

A Systematic Review and Meta-Analysis of the Effects of Pasteurization on Milk Vitamins, and Evidence for Raw Milk Consumption and Other Health-Related Outcomes

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MS 10-269; Received 26 June 2010/Accepted 3 May 2011

ABSTRACT

Pasteurization of milk ensures safety for human consumption by reducing the number of viable pathogenic bacteria. Although the public health benefits of pasteurization are well established, pro-raw milk advocate organizations continue to promote raw milk as “nature’s perfect food.” Advocacy groups’ claims include statements that pasteurization destroys important vitamins and that raw milk consumption can prevent and treat allergies, cancer, and lactose intolerance. A systematic review and meta-analysis was completed to summarize available evidence for these selected claims. Forty studies assessing the effects of pasteurization on vitamin levels were found. Qualitatively, vitamins B12 and E decreased following pasteurization, and vitamin A increased. Random effects meta-analysis revealed no significant effect of pasteurization on vitamin B6 concentrations (standardized mean difference [SMD], -2.66 ; 95% confidence interval [CI], $-5.40, 0.8$; $P = 0.06$) but a decrease in concentrations of vitamins B1 (SMD, -1.77 ; 95% CI, $-2.57, -0.96$; $P < 0.001$), B2 (SMD, -0.41 ; 95% CI, $-0.81, -0.01$; $P < 0.05$), C (SMD, -2.13 ; 95% CI, $-3.52, -0.74$; $P < 0.01$), and folate (SMD, -11.99 ; 95% CI, $-20.95, -3.03$; $P < 0.01$). The effect of pasteurization on milk’s nutritive value was minimal because many of these vitamins are naturally found in relatively low levels. However, milk is an important dietary source of vitamin B2, and the impact of heat treatment should be further considered. Raw milk consumption may have a protective association with allergy development (six studies), although this relationship may be potentially confounded by other farming-related factors. Raw milk consumption was not associated with cancer (two studies) or lactose intolerance (one study). Overall, these findings should be interpreted with caution given the poor quality of reported methodology in many of the included studies.

Pasteurization of milk is defined as the heating of every particle of milk to a standardized temperature for a defined period of time without allowing recontamination of that milk or milk product during the process (17). This treatment is used for two distinct reasons: (i) to make milk and milk products safe for human consumption by reducing the number of viable bacteria that may be harmful to health and (ii) to improve the shelf life of milk by reducing the numbers of spoilage bacteria (55).

Pasteurization is a requirement for consumer milk products in many developed countries. In Canada, pasteurization of all commercial milk is mandatory, and the distribution and sale of unpasteurized milk is illegal under the Food and Drug Regulations (15). Scotland introduced legislation in 1983 requiring the heat treatment of cow’s milk for sale to the public (74). Current regulations in the Australian dairy industry require the heat treatment of milk to ensure a high level of dairy product safety (25). Other countries have allowed flexibility with respect to pasteur-

ization requirements. In the United States, 29 states permit the sale of raw milk for human consumption; sales can occur at the farm where it is produced, in retail outlets, or through cow share agreements (34). Current controls on the sale of raw milk in England state that raw milk may be sold directly to consumers only by registered milk production holdings (farm gate or farmhouse catering operation) or through milk roundsmen. The cows must be from an official tuberculosis- and brucellosis-free herd, the facilities must comply with enhanced hygiene rules for raw milk producers, and the milk must bear a health warning label (85).

With the advent of mandatory pasteurization, the incidence of milkborne diseases has dropped dramatically. In the United States in 1938, milkborne outbreaks constituted approximately 25% of all disease outbreaks due to contaminated food and water, whereas at the beginning of the 21st century, milk and milk products were associated with less than 1% of all such outbreaks (89). Headrick et al. (34) reported 46 outbreaks of milkborne disease in the United States in the 19 years from 1973 to 1992, with 40 of these outbreaks in states where raw milk sale was legal. Similarly, morbidity associated with milk

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consumption in Scotland was substantially reduced compared with that in England and Wales after a ban on raw milk production and sales was introduced in 1983 (74).

Recent outbreaks associated with raw milk consumption have caused considerable morbidity. In 2005, an outbreak of 18 cases of infection with milkborne *Escherichia coli* O157:H7 occurred in Oregon and Washington states, mostly among children less than 14 years of age. In this outbreak, five patients were hospitalized, four with hemolytic uremic syndrome (18). In 2007, almost 30 cases of infection with *Salmonella enterica* serotype Typhimurium in the United States were associated with raw milk consumption (56). Other milkborne diseases include campylobacteriosis, salmonellosis, yersiniosis, listeriosis, tuberculosis, brucellosis, and streptococcal infections (34).

Despite the risk associated with consuming raw milk, raw milk advocate organizations promote the production and consumption of unpasteurized milk, “nature’s perfect food” (59, 69, 94). These organizations state that raw milk is more nutritious than pasteurized milk, because heat treatment may destroy natural vitamins (59, 69, 94). In addition to its nutritive properties, raw milk products are thought to be produced in a manner that ensures their safety, and raw milk is believed to prevent and treat a wide spectrum of conditions and diseases (59, 69, 94), including allergies, cancer, and lactose intolerance. LeJeune and Rajala-Schultz (55) noted that the public is bombarded with a large body of conflicting information surrounding this debate, and in some cases this information is presented in a biased fashion.

Our objective was to conduct a systematic review and meta-analyses to assess the potential benefits of drinking raw milk. Claims investigated were changes in vitamin levels associated with pasteurization and the effects of raw milk consumption on allergies, cancer, and lactose intolerance.

MATERIALS AND METHODS

To review the available evidence supporting or disputing the benefits of the consumption of raw bovine milk by humans, a systematic review procedure was followed.

Question definition. Four questions were investigated corresponding to four separate health claims made in support of raw milk consumption: (i) is pasteurization associated with destruction of selected vitamins present in raw milk, (ii) is there an association between raw milk consumption and development of allergies in children and/or adults, (iii) is there an association between raw milk consumption and cancer, and (iv) is there an association between raw milk consumption and lactose intolerance?

Only those studies involving raw or pasteurized bovine milk were included. In this review, raw milk was defined as any liquid milk product that had not undergone heat treatment of any sort and was clearly defined as “raw” or “unpasteurized.” Studies of farm milk or market milk were excluded from the analysis because it was unclear how these milk products were treated. Pasteurization was defined as the heat treatment of all particles of milk to a standardized temperature for a standardized amount of time. The standardized pasteurization conditions were those outlined by the U.S. Food and Drug Administration (FDA) (88). Although these standards were used as guidelines, all studies in which heat

treatment within the time and temperature ranges provided by the FDA were included. Studies in which the pasteurization conditions were not specified but in which the milk was described as “pasteurized” were also included. To assess the nutritive value of milk after pasteurization, selected vitamins found naturally in milk were examined: vitamins A, B1, B2, B6, B12, C, E, and folate (8, 32, 49). Vitamin D was not examined in this review because secreted bovine milk is deficient in vitamin D based on human nutrition needs (49), and fortification of milk with this vitamin is mandatory in Canada (14, 16). Studies in which animal models were used to evaluate the impact of pasteurization on vitamin concentrations in milk were not included.

