Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide[1–4]

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ABSTRACT

Concentrations of the long-chain polyunsaturated fatty acids (LCPUFAs) docosahexaenoic acid (DHA, 22:6n−3) and arachidonic acid (AA, 20:4n−6) in human breast milk are important indicators of infant formula DHA and AA concentrations, and recent evidence suggests that neural maturation of breastfed infants is linked to breast-milk LCPUFA concentrations. We report a descriptive meta-analysis that considered 106 studies of human breast milk culled to include only studies that used modern analysis methods capable of making accurate estimates of fatty acid (FA) profiles and criteria related to the completeness of reporting. The final analysis included 65 studies of 2474 women. The mean (±SD) concentration of DHA in breast milk (by wt) is 0.32 ± 0.22% (range: 0.06–1.4%) and that of AA is 0.47 ± 0.13% (range: 0.24–1.0%), which indicates that the DHA concentration in breast milk is lower than and more variable than that of AA. The highest DHA concentrations were primarily in coastal populations and were associated with marine food consumption. The correlation between breast-milk DHA and AA concentrations was significant but low ($r = 0.25$, $P = 0.02$), which indicates that the mean ratio of DHA to AA in regional breast milk varies widely. This comprehensive analysis of breast-milk DHA and AA indicates a broad range of these nutrients worldwide and serves as a guide for infant feeding. *Am J Clin Nutr* 2007;85:1457–64.

KEY WORDS Lactation, docosahexaenoic acid, arachidonic acid, infant nutrition, descriptive meta-analysis

INTRODUCTION

Human breast milk is universally recognized as the optimal food for term infants. Fat is a critical component of breast milk, providing energy and, importantly, nutrients key to the development of the central nervous system, which cannot be synthesized de novo by the infant (1). Principal among these FAs are the long-chain polyunsaturated FAs (LCPUFAs) docosahexaenoic acid (DHA) and arachidonic acid (AA), which are now components of infant formulas in developed countries throughout the world. The synthesis of DHA and AA from precursor FAs appears to be limited for at least some human infants (2, 3).

Both DHA and AA have been found in all breast milks examined to date via appropriate methods. Short-term diets clearly influences the LCPUFA content of breast milk, and there is evidence that habitual intake has an influence as well (4–6). In small studies, fish-eating populations have higher breast-milk DHA concentrations than do populations that do not consume marine foods (7, 8), and there is evidence that poorly nourished mothers conserve PUFAs and LCPUFAs in their breast milk at the expense of saturates (9). Breast-milk FA concentrations, therefore, vary with the lifestyle of the population of lactating mothers under study; thus, FA concentrations vary by region.

The concentrations of human breast-milk DHA and AA have been reported since at least the 1970s (10). They have been tabulated in reviews (1) from small cross-sections of references, and summary concentrations are quoted frequently. However, because breast-milk DHA and AA concentrations vary by diet, nutritional status, and other factors, analyses based on selected studies are biased to the samples considered. No extant systematic reviews of breast-milk DHA and AA concentrations exist in the peer-reviewed literature.

Our goal is to establish the distributions of DHA and AA concentrations in mature breast milk from free-living mothers. Our strategy was to identify all articles in the peer-reviewed literature that report DHA and AA concentrations in breast milk from mothers of term infants. The mothers must have consumed their normal diets, which were not purposefully influenced by experimental manipulations, such as marine-oil supplementation. From the database of all articles that were identified, we selected those that used modern capillary gas chromatography (GC) for analysis, which is capable of resolving DHA and AA from compounds that elute nearby. We also included selection criteria related to the completeness of reporting and sampling. Summary statistics were then provided for the main group of articles and the excluded group.

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TABLE 1
Studies included in the primary analysis[1]

