 protein sources (soybean meal and nondecorticated canola meal) and 2 I sources [ethylenediamine dihydriodide (**EDDI**) and ASCO (Tasco; Acadian Seaplants Ltd.)] fed as follows (DM basis): (1) 10% soybean meal plus 110 mg/d of EDDI, (2) 10% soybean meal plus 113 g/d of ASCO, (3) 12.5% nondecorticated canola meal plus 110 mg/d of EDDI, and (4) 12.5% nondecorticated canola meal plus 113 g/d of ASCO. All diets contained (DM basis): 30% mixed, mostly legume baleage, 25% mixed, mostly grass baleage, 2% roasted soybean, 2.5% sugarcane liquid molasses, and 2% mineral-vitamin premix. Diets with soybean meal or nondecorticated canola meal also contained 28.5 and 26% of ground corn, respectively. The mineral-vitamin premix fed was not fortified with I and diets were formulated to contain similar concentrations of I. Both ASCO and EDDI were administered to each cow twice daily after being mixed with 227 g of ground corn per feeding. Milk samples for I analysis were collected and analyzed as reported in study 1 (Antaya et al., 2015). Intake and milk yield were recorded daily throughout the experiment.

Milk Iodine Data Sets, Sensitivity Analysis, and Nonlinear Regression

The data sets built to perform the sensitivity analysis used individual observations of milk I concentrations from cows fed diets with (Table 1) or without ASCO (Table 2). Milk I from cows fed soybean meal plus EDDI or nondecorticated canola plus EDDI (i.e., study 4) were discarded because the goal was to use ASCO as the major source of I to dairy cows in the simulations.

The annual per capita consumption of 2% reduced-fat milk by the American population, converted to daily intake (0.26 cup; 1 cup = 236.6 mL; USDA-ERS,

Table 1. Descriptive statistics of the milk iodine concentration (µg/L) data set built from 4 studies in which Jersey cows were fed diets containing *Ascophyllum nodosum* meal (ASCO)

Study	Dietary treatments with ASCO	n[1]	Mean	SD	Minimum	Maximum
1[2]	56, 113, and 176 g/d of ASCO	48	996	509	288	2,103
2[2]	113 g/d of ASCO	29[3]	483	162	211	822
3[4]	56, 113, and 176 g/d of ASCO	15	1,007	416	508	1,833
4[4]	113 g/d of ASCO + soybean meal and 113 g/d of ASCO + canola meal	32	561	245	248	1,033
Overall	All ASCO-supplemented diets	124	765	444	211	2,103

[1]Number of individual cow observations derived from dietary treatments containing ASCO.

[2]Nutrient intake, milk yield and composition including milk iodine, apparent total-tract digestibility of nutrients, and blood metabolite concentration results from study 1 were published by Antaya et al. (2015) and those from study 2 were published by Antaya et al. (2019).

[3]One observation was deemed an outlier (>2.5 SD of the mean) and removed from the data set.

[4]Apart from milk iodine concentration and yield reported herein, remaining data from study 3 and study 4 are unpublished.

2019), was used as a fixed value (i.e., actual drinking amount) in the sensitivity analysis. Two percent reduced-fat milk was selected based on the 2015–2020 Dietary Guidelines for Americans, which recommend daily consumption of 3 cups-equivalent (~710 mL) of fat-free or reduced-fat milk (USDHHS-USDA, 2015). Five additional milk intake scenarios—2, 3, 4, and 5 times the actual per capita milk consumption and the 3 cups-equivalent recommended by the 2015–2020 Dietary Guidelines for Americans (USDHHS-USDA, 2015)—were used in the simulations with varying milk I concentrations (180, 765, and 483 µg/L). The 180 µg/L concentration is the mean milk I concentration derived from cows that were not fed ASCO (studies 1–3). The 765 µg/L concentration is the mean milk I concentration obtained from cows fed different amounts of ASCO (57, 113, or 176 g/d) in the diet (studies 1–4). Last, the 483 µg/L concentration is the mean milk I concentration calculated from cows receiving 113 g/d of ASCO during the grazing season (study 2). Therefore, the milk I concentration data sets encompass experiments done during the winter season using cows under confinement management (studies 1 and 4), as well as the summer season with animals under grazing (study 2) or confinement (study 3) settings. Both the US IOM recommended daily allowance (**RDA**; IOM, 2001) and the WHO recommended nutrient intake (**RNI**; WHO, 2007) thresholds for I consumption by gestating women were used as fixed values (220 and 250 µg/d, respectively) in the sensitivity analysis to assess the amount of milk needed to meet recommendations. Note that a limitation of the sensitivity analysis was the assumption that intake of 2% reduced-fat milk in the United States is constant at 0.26 cup daily, thereby not accounting for person-to-person variation in milk consumption.