Literature search and relevance screening. An independent literature search was conducted for each research question. Five electronic databases (PubMed, Biosis Previews, AGRICOLA, CAB Direct, and Food Science and Technology Abstracts) were searched for abstracts published between the time of database inception to May 2009. The literature search was limited to words present in the title or abstract, and initially there was no language restriction. Reference lists for studies identified as relevant were checked for additional related studies.

To identify all potentially relevant studies conducted to assess the effects of pasteurization on the vitamin content of bovine milk, the following search terms were compiled: (milk) AND (raw milk, pasteurize, pasteurise, pasteurization, pasteurisation, pasteurizing, pasteurising, heat treatment) AND (vitamin A, retinol, vitamin A acetate, vitamin A aldehyde, vitamin A acid, vitamin A alcohol, retinol acetate, retinol aldehyde, retinol acid, retinol alcohol, folate, folic acid, niacin, nicotinic acid, nicotinamide, vitamin B1, thiamin, vitamin B2, riboflavin, vitamin B6, pyridoxine, vitamin B12, cobalamin, cobamamide, cyanocobalamin, hydroxocobalamin, vitamin C, ascorbic acid, vitamin E, alpha-tocopherol, alpha-tocopheryl acetate, tocopheryl acetate, vitamin E acetate, tocopherols). Search terms within each component were combined using “OR” and components were linked using “AND”. To identify all potentially relevant studies of associations between consumption of raw milk and allergy, cancer, or lactose intolerance, the following search terms were compiled separately for each outcome: intervention (raw milk, unpasteurized milk, unpasteurised milk, pasteurize, pasteurise), allergy outcome (allergy, atopy, atopic sensitization, hypersensitivity, cow’s milk protein allergy), cancer outcome (cancer, neoplasm, carcinogen), and lactose intolerance outcome (lactose intolerance, lactose malabsorption, lactose, milk intolerance, lactase deficiency). Eligible articles included only those published in peer-reviewed journals. Retrieved references were collected in a reference management database (66), with duplicate abstracts (identified by title and primary author) removed.

Inclusion criteria for relevance screening were that the abstract described (i) primary (original) research, (ii) research pertaining to raw fluid bovine milk consumption by humans or the effects of pasteurization on fluid bovine milk, and (iii) vitamin content of milk and allergy, cancer, or lactose intolerance as an outcome of consumption. Three reviewers initially pretested the relevance screening questions by reviewing the same 75 abstracts. Thereafter, two reviewers independently read each abstract and excluded references not meeting all three inclusion criteria. Both reviewers needed to rate the abstract as relevant for that particular study to advance to the quality assessment stage. Disagreements between reviewers were resolved by consensus.

Quality assessment and data extraction. Using full articles, criteria for methodological soundness and completeness were

independently assessed for all relevant studies by two reviewers using checklists developed by the authors. Only those full articles published in English were included in the quality assessment. The assessment evaluated the materials and methods section of the manuscript for complete descriptions of exposures, outcomes, inclusion and exclusion criteria, randomization (for experimental studies), blinding, withdrawals or loss to follow-up, and statistical analysis. Studies were excluded from further analysis when the objectives of the paper did not address the systematic review question, exposure or outcome was not clearly defined, the sample size was not reported, or the statistical analysis was not described. Many studies did not include the sample size in a clear manner or the reported sample size was not appropriate based on the study design (e.g., different from the reported treatment allocation). The reviewers followed a set of predetermined rules for extracting sample size values. When sample size and sample size per treatment could be determined, those numbers were recorded. When sample size was described but not appropriate to the treatment allocation but was the value used by the authors in the statistical analysis, that number was recorded. Thus, in some trials, the sample size extracted may not have been statistically correct; however, it was the value included in this review. Initially, four articles were reviewed by all reviewers to pretest the quality assessment instrument. Thereafter, two reviewers independently reviewed each study. Disagreements between reviewers were resolved by consensus.

A standardized form was used to extract information from each manuscript. Two reviewers were responsible for the extraction of primary data, and disagreements were resolved by consensus. Data extracted included the characteristics of the population, sample size, interventions, exposures, outcomes, and results. When the results from multiple statistical models were reported in a study, only data from the model that statistically adjusted for confounders were extracted and included in this review. Preference was given to those data that had exact *P* values. When the exact *P* value was not reported, information provided on the range of significance testing (i.e., $P < 0.1$) was extracted. When the significance of the result was reported as such only in the text (e.g., “the association was [was not] significant”), then this information was extracted. All data were entered into EpiData 3.1 (54) for further analysis.

Meta-analysis. Where possible, the effect of pasteurization on vitamin concentrations in milk was assessed by fixed and random effects meta-analyses. Only those studies that included the standard deviation or a measure of dispersion used to derive the standard deviation were included in the meta-analysis. Studies in which pasteurization was not conducted by the experimenter (i.e., observational studies) were also omitted from the meta-analysis. Results of all studies were converted to the most commonly used unit of vitamin measurement, milligrams per liter. In the analyses, the standardized mean difference was used to estimate the pooled effect as vitamin concentrations in the various studies were assessed using a variety of techniques. The outcome of meta-analyses was the standardized mean difference in vitamin concentrations between unpasteurized and pasteurized milk at the study level. Heterogeneity between studies was evaluated by the *Q* statistic and Galbreith plots. When significant heterogeneity was observed ($P < 0.05$), the random effects estimator was used and included in the forest plot. Fixed effects estimation was carried out using the inverse variance method, and random effects estimation was carried out according to the method of DerSimonian and Laird (19). All analyses were conducted using STATA version 9.1 (STATA Corporation, College Station, TX).

Meta-regression. Meta-regression was used to estimate the extent to which one or more covariates might explain observed heterogeneity in treatment effects for the meta-analyses of vitamin studies. The meta-regression factors included sample size, temperature and time used for pasteurization, method used to quantify vitamin concentrations, and whether vitamins were added before pasteurization or occurred naturally in milk samples. When possible, time and temperature were combined in a meta-regression. These analyses were performed using the method of moments estimate (80) to maintain consistency with meta-analyses.

Publication bias. Publication bias can distort findings because studies with statistically significant results are more likely to get published than those without significant results (22). Among published studies, those with significant results are more likely to be published in English, more likely to be cited, and more likely to be published more than once; thus, they are more likely to be identified and included in reviews (22). To statistically assess whether publication bias was present, Egger's linear regression approach was used (23). For those meta-analyses that include a small number of studies, Egger's test will have higher power than other analytical tests for publication bias.