Reference	Site	Infant age	Subjects	DHA[2]	AA[3]
		mo	*n*	*% of total fatty acids*[4]	*% of total fatty acids*[4]
Yuhas et al, 2006 (11)	Australia	1–12	48	0.23	0.38
Yuhas et al, 2006 (11)	Canada	1–12	48	0.17	0.37
Yuhas et al, 2006 (11)	Chile	1–12	50	0.43	0.42
Yuhas et al, 2006 (11)	China	1–12	50	0.35	0.49
Yuhas et al, 2006 (11)	Japan	1–12	51	0.99	0.40
Yuhas et al, 2006 (11)	Mexico	1–12	46	0.26	0.42
Yuhas et al, 2006 (11)	Philippines	1–12	54	0.74	0.39
Yuhas et al, 2006 (11)	United Kingdom	1–12	44	0.24	0.36
Yuhas et al, 2006 (11)	USA	1–12	49	0.17	0.45
Sala-Vila et al, 2008 (12)	Spain	0.5–1	10	0.31	0.49
Olafsdottir et al, 2006 (7)	Iceland	2	59	0.30	0.32
Xiang et al, 2005 (12)	China	3	23	0.18	0.51
Kovacs et al, 2005 (14)	Denmark	4	39	0.35	0.30
Jensen et al, 2005 (15)	USA, Texas	4	77	0.20	0.44
Bopp et al, 2005 (10)	USA, North Carolina	3	22	0.21	0.41
Stoney et al, 2004 (17)	Australia	3	36	0.26	0.38
Sala-Vila et al, 2004 (10)	Spain	3	11	0.28	0.41
Minda et al, 2004 (19)	Hungary	1	18	0.19	0.59
Fraricois et al, 2003 (20)	USA, Oregon	2–11	14	0.20	0.50
Marangoni, et al, 2002 (21)	Italy	3	73	0.35	0.50
Krasevec et al, 2002 (22)	Cuba	2	52	0.43	0.67
Hawkes et al, 2002 (23)	Australia	1	27	0.26	0.46
Jorgensen et al, 2001 (24)	Denmark	4	39	0.35	0.30
Helland et al, 2001 (25)	Norway	3	111	0.47	0.37
Auestad et al, 2001 (26)	USA	4	29	0.15	0.48
Xiang et al, 2000 (27)	Sweden	3	19	0.25	0.38
Wang et al, 2000 (25)	Japan	0.3	20	1.10	1.00
Vander Jagt et al, 2000 (29)	Nigeria, Niger	0.3–6	34	0.20	0.51
Smit et al, 2000 (5)	Netherlands	3	25	0.14	0.33
Smith et al, 2000 (5)	Pakistan	12	8	0.06	0.26
Smith et al, 2000 (30)	Israel	3–10	10	0.15	0.49
Okolo et al, 2000 (21)	Nigeria	0.1–0.5	28	0.32	0.58
Okolo et al, 2000 (31)	Nigeria	6–7	15	0.33	0.44
Marangoni et al, 2000 (32)	Italy	6	10	0.28	0.50
Knox et al, 2000 (9)	Nigeria, Niger	0.3–16	89	0.20	0.57
Jensen et al, 2000 (33)	USA	2	6	0.19	0.53
Fidler et al, 2000 (34)	Germany	1.5	5	0.21	0.43
Xiang et al, 1999 (35)	China	1	18	0.33	0.63
Makrides et al, 1999 (36)	Australia	4	33	0.20	0.39
Dodge et al, 1999 (37)	Xichang, China	2–18	10	0.22	0.52
Dodge et al, 1999 (37)	Beijing, China	2–18	10	0.28	0.63
Dodge et al, 1999 (37)	Enshi, China	2–18	9	0.15	0.35
Woltil et al, 1998 (32)	Netherlands	>0.3	29	0.19	0.40
Yu et al, 1998 (39)	Sweden	6	17	0.18	0.34
Rueda et al 1998 (40)	Spain	0.5–1	8	0.38	0.69
Rueda et al, 1998 (40)	Panama	0.5–1	8	0.32	0.52
Rocquelin et al, 1998 (48)	Congo	5	102	0.55	0.44
Maurage et al, 1998 (42)	France	1.5	15	0.14	0.24
Helland et al, 1998 (43)	Norway	0.75–2	22	0.38	0.34
Francois et al, 1998 (44)	USA	6	7	0.20	0.40
Innis et al, 1997 (45)	Canada	3	56	0.20	0.50
Billeaud et al, 1997 (46)	France	NR	25	0.32	0.52
Auestad et al, 1997 (47)	Canada	4	43	0.12	0.51
Ratnayake and Chen et al, 1996 (48)	Canada	0.75–1	198	0.14	0.35
Makrides et al, 1998 (12)	Australia	3	12	0.21	0.41
Horby Jorgensen et al, 1996 (49)	Sweden	4	14	0.53	0.44
Huisman et al, 1996 (50)	Netherlands	3	25	0.19	0.34
de la Presa-Owens et al, 1996 (51)	Spain	0.6–1	40	0.34	0.50
Cherian et al, 1996 (52)	Canada	NR	5	0.3	0.40