A regression analysis between dietary I intake with feeding 0, 57, 113, and 176 g/d of ASCO and milk I yield or milk I concentration was done using the nonlinear procedure of SAS (version 9.4; SAS Institute Inc., Cary, NC) after determining that a curvilinear model better fit the data sets than a linear model based on R^2. This regression approach was used to estimate the amount of dietary ASCO supplementation that resulted in the maximum 500 µg/L threshold of I in milk recommended by the European Food Society Authority (EFSA, 2013).

RESULTS

Iodine Concentration in Dairy Cow Diets

In study 1, DMI and dietary I concentrations averaged 17.5 kg/d and 0.95 mg/kg of DM, 18.1 kg/d and 3.31 mg/kg of DM, 18.1 kg/d and 5.69 mg/kg of

Table 2. Descriptive statistics of the milk iodine concentration (µg/L) data set built from 3 studies in which Jersey cows were fed diets without *Ascophyllum nodosum* meal (ASCO)

Study	Dietary treatments without ASCO	n[1]	Mean	SD	Minimum	Maximum
1[2]	0 g/d of ASCO	16	178	53.0	76.0	277
2[2]	0 g/d of ASCO	30	118	65.6	60.0	433
3[3]	0 g/d of ASCO and 300 mg/d of monensin	10	372	163	197	715
Overall	All diets without ASCO supplementation	56	180	127	60.0	715

[1]Number of individual observations derived from dietary treatments without ASCO supplementation.

[2]Nutrient intake, milk yield and composition including milk iodine, apparent total-tract digestibility of nutrients, and blood metabolite concentration results from study 1 were published by Antaya et al. (2015) and those from study 2 were published by Antaya et al. (2019).

[3]Apart from milk iodine concentration and yield reported herein, remaining data from study 3 are unpublished.

DM, and 17.6 kg/d and 8.35 mg/kg of DM in dairy cows fed 0, 57, 113, and 176 g/d of ASCO, respectively (Antaya et al., 2015). In study 2, DMI and dietary I levels averaged 16.6 kg/d and 1.07 mg/kg of DM, and 17.7 kg/d and 5.29 mg/kg of DM in grazing dairy cows receiving 0 and 113 g/d of ASCO, respectively (Antaya et al., 2019). In study 3, DMI and I concentration in the diets averaged 20.1 kg/d and 0.43 mg/kg of DM, 19.8 kg/d and 1.46 mg/kg of DM, 19.7 kg/d and 2.47 mg/kg of DM, and 19.8 kg/d and 3.48 mg/kg of DM and in dairy cows offered 0, 57, 113, and 176 g/d of ASCO, respectively, and 19.2 kg/d and 0.54 mg/kg of DM when feeding a diet containing monensin. In study 4, DMI and I levels in the diets averaged 21 kg/d and 4.30 mg/kg of DM and 21.9 kg/d and 4.16 mg/kg of DM when dairy cows were fed 10% soybean meal plus 113 g/d of ASCO or 12.5% nondecorticated canola meal plus 113 g/d of ASCO, respectively. In addition, the I concentrations of ASCO fed in the UNH experiments averaged 820, 727, 356, and 702 mg/kg in studies 1, 2, 3, and 4, respectively.

Milk I Concentration and Interindividual Variation

The descriptive statistics for the milk I concentration data sets built from 4 studies containing diets supplemented with various amounts of ASCO is presented in Table 1. The overall milk I concentration in cows fed diets with ASCO averaged 765 μg/L and ranged from 211 to 2,103 μg/L. Large variation in milk I concentrations were also detected in individual experiments with study 1 (Antaya et al., 2015) showing the greatest SD. Cows from study 3 had the greatest mean milk I concentration (i.e., 1,007 μg/L) and those from study 2 (Antaya et al., 2019), which was conducted during the grazing season, showed the lowest mean I content (i.e., 483 μg/L). Figure 1 further demonstrates a wide variation in milk I concentration, with 68% of the individual observations (84 out of 124) above the maximum 500 μg/L threshold recommended by the European Food Society Authority (EFSA, 2013). Similarly, a large interindividual variation in milk I yield was observed in cows assigned to different ASCO levels, as illustrated in Figure 2, using data from study 1 (Antaya et al., 2015).