RESULTS

Literature search and relevance screening. The search identified 2,199 unique articles (Table 1). Based on the title and abstract, 1,883 articles did not meet the inclusion criteria. Of the 316 articles that passed the initial relevance screening, 98 were eliminated because they were in a language other than English. Overall, 123 full articles were collected for quality assessment. Hand-searching the reference lists of relevant articles generated one additional article on the effect of pasteurization on milk vitamin concentrations and two additional articles on the association between raw milk consumption and allergy. Of studies that included an examination of the effects of pasteurization on vitamin concentrations in milk, 40 were included in this review. Of these, two articles included descriptions of the results in the text without providing mean changes in vitamin concentrations. Of the 38 studies that did include mean values, 25 included data on a single vitamin and 13 included data on multiple vitamins (Table 2). In 22 studies, vitamin concentrations were measured under more than one pasteurization condition (Table 2). In one article (72), both allergy and cancer outcomes were reported (Table 3).

Study characteristics. Table 2 summarizes the characteristics of all articles on the effects of pasteurization on vitamin concentrations. The articles were published between 1936 and 2003, and the sample size ranged from 2 to 176 per study. In three studies, researchers supplemented the milk samples with known amounts of vitamins before pasteurization. Nine studies were observational, i.e., the heat treatments were carried out by an external entity. High-performance liquid chromatography (HPLC) and microbiological assay were the methods most commonly used to quantify all types of vitamins.

Table 3 summarizes the characteristics of those studies in which the possible association between raw milk consumption and allergy, cancer, or lactose intolerance

TABLE 1. Number of studies collected at each step of the systematic review based on whether they included the effects of pasteurization on milk vitamin concentrations or the association between raw milk consumption and allergy, cancer, and lactose intolerance

Systematic review step	No. of studies pertaining to:			
	Vitamins	Allergy	Cancer	Lactose intolerance
Total collected from search	3,048	139	114	1,129
After removal of duplicates	1,196	96	79	828
Passed relevance screening	289	13	6	8
Published in English	199 ^a	10	6	3
In collection of full paper				
Able to retrieve full article	105	10	6	2
Excluded, abstract only	−8	−1		
Excluded, conference proceeding	−1			
Included, hand search	+1	+2		
Following assessment of full paper				
Not relevant	29	5	2	1
Exposure or outcome not defined	1		1	
Sample size not provided	20			
No raw milk control	4			
Statistics not reported			1	
Results double published	2			
Total number of articles used in this review	40	6	2	1

^a When the language of the publication was unknown, full articles of those studies were also retrieved.

was examined. The majority of studies were cross-sectional, utilizing self-report mail surveys. In the two case-control studies, exposure was determined through telephone interviews. In five of six studies in which allergy was reported as the outcome, information was collected on prevalent cases of allergy and both past and present raw milk exposure (4, 64, 67, 72, 95). Two of these five studies included assessment of raw milk consumption at any point in a respondent's lifetime (64, 72), whereas in the remaining three studies exposure was assessed currently and during the first 5 years of life (4), at age 6 years (67), and during the first 2 years of life (95). The remaining allergy study was a double-blind clinical trial for milk allergic individuals, with assigned doses of raw and processed milk. One study in which cancer was reported as the outcome, researchers investigated historical and current raw milk exposure in relation to prevalent acute lymphoid leukemia diagnoses (20); in the other study, both past and present raw milk consumption was assessed in relation to incident cancer cases (72). The single study in which the effects of raw milk consumption on lactose intolerance was investigated was a randomized double-blind cross-over study that included lactose intolerant individuals exposed to predetermined quantities of various processed milk samples and a raw milk comparison group.

Studies of vitamin concentrations in milk. For vitamin A, two of the four studies were observational, and in one no measure of data dispersion was reported. Of the eight studies of vitamin B12, three included a measure of data dispersion; however, in two of these studies the mean outcome was reported in units that could not be converted to milligrams per liter. None of the studies of vitamin E included a standard deviation of the mean or other measures

of data dispersion. As a result, meta-analysis could not be carried out for these vitamins; descriptive results are provided in Table 4. Results of studies on vitamin A are inconsistent; an increase was reported in two studies, and a slight decrease was reported in two other studies (Table 4). Panfili et al. (62) reported a numeric increase in vitamin A concentrations across a range of pasteurization conditions, all of which were significant in seven of eight studies. Vitamin B12 levels were numerically reduced after pasteurization at a range of temperatures (9, 10, 13, 26, 28, 60, 61). Similarly, vitamin E concentrations were numerically lower after pasteurization in three of four studies (58, 71, 81). For vitamins A, B12, and E, significant variability between studies was noted, and the pasteurization time and significance of results often were not reported. Thus, these descriptive results should be interpreted with caution.

Meta-analysis. Meta-analysis was carried out for vitamins B1, B2, B6, C, and folate. The results of studies that could not be included in the meta-analysis (because measures of data dispersion were not reported, units could not be standardized, or studies were observational) are reported in Table 4.

Of the 14 studies in which the effect of pasteurization conditions on vitamin B1 concentrations in milk were assessed, 3 articles did not include a measure of data dispersion (9, 26, 28), 1 included the results in text only (7), 1 study was observational (71), and 1 article provided results in units that could not be standardized (76). Of the remaining eight studies, six included multiple experiments, resulting in 18 separate comparisons that were included in the meta-analysis for vitamin B1 (Fig. 1). The standardized mean difference obtained with the random effects model was −1.77 (95% confidence interval [CI], −2.57, −0.96)

TABLE 2. Characteristics of all studies in which the effects of pasteurization on vitamin concentrations in bovine milk were investigated