(*Continued*)

TABLE 1 (*Continued*)

Reference	Site	Infant age	Subjects	DHA[2]	AA[3]
		mo	*n*	*% of total fatty acids*[4]	*% of total fatty acids*[4]
Makrides et al, 1995 (53)	Australia	4	23	0.21	0.40
Luukkainen et al, 1995 (54)	Finland	3	10	0.18	0.33
Chardigny et al, 1995 (55)	France	0–3	10	0.32	0.50
Luukkainen et al, 1994 (56)	Finland	4	16	0.18	0.33
Innis et al, 1994 (57)	Canadian Arctic	1–7	5	1.40	0.60
Innis et al, 1994 (57)	Vancouver	2–4	12	0.40	0.70
Budowski et al, 1994 (58)	Israel	1.5–2.5	26	0.38	0.59
van Beusekom et al, 1993 (59)	Netherlands	0.5–1	5	0.26	0.47
van Beusekom et al, 1993 (60)	Dominican Republic	0.75	7	0.40	0.50
Martin et al, 1993 (61)	France	1	24	0.24	0.36
Guesnet et al, 1993 (62)	France	3	28	0.38	0.50
Henderson et al, 1992 (63)	USA, Connecticut	0.5	5	0.37	0.67
Ogunleye et al, 1991 (8)	Nigeria	2–3	20	0.34	0.56
Ogunleye et al, 1991 (8)	Japan	2.3–3.3	53	0.53	0.36
Boersma et al, 1991 (64)	Saint Lucia	1	12	0.53	0.58
van Beusekom et al, 1990 (65)	Dominican Republic	>0.3	6	0.91	0.33
van Beusekom et al, 1990 (65)	Belize	>0.3	6	0.21	0.44
van der Westhuyzen et al, 1988 (66)	Urban south Africa	6.8	12	0.20	0.60
van der Westhuyzen et al, 1988 (66)	Rural south Africa	6.5	18	0.10	1.00
Koletzko et al, 1988 (67)	Germany	3–4	15	0.22	0.36
Innis et al, 1988 (68)	Canada	>3	17	0.20	0.50
Muskiet et al, 1987 (69)	Tanzania	>0.3	11	0.27	0.60
Muskiet et al, 1987 (69)	Curao	>0.3	47	0.43	0.71
Muskiet et al, 1987 (69)	Suriname	>0.3	20	0.41	0.58
Carlson et al, 1986 (70)	USA	0.5	11	0.19	0.59

[1] A total of 84 studies including a total of 2974 subjects are reported. NR, not reported; DHA, docosahexaenoic acid, AA, arachidonic acid.
[2] $\bar{x} \pm$ SD: 0.32 ± 0.22.
[3] $\bar{x} \pm$ SD: 0.47 ± 0.13.
[4] By weight.

SUBJECTS AND METHODS

Inclusion criteria

PubMed searches were performed with the keywords "breast milk" and "docosahexaenoic" periodically over several years, most recently in November 2006. All data were from mothers of term infants in good health who consumed free-living or control diets during the intervention studies. Data from experimental groups who had special diets or consumed LCPUFA supplements were excluded in the primary analysis, as were experiments that analyzed pooled breast milk. Studies that included data from only one mother, pooled or banked milk samples, and mothers of preterm infants were excluded. Because DHA and AA are more concentrated in phospholipids than are triacylglycerols, studies that reported concentrations by lipid class only were excluded. When values from multiple time points postpartum were available, the 2–6 mo postpartum data were used.

Studies meeting these criteria were split into 2 groups; the primary group consisted of those that used capillary GC columns that can fully resolve FA methyl esters with retention times very similar to those for DHA and AA; the secondary group consisted of mostly older studies that used packed GC columns, which cannot resolve DHA and AA and thus may provide artifactually high values. We calculated means and SDs from both groups for comparison and reserved the analysis of the distribution of values for the primary group.

FA concentrations are most often reported as a percentage of the total, by weight (wt:wt, or weight for weight). Several studies did not report FA data for saturates, monounsaturates, and PUFAs. Because percentages are the norm for reporting FAs, and percentages depend on the total number of FAs included in the calculation, we included only those values reported in the context of a full FA profile.