The descriptive statistics for the milk I concentration data set built from 3 studies containing diets without ASCO is presented in Table 2. The overall milk I concentration in cows fed diets not supplemented with ASCO averaged 180 μg/L and ranged from 60 to 715 μg/L. Compared with the overall milk I concentration observed for cows fed ASCO (Table 1), that for cows without seaweed supplementation was 76.5% lower (Table 2). Likewise, the overall minimum and maximum milk I concentrations from cows not receiving ASCO were 71.6 and 66% lower than those measured in cows with seaweed supplementation in their diets.

Sensitivity Analysis and Regression Approach

Results of the sensitivity analysis with 6 milk intake scenarios and 3 milk I concentrations are presented in Table 3. Using the actual annual milk per capita consumption of 2% reduced-fat milk in the United States (USDA-ERS, 2019), which is equivalent to 0.26 cup/d, resulted in milk I intakes of 11.2, 47.4, and 29.9 μg/d with milk I concentrations of 180, 765, and 483 μg/L, respectively. Based on the RDA for I of 220 μg/d for pregnant women (IOM, 2001), milk I intakes of 11.2, 47.4, and 29.9 μg/d would meet 5.09, 21.7, and 13.6% of required I consumption, respectively. A similar calculation adopting the RNI for I of 250 μg/d (WHO, 2007) would satisfy 4.48, 19.0, and 12% of I needed for pregnant women with milk I intakes of 11.2, 47.4, and 29.9 μg/d, respectively.

Increasing the daily per capita consumption of 2% reduced-fat milk from 0.26 to 3 cups-equivalent, as recommended by the 2015–2020 Dietary Guidelines for Americans (USDHHS-USDA, 2015), led to milk I intakes ranging from 11.2 to 128 μg/d (Table 3), adopting the mean milk I concentration of 180 μg/L obtained from cows fed diets without ASCO (Table 2). This 11.2 to 128 μg/d range in milk I intakes fulfilled 5.09 to 58.2% and 4.48 to 51.2% of the RDA (IOM, 2001) and the RNI (WHO, 2007) for I required by pregnant women, respectively. A similar exercise using the mean milk I concentration of 765 μg/L from cows fed various

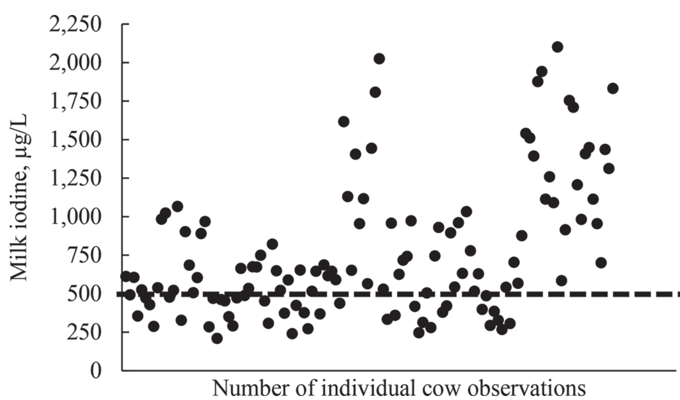

Figure 1. Milk iodine concentration in cows fed various amounts (56, 113, or 176 g/d) of *Ascophyllum nodosum* meal using data from study 1 (Antaya et al., 2015), study 2 (Antaya et al., 2019), study 3 (A. F. Brito, unpublished), and study 4 (A. F. Brito, unpublished). The dashed line indicates the 500 μg/L maximum threshold recommended by the European Food Society Authority (EFSA, 2013); n = 124 observations.

Table 3. Sensitivity analysis using different milk iodine (I) concentrations and milk I intakes relative to the United States Institute of Medicine (IOM, 2001) recommended dietary allowance (RDA) and the World Health Organization (WHO, 2007) recommended nutrient intake (RNI) for I needed by pregnant women