Author	Country	Vitamin(s)	Vitamin(s) added	Experimental vs observational	Pasteurization conditions	Vitamin determination
Andersson and Oste, 1994 (2) ^a	Sweden	B12, C, folate	No	Observational	HTST ^b	Radioisotope assay, HPLC ^c
Bector and Rani, 1998 (6)	India	A	Yes	Experimental	72°C, 15 s	Colorimetric method
Bendicho et al., 2002 (7) ^a	Spain	B1, B2, C, D3, E	Yes	Experimental	63°C, 30 min 75°C, 15 s	HPLC
Burton et al., 1967 (9)	UK	B1, B6, B12, folate	No	Experimental	72°C, 15 s 110°C, 20 min	Microbiological methods
Burton et al., 1970 (10)	UK	A, B1, B6, B12, C, folate	No	Experimental	144°C direct 141°C indirect	Ford et al., 1969 (27)
Callieri, 1959 (13)	Sweden	B12	No	Observational	74°C, 16 s	Microbiological methods
Ford et al., 1959 (26)	UK	B12, C	No	Experimental	110°C, 20 min 120°C, 30 min	Colorimetric (vitamin C) and microbiological (vitamin B12) methods
Gregory and Burton, 1965 (28)	UK	B1, B6, B12	No	Experimental	135°C, 15 s 127°C, 10 s 132°C, 10 s 135°C, 10 s 138°C, 3.5 s 131°C, 3 s 136°C, 3 s 140°C, 3 s 140°C, 4 s 145°C, 4 s	Microbiological methods
Haddad and Lowenstein, 1981 (29)	USA	B1, B2, C	No	Experimental	72°C, 16 s 80°C, 16 s 110°C, 3.5 s 140°C, 3.5 s	Fluorometric method
Hand, 1943 (30)	USA	C	No	Experimental	63°C, 30 min	Microbiological methods
Hawley, 1938 (33)	USA	C	No	Observational	Pasteurized	2,6 dichlorophenolindophenol
Henry and Kon, 1938 (35)	UK	C	No	Experimental	Sterilized	Indophenol titration
Holmes et al., 1939 (42)	USA	C	No	Experimental	62°C, 30 min	Indophenol titration
Holmes et al., 1943 (40)	USA	B1, B2, C	No	Experimental	62°C, 33 min	Thiochrome method (B1), fluorometric method (B2), 2,6 dichlorophenolindophenol (vitamin C)
Holmes, 1944 (37)	USA	B2	No	Experimental	62°C, 33 min 72°C, 15 s 83°C, 15 s	Fluorometric method

TABLE 2. Continued

Author	Country	Vitamin(s)	Vitamin(s) added	Experimental vs observational	Pasteurization conditions	Vitamin determination
Holmes et al., 1945 (41)	USA	B1, B2, C	No	Experimental	72°C, 22 s 73°C, 22 s 75°C, 22 s 76°C, 22 s 81°C, 22 s 82°C, 22 s 83°C, 22 s 62°C, 30 min Pasteurized Pasteurized Sterilized 63°C, 30 min Pasteurized 72°C 78°C	2,6 dichlorophenolindophenol (vitamin C), fluorometric method (vitamin B2), thiochrome method (vitamin B1)
Holmes, 1952 (39)	USA	C	No	Experimental		Holmes, 1950 (38) HPLC
Holt et al., 1988 (43)	USA	Folate	No	Observational	Pasteurized	Fluorometric method
Houston et al., 1940 (46)	UK	B1, B2	No	Experimental	Pasteurized	Fluorometric method
Kon and Watson, 1936 (51)	UK	C	No	Experimental		2,6 dichlorophenolindophenol
Kon and Watson, 1937 (52)	UK	C	No	Experimental	Pasteurized	2,6 dichlorophenolindophenol
Millar and Sheppard, 1972 (58)	New Zealand	E	No	Experimental	72°C 78°C	HPLC
Neujahr et al., 1960 (60)	Sweden	B12	No	Observational	Pasteurized	Microbiological methods
Oamen et al., 1989 (61)	USA	B2, B6, B12, C, folate	No	Experimental	138°C, 20.3 s 149°C, 3.4 s	Colorimetric and AOAC microbiological methods HPLC
Panfilii et al., 1998 (62)	Italy	A	No	Observational	72°C, 15 s 72°C, 15 s HQP ^d UHT ^e In-container sterilized	
Pizzoferrato, 1992 (65)	Italy	C	No	Observational	72°C, 15 s 75°C, 15 s 80°C, 15 s 85°C, 15 s 90°C, 15 s 140°C, 3 s	HPLC
Schone et al., 2003 (71)	Germany	A, B1, B2, E	No	Observational	Pasteurized	HPLC
Sharma and Darshan, 1998 (73)	India	B1, B2, B6, folate	No	Experimental	63°C, 30 min 121°C, 15 min 72°C 80°C, 0 s 80°C, 40 s 80°C, 15 s 90°C, 18 s	Fluorometric and microbiological methods Not reported HPLC HPLC
Sharp et al., 1940 (75)	USA	C	No	Experimental		
Sierra et al., 1999 (78)	Spain	B1	No	Experimental		
Sierra and Vidal-Valverde, 2000 (76)	Spain	B1	No	Experimental		
Sierra and Vidal-Valverde, 2001 (77)	Spain	B1, B6	No	Experimental	90, 110, and 120°C	HPLC
Singh and Deodhar, 1993 (79)	India	B1, B2	No	Experimental	63°C, 30 min	Fluorometric method
Syvaöja et al., 1985 (81)	Finland	E	No	Observational	Pasteurized	HPLC
Theophilus and Stamberg, 1945 (82)	USA	B2	No	Experimental	62°C, 30 min	Fluorometric method

TABLE 2. *Continued*

Author	Country	Vitamin(s)	Vitamin(s) added	Experimental vs observational	Pasteurization conditions	Vitamin determination
Tobias and Herreid, 1959 (83)	USA	C	No	Experimental	Pasteurized 62°C, 30 min	2,6 dichlorophenolindophenol
Varadharaju et al., 1988 (90)	India	C	No	Experimental	115°C, 18 min 115°C, 20 min 120°C, 4 min 120°C, 5 min	Harris and Ray, 1935 (31)
Wigertz et al., 1996 (96)	Sweden	Folate	No	Experimental	74°C, 15 s 140°C, 5 s	Radioprotein binding assay
Woessner et al., 1940 (97)	USA	C	Both	Experimental	66°C, 30 min 63°C, 30 min	Chromatography
Ziegler and Keevil, 1944 (98)	Canada	B2	No	Experimental	Commercial pasteurization	Microbiological methods

^a Results reported in text of the article.^b HTST, high-temperature—short-time pasteurization.^c HPLC, high-performance liquid chromatography.^d HQP, high-quality pasteurization.^e UHT, ultrahigh-temperature pasteurization.

(Fig. 1). There was significant heterogeneity between studies ($P < 0.0001$), with an estimated between-study variance (T^2) of 1.94. Six of the 18 trials contributed to the heterogeneity (46, 73, 77–79).

Of the 12 studies in which the effect of pasteurization on vitamin B2 concentrations in milk were assessed, 3 articles did not include the standard deviation (29, 61, 98) or any other measure of data dispersion, 1 study was observational (71), and 1 article did not provide numerical results (7); thus, these 5 articles were excluded from the meta-analysis. Multiple experiments were reported in three of the seven studies suitable for meta-analysis, resulting in a total of 15 included trials. The effect size obtained with the random effects model was -0.41 (95% CI, $-0.81, -0.01$) (Fig. 2). This result was significant ($P = 0.045$), and heterogeneity was observed between studies ($P < 0.01$; $T^2 = 0.30$). Vitamin B2 studies that did not fall within the 95% CI of the Galbreith plot included that of Singh and Deodhar (79) and one experiment reported by Sharma and Darshan (73).