All of the articles considered in this meta-analysis are listed in **Table 1** and **Table 2**. Sixty-five articles providing 84 mean values from 2474 subjects reported analyses with capillary columns and were judged to provide sufficient detail to be included in the primary analysis group (Table 1).The 41 articles judged to be outside the stated criteria and assigned to the secondary group are listed in Table 2.

RESULTS

The distribution of DHA and AA concentrations (wt:wt) are shown in **Figure 1**, and the summary statistics are shown in **Table 3**. The mean (±SD) concentrations of DHA and AA in the primary analysis group were 0.32 ± 0.22% and 0.47 ± 0.13%, respectively.

The secondary analysis group yielded somewhat greater values for DHA of 0.40 ± 0.41% and for AA of 0.56 ± 0.26%. The mean value for AA deviates by 0.09% (wt:wt) from that of the primary reference group, whereas the mean value for DHA deviates by 0.08% (wt:wt). These statistics are consistent with the hypothesis that the poorer resolution of packed-column GC yields higher values for DHA and AA than does capillary GC; these data also included a few studies with DHA and AA values

TABLE 2
Studies excluded from the primary analysis[1]

Reference	Reason for exclusion
Straarup et al, 2006 (71)	Preterm, pooled sample
Agostoni et al, 2003 (72)	Pooled sample
Lapillone et al, 2000 (73)	Pooled sample
Fidler et al, 2000 (74)	Analysis of colostrum
Schmeits et al, 1999 (75)	Analysis of milk TG only
Pugo-Gunsam et al, 1999 (76)	Analysis of milk TG only
Kaila et al, 1999 (77)	Banked samples
Guesnet et al, 1999 (78)	Few FAs reported
Bougle et al, 1999 (79)	Few Fas reported
Babin et al, 1999 (80)	Preterm
Agostoni et al, 1999 (81)	Only DHA and AA reported
Henderson et al, 1998 (82)	Few FAs reported
Fidler et al, 1998 (83)	Pooled sample
Carnielli et al, 1998 (84)	Preterm
Clandinin et al, 1997 (85)	Preterm
Makrides et al, 1996 (12)	Pooled sample
Jacobs et al, 1996 (86)	Preterm
Foreman-van Drongelen et al, 1996 (87)	Preterm
Beijers and Schaafsma, 1996 (88)	Preterm
Ruan et al, 1995 (89)	Packed column
Luukainen et al, 1995 (90)	Banked samples
Glew et al, 1995 (91)	Packed column
Jackson et al, 1994 (92)	Packed column
Hoffman et al, 1993 (93)	Preterm
Spear et al, 1992 (94)	One subject only
Sanders et al, 1992 (6)	Packed column
Dotson et al, 1992 (95)	*n* not provided
Prentice et al, 1989 (96)	Pooled sample
De-Lucchi et al, 1988 (97)	Packed column
Specker et al, 1987 (4)	Few FA reported
Kneebone et al, 1985 (98)	Packed column
Finley et al, 1995 (99)	Packed column
Harris et al, 1984 (100)	One subject consumed fish oil
Okolska et al, 1983 (101)	Packed column
Harzer et al, 1983 (102)	Pooled sample
Bitman et al, 1983 (103)	Packed column
Putnam et al, 1982 (104)	Packed column
Jansson et al, 1981 (105)	Packed column
Gibson and Kneebone, 1981 (106)	Packed column
Gibson and Kneebone, 1980 (107)	Analysis of colostrum
Hall et al, 1979 (10)	Packed column

[1] TG, triacylglycerol; DHA, docosahexaenoic acid; AA, arachidonic acid; FA, fatty acid.

from colostrum, which is considered richer in LCPUFA than mature milk. We conclude that our exclusion criteria yielded slightly lower overall mean LCPUFA concentrations.