Daily per capita milk consumption		Milk I intake, µg/d	Milk I intake, % of RDA or RNI	
			RDA (220 µg of I/d)	RNI (250 µg of I/d)
Milk I concentration (180 µg/L)[1]				
Actual[2]	0.26 cup	11.2	5.09	4.48
2 × actual	0.52 cup	22.1	10.0	8.84
3 × actual	0.78 cup	33.3	15.1	13.3
4 × actual	1.04 cup	44.3	20.1	17.7
5 × actual	1.30 cup	55.4	25.2	22.2
2015–2020 Dietary Guidelines[3]	3 cups	128	58.2	51.2
Milk I concentration (765 µg/L)[4]				
Actual	0.26 cup	47.4	21.7	19.0
2 × actual	0.52 cup	94.1	42.8	37.6
3 × actual	0.78 cup	142	64.5	56.8
4 × actual	1.04 cup	188	85.5	75.2
5 × actual	1.30 cup	236	107	94.4
2015–2020 Dietary Guidelines	3 cups	543	247	217
Milk I concentration (483 µg/L)[5]				
Actual	0.26 cup	29.9	13.6	12.0
2 × actual	0.52 cup	59.4	27.0	23.8
3 × actual	0.78 cup	89.4	40.6	35.8
4 × actual	1.04 cup	119	54.1	47.6
5 × actual	1.30 cup	149	67.7	59.6
2015–2020 Dietary Guidelines	3 cups	343	156	137

[1]Where 180 µg/L is the mean milk I concentration derived from cows that were not fed *Ascophyllum nodosum* meal (ASCO; study 1, Antaya et al., 2015; study 2, Antaya et al., 2019; and study 3, A. F. Brito, unpublished).

[2]Annual per capita consumption of 2% reduced-fat milk by the American population, converted to daily intake (0.26 cup; 1 cup = 236.6 mL; USDA-ERS, 2019).

[3]2015–2020 Dietary Guidelines for Americans recommends the consumption of 3 cups-equivalent of reduced-fat milk for adults (USHHS USDA, 2015).

[4]Where 765 µg/L is the mean milk I concentration derived from cows fed different amounts of ASCO (56, 113, or 176 g/d) in the diet [study 1, study 2, study 3, and study 4 (A. F. Brito, unpublished)].

[5]Where 483 µg/L is the mean milk I concentration derived from cows receiving 113 g/d of ASCO during the grazing season (study 2).

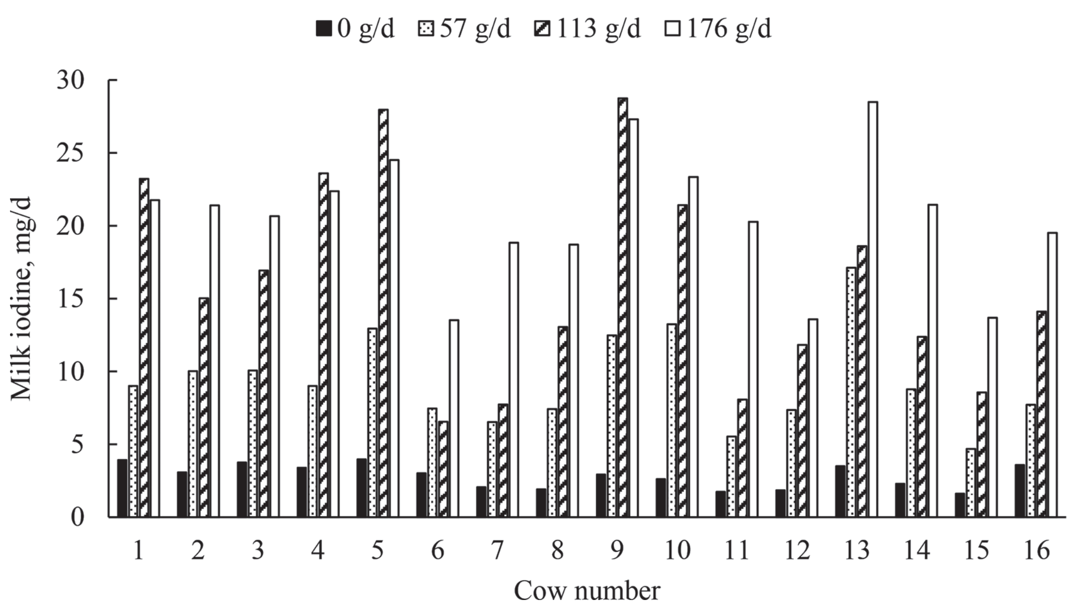

Figure 2. Interindividual variation in milk iodine yield in dairy cows fed incremental amounts of *Ascophyllum nodosum* meal (ASCO) in study 1 (Antaya et al., 2015). Milk iodine yield averaged 2.82, 9.33, 16.1, and 20.6 mg/d (SEM = 0.86 mg/d) when feeding 0, 57, 113, and 176 g/d of ASCO, respectively.