For the six studies that included pasteurization effects on vitamin B6, three could not be included in the meta-analysis because the standard deviation or other measures of data dispersion were not reported (10, 28, 61). A total of 10 trials from three studies were included in the meta-analysis for vitamin B6. The effect size determined with random effects modeling was -2.66 (95% CI, $-5.40, 0.08$) (Fig. 3); however, this change was not significant ($P > 0.05$). This meta-analysis also revealed significant heterogeneity ($P < 0.001$; $T^2 = 15.03$). The data within the 95% CIs of the Galbreith plot were from the study by Burton et al. (9) and from one trial from the study by Sierra and Vidal-Valverde (77).

In total, 19 studies were conducted on the effects of pasteurization on vitamin C. Of these, nine did not include a measure of data dispersion (10, 26, 29, 33, 39, 51, 61, 83, 97), two articles included the results in text (2, 7), and one study was observational (65); therefore, only seven studies were included in the meta-analysis. In the majority of trials, a numeric decrease in vitamin C was found after heat treatment. Of the seven studies included in the meta-analysis, one included multiple experiments for a total of 11 unique trials (Fig. 4). The effect size obtained with the random effects model was -2.13 (95% CI, $-3.52, -0.74$) (Fig. 4), and this difference was significant ($P = 0.003$). Heterogeneity also was significant ($P < 0.001$; $T^2 = 4.85$); five studies contributed to this heterogeneity (30, 35, 40, 41, 52).

For the seven studies conducted on the effects of pasteurization on the folate content of milk, only two were included in the meta-analysis; four did not include a measure of data dispersion (2, 9, 10, 61), and one was observational (43). The effect size obtained with the random effects model was -11.99 (95% CI, $-20.95, -3.03$) (Fig. 5), and this result was significant ($P < 0.01$). Significant heterogeneity also was observed ($P < 0.001$; $T^2 = 76.96$), and all studies were outside the 95% CIs in the Galbreith plot.

TABLE 3. Characteristics of studies in which the effects of raw milk consumption on allergy, cancer, or lactose intolerance were reported

Author	Country	Study type	How exposure assessed	Outcome assessment	Withdrawal or loss to follow-up	Blinding
Allergy						
Barnes et al., 2001 (4)	Greece	Cross-sectional	Self-reported mail survey	Positive SPT ^a	Nos. reported	NA ^b
Host and Samuelsson, 1988 (45)	Denmark	Randomized trial	Known doses of milk assigned to each subject	Physician or parent diagnosed	Not discussed	Double blind
Perkin and Strachan, 2006 (64)	England	Cross-sectional	Self-reported mail survey	SPT $\geq$ 3 mm wheal	Nos. reported	NA
Radon et al., 2004 (67)	Germany	Case control	Telephone interview	SPT immunoglobulin E > 0.70 kU/liter	Possible to determine	Yes
Sellers et al., 2008 (72)	USA	Prospective cohort	Self-reported mail survey	State Health Registry of Iowa records	Nos. reported	NA
Wickens et al., 2002 (95)	New Zealand	Cross-sectional	Self-reported mail survey	Physician or parent diagnosed	Nos. reported	NA
Cancer						
Donham et al., 1987 (20)	USA	Case control	Telephone interview	Hospital records	Nos. reported	No
Sellers et al., 2008 (72)	USA	Prospective cohort	Self-reported mail survey	State Health Registry of Iowa records	Nos. reported	NA
Lactose intolerance						
Korpela et al., 2005 (53)	Finland	Randomized double blind cross-over study	Milk samples consumed according to predetermined schedule	Personal diary of symptoms using 100-mm VAS ^c	Nos. reported	Yes

^a SPT, skin prick test.^b NA, not applicable.^c VAS, visual analog scale.

TABLE 4. Sample size, pasteurization conditions, and results of those studies on the effects of pasteurization on vitamins that were not included in the meta-analysis

Vitamin	Author	Sample size			Treatment	Pasteurization conditions	Mean difference from control	Statistical significance
		Control	Treatment					
A	Bector and Rani, 1998 (6) Burton et al., 1970 (10)	8	8		72°C, 15 s		-2.07×10^{-4} mg/liter	Not reported
		3	3		144°C direct		+0.2 µg/g fat	Not reported
	Panfili et al., 1998 (62)	4	12		141°C indirect		+0.1 µg/g fat	
		4	6		72°C, 15 s		+0.101 mg/liter	$P < 0.001$
		4	9		72°C, 15 s HQP ^a		+0.1872 mg/liter	$P < 0.001$
		4	4		UHT ^b		+0.0326 mg/liter	$P < 0.001$
	Schone et al., 2003 (71) Bendicho et al., 2002 (7)	23	9		In-container sterilized		+0.041 mg/liter	$P < 0.001$
		2	2		Pasteurized		-0.10 mg/liter	$P < 0.05$
		3	3		63°C, 30 min		No significant difference	$P > 0.05$
		3	3		75°C, 15 s			
B1	Burton et al., 1970 (10)	1	1-3 per treatment		144°C direct		No change	Not reported
	Gregory and Burton, 1965 (28)	1	1-3 per treatment		141°C indirect		No change	Not reported
					135°C, 15 s		No change	
					127°C, 10 s		No change	
					132°C, 10 s		No change	
					135°C, 10 s		-10%	
					138°C, 3.5 s		No change	
					131°C, 3 s		No change	
					136°C, 3 s		No change	
					140°C, 3 s		No change	
					140°C, 4 s		No change	
B2	Haddad and Lowenstein, 1981 (29)	5	5		145°C, 4 s		No change	
	Schone et al., 2003 (71) Sierra and Vidal-Valverde, 2000 (76)				72°C, 15 s		-11.90%	$P > 0.05$
					80°C, 16 s		-9.40%	
					110°C, 3.5 s		-7.90%	
					140°C, 3.5 s		-9.40%	
		23	9		Pasteurized		-0.04 mg/liter	$P < 0.05$
		3	3		80°C, 15 s		-1%	$P > 0.05$
	Bendicho et al., 2002 (7)	2	2		90°C, 18 s		-1%	
		5	5		63°C, 30 min		No significant difference	$P > 0.05$
					75°C, 15 s			
					72°C, 15 s		-0.90%	$P > 0.05$
B2	Haddad and Lowenstein, 1981 (29)				80°C, 16 s		-1.50%	
					110°C, 3.5 s		-2.10%	
					140°C, 3.5 s		-2.70%	
		8	8		138°C, 20.3 s		-4.0×10^{-5} mg/liter	$P > 0.05$
	Oamen et al., 1989 (61)				149°C, 3.4 s		-6.0×10^{-5} mg/liter	
		23	9		Pasteurized		-0.06 mg/liter	$P < 0.05$
		4	4		Commercial pasteurization		-0.24 γ/ml	Not reported
	Schone et al., 2003 (71) Ziegler and Keevil, 1944 (98)							