Considering only the primary analysis, the CV for DHA was 0.22/0.32 = 69%, whereas that for AA was 0.13/0.47 = 28%. SDs are a composite of *1*) analytic error (including variability in sampling, extraction, derivatization, and signal processing) and *2*) real biological variability, each of which contributes variance to the overall spread in the data. It is not possible to reliably estimate the relative contributions of each of these 2 components of variability from so many studies. However, we note that the typical analytic test-retest precision for capillary GC analysis of FAs of 0.1–1.0% abundance is ≈0.1%, and there is no reason to expect that the analytic variance for DHA should differ from that of AA. We can confidently assign excess spread in the data to real biological variability, induced primarily by diet but by other

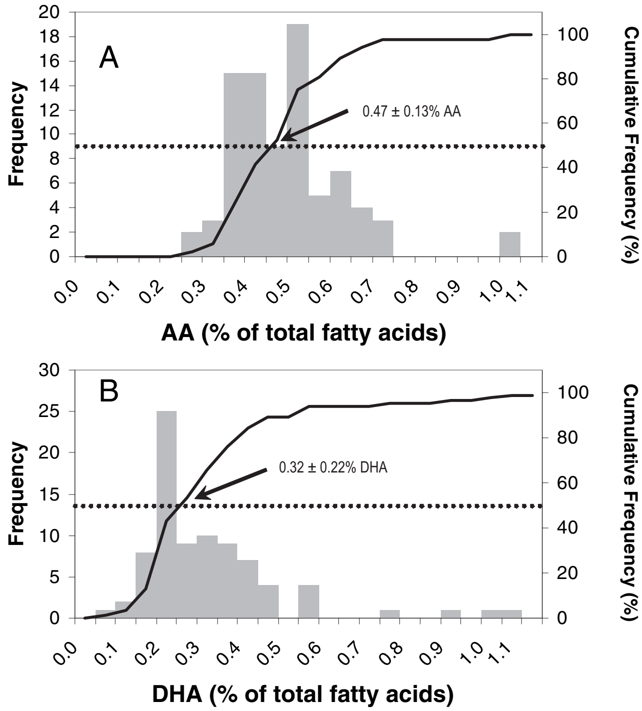

FIGURE 1. Distribution of arachidonic acid (AA) and docosahexaenoic acid (DHA) in human breast milk in the primary analysis group, presented as a histogram. The arrow refers to the location of the average at the 50th percentile.

factors as well. We conclude that the excess variance in DHA distribution is evidence of the tighter control of AA concentrations in breast milk, which is consistent with many other data, which show that tissue AA concentrations are more refractory to dietary manipulation than are DHA concentrations (108).

A plot of AA versus DHA concentrations for the primary analysis group is shown in **Figure 2**. The correlation was significant but low (r = 0.25, P = 0.02), which indicated that the prediction of the concentration of one mean LCPUFA from the other is nearly meaningless for a set of regional samples. This implies that the correlation of DHA and AA in any particular breast-milk sample is still lower because of the mathematical fact that the correlation between mean values is always greater than the correlation between data points making up those means. The shallow slope (0.15) shows that AA concentrations, on average, vary much less than do DHA concentrations, and inspection of

TABLE 3
Summary statistics for the primary analysis group[1]

	DHA	AA
	% of total fatty acids[2]	
Mean	0.32	0.47
Median	0.26	0.46
Mode	0.20	0.50
Range	0.06–1.40	0.24–1.0
SD	0.22	0.13
Kurtosis	9.85	3.95
Skewness	2.82	1.46

[1] DHA, docosahexaenoic acid; AA, arachidonic acid.
[2] By weight.

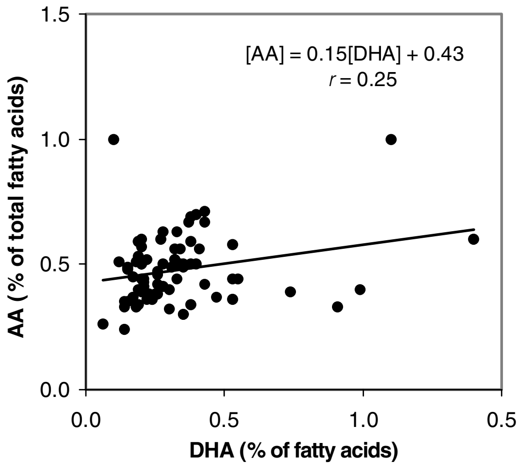

FIGURE 2. Mean concentrations of arachidonic acid (AA) versus docosahexaenoic acid (DHA) in breast milk. The slope is significant ($P = 0.02$).

the plot indicates that the significance of the slope is driven by a few high values for DHA.