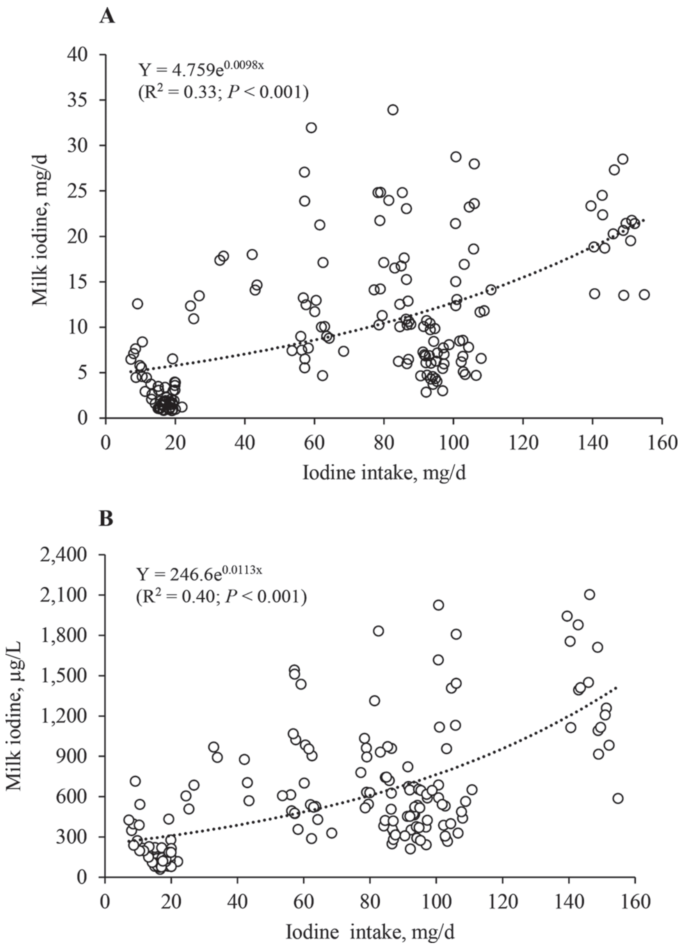

Figure 3. Nonlinear regression models between iodine intake from cows fed various amounts of *Ascophyllum nodosum* meal (0, 57, 113, or 176 g/d) and milk iodine yield (A) or milk iodine concentration (B) using data from study 1 (Antaya et al., 2015), study 2 (Antaya et al., 2019), study 3 (A. F. Brito, unpublished), and study 4 (A. F. Brito, unpublished).

amounts of ASCO (56, 113, and 176 g/d) yielded intakes of milk I that ranged from 47.4 to 543 μg/d (Table 3). With this range in milk I intakes, 21.7 to 247% and 19 to 217% of the RDA and the RNI for I required by pregnant women were satisfied, respectively. It should be emphasized that consumption of 1.35 and 3 cups of milk with I concentration of 765 μg/L exceeded the RDA for I for gestating women, whereas the RNI for I was surpassed only by ingestion of 3 cups of milk daily (Table 3). When the mean milk I concentration of 483 μg/L from grazing cows fed 113 g/d of ASCO was included in the simulations, intake of milk I went from 29.9 to 343 μg/d (Table 3). Based on the RDA and RNI for I for pregnant women, the 29.9 to 343 μg/d range in milk I intakes met 13.6 to 156% and 12 to 137% of the recommendations, respectively. Again, consumption of 3 cups of milk with I concentration of 483 μg/L exceeded the RDA and RNI for I needed by pregnant women (Table 3).

The regressions between dietary I intake in cows fed 0, 57, 113, or 176 g/d of ASCO and milk I yield or milk I concentration are presented in Figure 3A and 3B, respectively. Nonlinear models best fit both data sets yielding the following exponential equations: $Y = 4.759e^{0.0098x}$ ($R^2 = 0.33$; $P < 0.001$) for milk I yield and $Y = 246.6e^{0.0113x}$ ($R^2 = 0.40$; $P < 0.001$) for milk I concentration.