TABLE 4. *Continued*

Vitamin	Author	Sample size		Treatment	Pasteurization conditions	Mean difference from control	Statistical significance
		Control	Treatment				
B6	Burton et al., 1970 (10)	3	3	144°C direct	144°C direct	-3.0×10^{-8} mg/liter	Not reported
	Gregory and Burton, 1965 (28)	1	1-3 per treatment	141°C indirect	141°C indirect	-5.0×10^{-8} mg/liter	Not reported
				135°C, 15 s	135°C, 15 s	No change	
				127°C, 10 s	127°C, 10 s	-12%	
				132°C, 10 s	132°C, 10 s	No change	
				135°C, 10 s	135°C, 10 s	-7%	
				138°C, 3.5 s	138°C, 3.5 s	No change	
				131°C, 3 s	131°C, 3 s	-6%	
				136°C, 3 s	136°C, 3 s	-8%	
				140°C, 3 s	140°C, 3 s	-4%	
				140°C, 4 s	140°C, 4 s	-13%	
				145°C, 4 s	145°C, 4 s	-35%	
				138°C, 20.3 s	138°C, 20.3 s	-1.0×10^{-8} mg/liter	
				149°C, 3.4 s	149°C, 3.4 s	-1.0×10^{-8} mg/liter	
	Oamen et al., 1989 (61)	8	8	HTST ^c	HTST ^c	No change	$P < 0.05$
B12	Andersson and Oste, 1994 (2)	5	5	72°C, 15 s	72°C, 15 s	-0.14 mμg/ml	Not reported
	Burton et al., 1967 (9)	3	3	110°C, 20 min	110°C, 20 min	-2.96 mμg/ml	Not reported
	Burton et al., 1970 (10)	3	3	144°C direct	144°C direct	-0.50×10^{-9} mg/liter	Not reported
				141°C indirect	141°C indirect	-0.20×10^{-9} mg/liter	
	Callieri, 1959 (13)	2	2	74°C, 16 s	74°C, 16 s	-1.1 mμg/ml	Not reported
	Ford et al., 1959 (26)	1	2	110°C, 20 min	110°C, 20 min	-1.5 mμg/ml	Not reported
				120°C, 30 min	120°C, 30 min	-1.5 mμg/ml	
	Gregory and Burton, 1965 (28)	1	1-3 per treatment	135°C, 15 s	135°C, 15 s	-30%	Not reported
				127°C, 10 s	127°C, 10 s	-30%	
				132°C, 10 s	132°C, 10 s	No change	
				135°C, 10 s	135°C, 10 s	-26%	
				138°C, 3.5 s	138°C, 3.5 s	-12%	
				131°C, 3 s	131°C, 3 s	-11%	
				136°C, 3 s	136°C, 3 s	-21%	
				140°C, 3 s	140°C, 3 s	-23%	
				140°C, 4 s	140°C, 4 s	-4.40%	
				145°C, 4 s	145°C, 4 s	4.10%	
	Neujahr et al., 1960 (60)	15	10	Pasteurized	Pasteurized	-1.5×10^{-4} mg/liter	Not reported
	Oamen et al., 1989 (61)	8	8	138°C, 20.3 s	138°C, 20.3 s	-0.40×10^{-9} mg/liter	$P < 0.05$
				149°C, 3.4 s	149°C, 3.4 s	-0.50×10^{-9} mg/liter	

TABLE 4. *Continued*

Vitamin	Author	Sample size			Treatment	Pasteurization conditions	Mean difference from control	Statistical significance
		Control						
C	Andersson and Oste, 1994 (2)	5	5	HTST		No change	Not reported	
	Bendicho et al., 2002 (7)	2	2	63°C, 30 min 75°C, 15 s		Small decrease	$P > 0.05$	
	Burton et al., 1970 (10)	3	3	144°C direct 141°C indirect		−0.01 mg/liter −0.012 mg/liter	Not reported	
	Ford et al., 1959 (26)	1	2	110°C, 20 min		+2.0 × 10 ^{−7} mg/liter	Not reported	
	Haddad and Lowenstein, 1981 (29)	5	5	72°C, 15 s 80°C, 16 s 110°C, 3.5 s 140°C, 3.5 s		−4.2 mg/liter −5.32 mg/liter −6.32 mg/liter −7.27 mg/liter	$P < 0.05$	
	Hawley, 1938 (33)	19	100	Pasteurized		−0.075 mg/liter	Not reported	
	Holmes, 1952 (39)	22	22	62°C, 30 min		−1.1 mg/liter	Not reported	
	Kon and Watson, 1936 (51)	2	2	63°C, 30 min		−0.026 mg/liter	Not reported	
	Oamen et al., 1989 (61)	8	8	138°C, 20.3 s 149°C, 3.4 s		−6.83 × 10 ^{−6} mg/liter −7.03 × 10 ^{−6} mg/liter	$P < 0.05$	
	Pizzoferrato, 1992 (65)	3	3	72°C, 15 s		+3.82 mg/liter	Not reported	
		3	3	75°C, 15 s		+4.58 mg/liter		
		3	3	80°C, 15 s		+6.55 mg/liter		
		3	3	85°C, 15 s		+25.46 mg/liter		
		3	3	90°C, 15 s		+5.86 mg/liter		
	E	Tobias and Herreid, 1959 (83)	6	5	140°C, 3 s Pasteurized		+0.76 mg/liter −0.008 mg/liter	Not reported
Woessner et al., 1940 (97)		7	7	62°C, 30 min 66°C, 30 min 63°C, 30 min		−0.079 mg/liter −19.70% −18%	Not reported	
Bendicho et al., 2002 (7)		2	2	63°C, 30 min 75°C, 15 s		No significant difference	$P > 0.05$	
Millar and Sheppard, 1972 (58)		1	1	72°C 78°C		−2.0 × 10 ^{−9} mg/liter −5.0 × 10 ^{−9} mg/liter	Not reported	
Schone et al., 2003 (71)		23	9	Pasteurized		−0.23 mg/liter	Not reported	
Syvaoja et al., 1985 (81)		2	2	Pasteurized, high fat Pasteurized, low fat		−0.001 mg/liter −0.004 mg/liter	Not reported	
Andersson and Oste, 1994 (2)		5	5	HTST		No change	Not reported	
Burton et al., 1967 (9)		3	3	72°C, 15 s		−2.67 µg/ml	Not reported	
Burton et al., 1970 (10)		3	3	110°C, 20 min 144°C direct 141°C indirect		−20 µg/ml −2.0 × 10 ^{−10} mg/liter −5.0 × 10 ^{−10} mg/liter	Not reported	
Holt et al., 1988 (43)		3	7	Pasteurized		−1.71 × 10 ^{−9} mg/liter	Not reported	
Oamen et al., 1989 (61)		8	8	149°C, 3.4 s		−12.50%	$P > 0.05$	

^a HQP, high-quality pasteurization.^b UHT, ultrahigh-temperature pasteurization.^c HTST, high-temperature–short-time pasteurization.