DISCUSSION

Using strict selection criteria for data quality in this meta-analysis, we found that worldwide mean DHA and AA concentrations in human milk are 0.32 ± 0.22% and 0.47 ± 0.13%, respectively.

There are ≥2 ways to compute worldwide mean LCPUFA values, both of which have inherent weightings that should be borne in mind. A simple mean of mean values, as we computed, is inherently weighted evenly by study and against the number of subjects in each study. For instance, a study with 8 subjects is weighted the same as a study with 100 subjects. It is also biased toward regions in which more studies have been conducted, and away from regions in which fewer have been studied. This procedure has the advantage of effectively estimating a mean for each study population, which then contributes one data point (for DHA) to the meta-analysis.

An alternative is to compute mean DHA and AA values by using weightings according to the number of subjects in each study. This mean is biased toward studies, and therefore regions, in which most of the subjects have been enrolled, and intuitively we see no rationale for doing so. Nevertheless, we computed this mean for comparison with our reported value. The weighted mean DHA was 0.32%, equivalent to the nonweighted mean, and thus the 2 approaches yield the same result. The AA weighted mean was 0.45%, which represents a deviation of −0.02% from our reported value. There are data from many more natives of developed countries than for natives of traditional cultures, and this selection bias may have contributed to the deviation. Nevertheless, the magnitude of the deviation is a fraction of the AA SD, 0.13%. We know of no data to suggest that a difference of this magnitude is biologically significant.

Concentrations of DHA and AA in breast milk depend on the amount of these preformed FAs in the mother's diet and their biosynthesis from precursors. Milk DHA content appears to be closely linked to maternal dietary DHA intake, with dose-dependent linear increases in breast-milk concentrations of this nutrient with increased maternal intake (109). In our study, the 5 locales with the greatest breast-milk DHA concentration are Canadian Arctic, Japan, Dominican Republic, Philippines, and Congo (1.4–0.6%); all but Congo are coastal or island populations that have a high marine food intake. In contrast, the lowest breast-milk DHA values are for Pakistan, rural South Africa, Canada, the Netherlands, and France (0.06–0.14%). These populations are either inland or are developed countries, both of which are usually associated with low marine food consumption. Thus, the extreme values are consistent with studies suggesting that marine food–consuming populations have greater breast-milk DHA concentrations (7, 8).

The response of milk AA concentrations to maternal dietary AA intake is less predictable than that of DHA and may be more sensitive to the profile of other maternal dietary FAs (30). Several studies have shown that the biosynthesis of DHA and AA from precursors is low: in 2 studies of men, <0.01% of labeled linolenic acid (18:3n−3) was converted to DHA as measured in plasma (110, 111), although there is evidence that conversion is greater in women (112). Importantly, sustained high supplementary dietary linolenic acid (10.7 g/d) did not increase breast-milk DHA (20). The majority of AA in milk was not from dietary LA conversion but rather from maternal stores (113). The weight of current evidence is that biosynthesis of DHA and AA is low, and augmentation of breast-milk DHA and possibly AA during lactation is best accomplished by consumption of preformed DHA and AA.

The higher variability of DHA than of AA is consistent with the conclusions of a recent study, which was included in the present analysis (11). This study conducted a comprehensive analysis of FA profiles in breast milk from women from 9 countries and concluded that DHA was the most variable of all the FAs, and that AA was much less so.

The best estimates of worldwide mean breast-milk DHA and AA concentrations (wt:wt) from the primary analysis group are 0.32 ± 0.22% for DHA and 0.47 ± 0.13% for AA. These means are not much different from those obtained by weighting according to numbers of subjects and are lower than those obtained in studies that used packed columns and protocols that fall outside the other inclusion criteria. The correlation between DHA and AA is surprisingly low, which reflects a high degree of variability in the ratio of DHA to AA in individual breast-milk samples.

We thank Diane Benisek for technical assistance. We dedicate this publication to the memory of our coauthor, mentor, friend, and colleague, the late Robert G Jensen, who contributed more to the science of milk lipid composition than any single scientist of the 20th century.

The authors' responsibilities were as follows—JTB, RGJ, DAD-S, and LMA: designed the project; JTB, BV, RGJ, and JAB: analyzed the data; JTB and BV: wrote the paper; all authors: performed the research and edited the paper. None of the authors reported a conflict of interest.

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