DISCUSSION

Study Limitations

The data sets used in the present study originated from experiments conducted at the UNH and, therefore, are limited by the management and feeding conditions of 2 dairy herds under similar climatic conditions. Consequently, the sensitivity and nonlinear regression analyses performed using site-specific data sets should be interpreted cautiously. Further, Jersey was the only breed used in all studies done at the UNH. According to Aikman et al. (2008), there are significant differences in ruminal passage rate, particle breakdown, chewing behavior, and fiber digestibility between Jersey and Holstein cows. Hence, it is conceivable that ASCO could be metabolized differently by Jersey versus non-Jersey dairy breeds, ultimately changing I digestibility and bioavailability. Nevertheless, milk I concentration increased significantly in both Jersey (Antaya et al., 2015, 2019) and Holstein (Chaves Lopez et al., 2016) cows fed various amounts of ASCO.

Dietary I Concentration and NRC (2001) Recommendation

Except for the diet without ASCO and monensin in study 3, whose I concentration averaged 0.43 mg/kg of DM, all remaining dietary I levels were above the 0.5 mg/kg threshold recommended by the NRC (2001) and ranged from 0.54 to 8.35 mg/kg of DM. However, there is no governmental policy enforcing the NRC (2001) recommended 0.5 mg/kg I concentration in livestock diets in the United States.

Milk I Concentration and Variation

The overall milk I concentration in cows fed diets with various amounts of ASCO averaged 765 μg/L and was 325% greater than the mean value (180 μg/L) obtained for cows without ASCO. Increased concentration of milk I in cows offered ASCO is not surprising because *A. nodosum* is known to bioaccumulate I through the uptake of I^- from seawater (Baily and Kelly, 1955; Küpper et al., 1998; Muramatsu and Wedepohl, 1998; Fuge and Johnson, 2015), which can be transferred into milk via ASCO supplementation (Antaya et al., 2015, 2019; Chaves Lopez et al., 2016; Sorge et al., 2016b). A large variation in milk I concentration was observed within and across experiments, reflecting differences in content and bioavailability of I present in *A. nodosum* used to produce ASCO, the amount of ASCO fed, ingredient composition of the basal diet, and management system (grazing vs. confinement). A relatively large variation in milk I concentration was also seen with feeding diets without ASCO supplementation, which may be explained by differences in I concentrations of the basal diets and types of forage sources used, as further discussed below.

The large variation in milk I concentration observed herein is consistent with that in the ASCO sources used in the 4 experiments (356 to 820 mg/kg). An additional factor involved in the variation of milk I concentration is the type of forage source used in the diet. For instance, milk I (mean = 483 μg/L) in grazing cows supplemented with 113 g/d of ASCO (study 2; Antaya et al., 2019) was 35.1% lower than that (mean = 744 μg/L; data not shown) from cows receiving conserved forages (baleage, haylage, and silage) and the same level of ASCO (i.e., 113 g/d) in studies 1 (Antaya et al., 2015), 3, and 4. Cool-season pastures used in study 2 consisted of perennial grass and legume herbages, with orchardgrass (*Dactylis glomerata* L.) and white clover (*Trifolium repens* L.) being among the most predominant species (Antaya et al., 2019). White clover can release hydrogen cyanide following the action of cyanogenic β-glucosidases (Crush and Caradus, 1995; Seigler, 1998; Osman et al., 2013) that become active after herbivory or damaged plant tissues (Gleadow and Woodrow, 2002). Detoxification of hydrogen cyanide by the ruminal microbiota and liver cells forms thiocyanates and other derivatives known to competitively inhibit I^- uptake by the Na-I^- symporter into bodily tissues such as the thyroid and mammary glands (Greer et al., 1966; Tripathi and Mishra, 2007; Osman et al., 2013), ultimately impairing the transfer of I into milk (Brown-Grant, 1957; Franke et al., 2009; Weiss et al., 2015). Further, herbage grazed in study 2 had an average glucosinolates concentration of 89.6 mg/kg compared with 80.1 and 34.1 mg/kg of the concentrate blend and baleage, respectively (Antaya et al., 2019). Glucosinolates are a group of sulfur-containing secondary plant compounds that, after degradation by the ruminal microbiota, yield thiocyanates and derivative compounds that interfere with the uptake of I^- (Tripathi and Mishra, 2007; Osman et al., 2013).