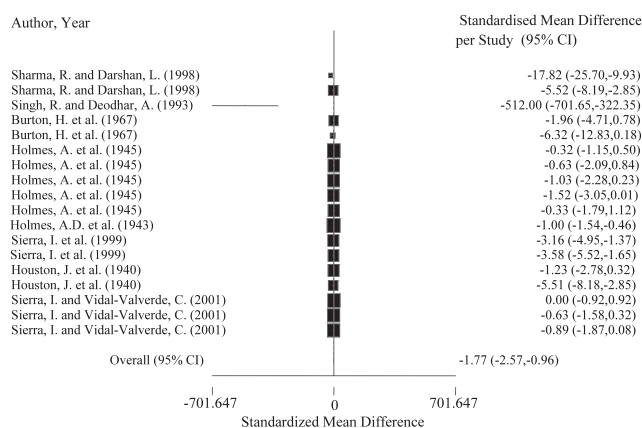


FIGURE 1. Forest plot of the effect of various pasteurization conditions on the standardized mean difference of vitamin B1 concentration in bovine milk samples. The results were derived from a random effects model ($\chi^2 = -1.77$, $P < 0.001$; $T^2 = 1.94$). The length of the horizontal line represents the 95% CI for the effect size from each study, the center of the square represents the point estimate from that study, and the area of the square is proportional to the weight of that study.

Publication bias. Egger's test revealed a significant publication bias ($P < 0.05$) within both the vitamin B1 and folate meta-analyses. Publication bias was not significant for vitamins B2, B6, and C ($P > 0.05$).

Meta-regression. All variables were evaluated in an unconditional meta-regression for vitamin B1, except for natural versus added vitamins, because each study included vitamins found naturally in milk samples. Study sample size, time, temperature, and study type were not significantly associated with vitamin B1 concentrations after pasteurization. However, when combined in a multivariate meta-regression, time and temperature had a significant negative effect on the standardized mean difference ($P <$

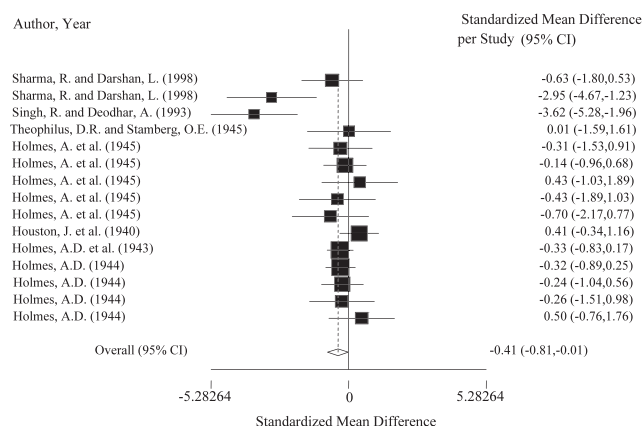


FIGURE 2. Forest plot of the effect of various pasteurization conditions on the standardized mean difference of vitamin B2 concentration in bovine milk samples. The results were derived from a random effects model ($\chi^2 = -0.41$, $P < 0.05$; $T^2 = 0.30$). The length of the horizontal line represents the 95% CI for the effect size from each study, the center of the square represents the point estimate from that study, and the area of the square is proportional to the weight of that study.

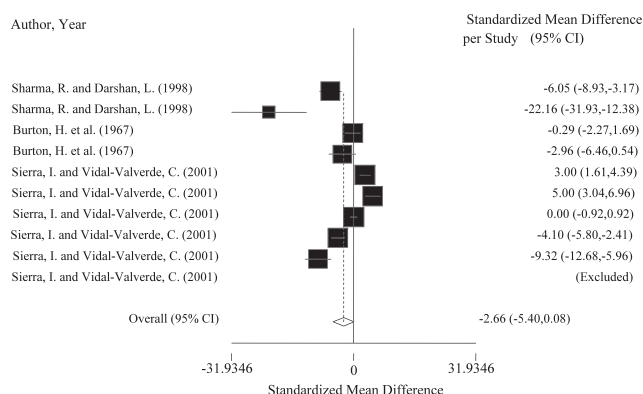


FIGURE 3. Forest plot of the effect of various pasteurization conditions on the standardized mean difference of vitamin B6 concentration in bovine milk samples. The results were derived from a random effects model ($\chi^2 = -2.66$, $P = 0.06$; $T^2 = 15.03$). The length of the horizontal line represents the 95% CI for the effect size from each study, the center of the square represents the point estimate from that study, and the area of the square is proportional to the weight of that study.

0.05). In addition, method used to quantify vitamins was significantly associated with vitamin B1 effect size ($P = 0.001$). Compared with HPLC, chromatography generated significantly different results.

All studies included in the vitamin B2 meta-analysis involved vitamins found naturally in milk samples; therefore, a meta-regression of this variable could not be done. Temperature was the only variable significantly associated with effect size of pasteurization on vitamin B2 concentrations ($P < 0.05$) when combined in the multivariate meta-regression with pasteurization time; for every increase in degrees Celsius, there was a significant decrease in the standardized mean difference.

Similarly, all studies included in the vitamin B6 analysis involved vitamins found naturally in milk, so meta-regression was not completed for this variable. No

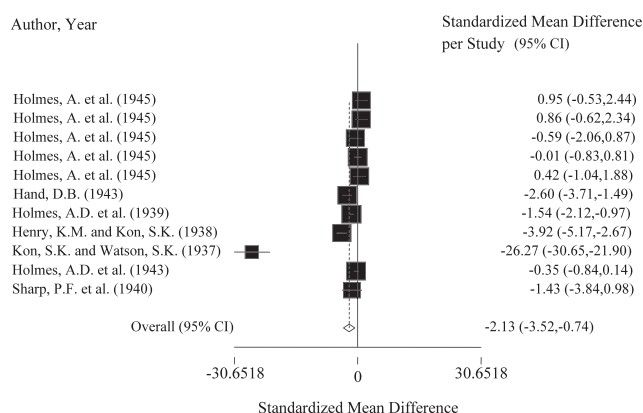


FIGURE 4. Forest plot of the effect of various pasteurization conditions on the standardized mean difference of vitamin C concentration in bovine milk samples. The results were derived from a random effects model ($\chi^2 = -2.13$, $P < 0.05$; $T^2 = 4.85$). The length of the horizontal line represents the 95% CI for the effect size from each study, the center of the square represents the point estimate from that study, and the area of the square is proportional to the weight of that study.