Sensitivity Analysis and Milk I Intake by Pregnant Women

According to the present sensitivity analysis, the consumption of 3 cups/d of 2% reduced-fat milk containing 180 μg/L of I from cows fed diets without ASCO led to 128 μg of milk I intake daily or 58.2 and 51.2% of the RDA (IOM, 2001) and RNI (WHO, 2007) for I needed by pregnant women, respectively. When the actual milk consumption of 0.26 cup/d was included in the simulations, milk I intake decreased by over 91.3% compared with 3 cups-equivalent, and only 5.09 and 4.48% of the RDA and RNI for I were met, respectively. Despite milk being a major source of I for humans in industrialized countries (Pennington, 1990a; Pearce et al., 2004; Borucki Castro et al., 2010; van der Reijden et al., 2017; Walther et al., 2018), per capita consumption of fluid milk by the American population has declined steadily over time (USDA-ERS, 2019). For instance, the national annual per capita consumption of 2% reduced-fat fluid milk decreased from 35.6 to 22.5 kg over about 3 decades (1990 to 2017; USDA-ERS, 2019). Although poor milk consumption is concerning and likely contributes to insufficient dietary I intake by American women during pregnancy (Sullivan et al., 2013; IGN, 2017), other food items such as salt, cheese, breads, cereals, fish, seafood, and prenatal multivitamins and supplements also provide I (Pehrsson et al., 2016; Lee et al., 2017; Ershow et al., 2018). However, 53% of the table salt sold in the United States is not iodized (Maalouf et al., 2015) and, despite the 2015–2020 Dietary Guidelines for Americans recommendation of <2,300 mg of daily sodium consumption (USDHHS-USDA, 2015), most adults and children in the country exceeded this threshold (Jackson et al., 2016). Nevertheless, it is possible to cost-effectively reduce sodium intake while meeting I requirements by increasing the concentration of I in iodized salt (WHO, 2014). Moreover, full implementation of universal salt iodization could also mitigate I deficiency, but lack of natural dietary I sources is a major concern for public health worldwide (WHO, 2014). Therefore, naturally enriching milk by supplementing dairy cows with ASCO in addition to changes in salt iodization policies are complementary strategies to optimize I intake during pregnancy and lactation. Note that a large interindividual variation in milk I yield was observed in cows assigned to the same treatment in study 1 (Figure 2), suggesting that any approach to use ASCO-based supplementation in dairy diets would need to take this variation into consideration.

The sensitivity analysis revealed that daily consumption of 3 cups of 2% reduced-fat milk containing 765 μg/L of I from cows fed various amounts of ASCO resulted in 543 μg of milk I intake/d or 247 and 217% of the RDA (IOM, 2001) and RNI (WHO, 2007) for I required by pregnant women, respectively. Therefore, following the recommendation by the 2015–2020 Dietary Guidelines for Americans of 3 cups-equivalent of fat-free or reduced-fat milk for adults in the United States (USDHHS-USDA, 2015) culminated in milk I intake (543 μg/d), which was 49.4% of the tolerable upper limit consumption of 1,100 μg of I/d for 19- to 50-yr-old adults according to the US IOM (IOM, 2001). In contrast, a daily intake of 543 μg of milk I would slightly exceed the maximum recommended 500 μg of I/d for pregnant women following the WHO guidelines (Andersson et al., 2007). However, a lower consumption of milk (e.g., 0.78 cup) with an I concentration of 765 μg/L would meet 64.5 and 56.8% of the RDA and RNI for I needed by pregnant women, respectively, while minimizing toxicity risks, as other I sources in addition to milk are available in humans' diets (Pehrsson et al., 2016; Lee et al., 2017; Ershow et al., 2018). Although chronic consumption of excess I does not generally represent an important public health concern in the United States (Pearce et al., 2004), it may increase the risk of thyroiditis, hyperthyroidism, hypothyroidism, and goiter in individuals with underlining thyroid issues or in vulnerable groups (e.g., seniors, fetuses, and neonates; Pennington, 1990b; Katagiri et al., 2017).

Daily consumption of 3 cups of 2% reduced-fat milk containing 483 μg/L of I from cows fed 113 g/d of ASCO during the grazing season (study 2; Antaya et al., 2019) resulted in 343 μg of milk I intake or 156 and 137% of the RDA (IOM, 2001) and RNI (WHO, 2007) for I needed by pregnant women, respectively, based on the sensitivity analysis. This daily intake of 343 μg of milk I is equivalent to about one-third of the tolerable upper limit consumption of 1,100 μg of I/d for 19- to 50-yr-old adults according to the US IOM (IOM, 2001), and 69% of the maximum recommended 500 μg of I/d during pregnancy following the WHO (Andersson et al., 2007). However, using the actual 2% reduced-fat milk per capita intake of 0.26 cup/d in the United States and assuming I concentration of 483 μg/L would result in 29.9 μg of milk I consumed daily, thus satisfying only 13.6 and 12% of the RDA and RNI for I required by pregnant women, respectively.

Milk I Concentration Healthy Threshold for Humans

Despite the lack of conclusive standards for I levels in milk relative to human health, a maximum of 500 μg/L has been advised by the European Food Society Authority (EFSA, 2013). As shown in Figure 1, 68% of the individual cow observations (84 out of 124) for milk I concentration were >500 μg/L. However, the mean milk I concentration of 483 μg/L (study 2; Antaya et al., 2019) was below 500 μg/L, suggesting that American pregnant women consuming milk from grazing dairy cows would need more than 0.26 cup/d to ensure healthy I status. In fact, consumption of dairy products by pregnant women contributed decisively to keeping their I status within a safe range (Perrine et al., 2010). Specifically, pregnant women who did not consume dairy products in the past 24 h had a median urinary I concentration <100 mg/L compared with 163 mg/L for those who had consumed dairy foods in the previous 24 h (Perrine et al., 2010). It is well established that I is a key component of the hormones produced by the thyroid gland, which are particularly important during pregnancy for promoting fetal brain development and cognitive development of newborns (Zimmermann, 2009; Leung et al., 2011).

Estimation of I Intake by Dairy Cows to Meet Milk I Concentration Recommendation

Based on the regression analysis between I intake and milk I concentration, consumption of 63 mg/d of I by Jersey cows would reach the recommended maximum milk I concentration of 500 μg/L. This 63 mg/d I intake would be equivalent to 103 g/d of ASCO supplementation assuming I concentration of 611 mg/kg calculated through weighted average according to the proportion of individual cow observations from each study to the milk I data sets. Pregnant women drinking 3 cups of milk daily (USDHHS-USDA, 2015) would ingest 355 μg of milk I if cows were offered 103 g/d of ASCO. Further, 355 μg of milk I intake would meet 161 and 142% of the RDA (IOM, 2001) and RNI (WHO, 2007) for I required by pregnant women, respectively. To achieve the 220 μg/d RDA and 250 μg/d RNI for I, the I intakes of cows should be 23.7 mg/d (38.6 g/d of ASCO) or 34.7 mg/d (56.5 g/d of ASCO), which would correspond to 310 and 352.2 μg/L of milk I, respectively, based on the nonlinear regression analysis. It is important to note that factors such as intake of goitrogenic compounds were not included in the regression analysis, which could have improved the accuracy of the model as reported by Trøan et al. (2015), who also observed a curvilinear relationship between I intake and milk I concentration in dairy cows. According to the EFSA (2013), in diets without glucosinolates, the 500 μg/L threshold can be exceeded at 2 mg of I/kg, whereas more than 4 mg of I/kg is needed to surpass 500 μg/L in rations containing high concentrations of glucosinolates.

CONCLUSIONS

Overall, results of the sensitivity analysis suggested that pregnant American women should consume either 1.3 to 3 cups/d of milk from cows not supplemented with ASCO or between 0.52 and 1.04 cup/d of milk from cows that received various amounts of ASCO to meet about 22 to 86% of the RDA (United States Institute of Medicine) and RNI (World Health Organization) for I. However, using the recommend consumption of 3 cups-equivalent of milk by the 2015–2020 Dietary Guidelines for Americans and the mean milk I concentration of 765 μg/L from cows offered ASCO resulted in milk I intake (i.e., 543 μg/d) that was 247 and 217% of the RDA and RNI for I needed by pregnant women, respectively. Sixty-eight percent of the milk I observations were above the maximum 500 μg/L threshold advised by the European Food Safety Authority to minimize risks of I toxicity, suggesting that no more than 103 g/d of ASCO should be supplemented to dairy cows based on the regression analysis between I intake and milk I concentration. In addition, a large interindividual variation in milk I concentration between cows fed the same amount of ASCO was observed. This, together with the within- and across-experiment variation in milk I output, makes the use of ASCO challenging as a natural source of I to mitigate I deficiency in pregnant women via milk I consumption. Further research is warranted to gain insights into I bioavailability of ASCO from different sources. Research is also required to better understand the interactions between goitrogenic compounds present in forages and concentrate sources and milk I concentration in cows fed ASCO under pasture- and confinement-based management systems. Finally, research to evaluate the concentration of I in retail organic milk should be conducted because of the high prevalence of ASCO supplementation in organic dairies in the United States.

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