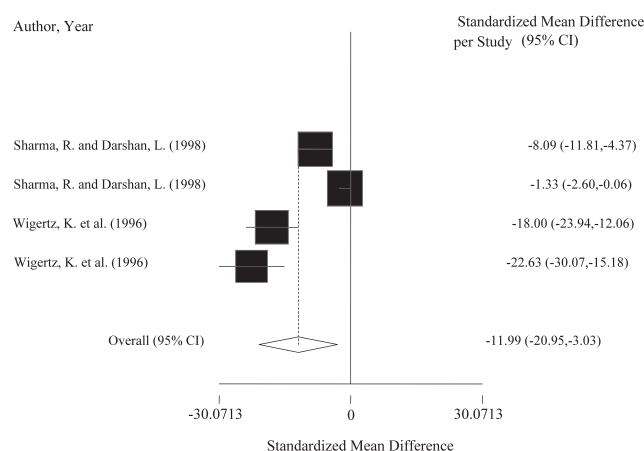


FIGURE 5. Forest plot of the effect of various pasteurization conditions on the standardized mean difference of folate concentration in bovine milk samples. The results were derived from a random effects model ($\chi^2 = -11.99$, $P < 0.05$; $T^2 = 76.96$). The length of the horizontal line represents the 95% CI for the effect size from each study, the center of the square represents the point estimate from that study, and the area of the square is proportional to the weight of that study.

other variables had a significant effect on the standardized mean difference for this vitamin.

Univariate meta-regression revealed that sample size and temperature of pasteurization had a significant effect on the standardized mean difference of vitamin C concentrations. As sample size decreased and temperature increased, the standardized mean difference of vitamin C concentrations increased. The effect of temperature on the standardized mean difference was no longer significant when combined with time of pasteurization in the meta-regression. No other variables had a significant effect on the pooled estimate for this vitamin.

All studies of folate included vitamins found naturally in milk samples; therefore, this variable was not included in meta-regression analysis. Temperature was the only variable not significantly associated with the standardized mean difference for this vitamin when assessed in the unconditional meta-regression. As the sample size decreased, the pooled estimate increased significantly ($P < 0.005$). For the length of time for which the milk was pasteurized, a significant increase in time was associated with an increase in the standardized mean difference of folate concentrations before and after pasteurization. This result was still significant when the time of pasteurization was combined with temperature in the multivariate regression. Fluorometric quantification of folate was significantly associated with an increase in the standardized mean difference compared with quantification by HPLC ($P < 0.05$).

Studies on allergy, cancer, and lactose intolerance.

Study population, exposure, and outcome variables are reported in Table 5 for studies of the effects of raw milk consumption on allergy. Exposure and outcome variables differed among studies. Studies most commonly included measures of raw milk consumption during early childhood, with exposure classified as “ever drinking raw milk” versus

“never drinking raw milk.” Atopy or allergy was the most common outcome variable, which was measured in most cases based on the skin prick test (Tables 3 and 5). Other outcomes included skin rash, conjunctivitis, rhinitis, vomiting, wheeze, asthma, hay fever, eczema, or atopic eczema dermatitis syndrome. Overall, the consumption of raw milk was associated with a numerical decrease in the odds of having allergies compared with the odds associated with not consuming raw milk in those studies that reported odds ratios (4, 64, 67, 95). The results were significant in three of four studies (4, 64, 95). All four studies included age, sex, parental history of allergy, and farm-related factors as confounders in the multivariable model. Sellers et al. (72) found higher proportions of asthma ($P < 0.01$) and eczema ($P = 0.02$) in women who consumed raw milk as a child or as an adult. Conversely, these authors also reported a decrease in hay fever ($P < 0.01$) among women who consumed raw milk compared with those who did not. Host and Samuelsson (45) investigated the allergenicity of raw milk in children with diagnosed milk allergy. These children had one or more allergic outcomes after consuming both raw milk and milk pasteurized at 75°C for 15 s.

Study population, exposure, and outcome variables are reported in Table 6 for those studies involving the association between raw milk consumption and both cancer and lactose intolerance. Of the two studies of raw milk consumption and cancer, in one acute lymphoid leukemia was examined as the outcome (20), and in the other 13 distinct cancers by body site were examined, as well as “all cancers” combined (72). Donham et al. (20) found no association between raw milk consumption and acute lymphoid leukemia. Similarly, Sellers et al. (72) reported a slight decrease in the relative risk of developing rectal cancer in women who consumed raw milk as an adult, with or without consumption as a child ($P = 0.02$). No other cancers were associated with consumption of raw milk during childhood or adulthood (72). Korpela et al. (53) reported that lactose intolerant adults reported symptoms associated with this condition after consumption of both raw and pasteurized milk (72°C for 15 s), and the severity of these symptoms was not significantly different ($P = 0.39$) between milk types.

DISCUSSION

This systematic review was conducted to collect and assess available evidence that supports or disputes purported benefits of consuming raw milk.

Vitamins. We evaluated the effect of pasteurization on multiple vitamins found naturally in milk, including those found in relatively low concentrations. Given the available literature, it was not possible to quantitatively measure the effect of pasteurization on vitamins A, B12, and E. However, pasteurization appeared to qualitatively reduce concentrations of vitamins B12 and E and increase concentrations of vitamin A. Milk is not an important source of vitamins B12 or E in the North American diet (86, 87); thus, the effects of pasteurization on the adult daily intake of these vitamins is negligible. Dairy products are

TABLE 5. Population, exposure, outcome, and results of six studies on the effects of raw milk consumption on allergy

Author	Population assessed	Exposure	Sample size	Outcome	Measure of association (95% CI)	P value	Confounders controlled for ^b
Barnes et al., 2001 (4)	School children 11–19 yr	Raw milk consumption before age 5	929	Atopy	OR ^a = 0.58 (0.34–0.98)		Rural living status, farm animal contact
Host and Samuelsson, 1988 (45)	Milk allergic children 12–40 mo	Raw milk never Raw milk ever Raw untreated milk Milk pasteurized at 75°C for 15 s	5	Skin rash Conjunctivitis Rhinitis Vomiting Wheezing Allergy	All children were positive for one or more outcomes after consuming both types of milk OR = 0.27 (0.12–0.6)	<0.025	
Perkin and Strachan, 2006 (64)	Primary school children	Raw milk consumption, no ^c Raw milk consumption, yes	683				Farming status, breast feeding duration
Radon et al., 2004 (67)	Town residents 18–44 yr	At age 6 yr: Raw milk consumption, no ^c Raw milk consumption, yes	144 169	Atopy	OR = 0.65 (0.36–1.18)		Smoking, currently living on farm
Sellers et al., 2008 (72)	Iowa women 55–69 yr	Never consumed raw milk ^a Consumed only as a child ^b Consumed as adult with or without consumption as a child ^c	1,300 ^a 3,484 ^b 1,105 ^c	Asthma ¹ Hay fever ^{II} Eczema ^{III}	I: α , 6.6%; β , 7.1%; γ , 7.6% II: α , 8.8%; β , 7.3%; γ , 7.3% III: α , 10.9%; β , 11.7%; γ , 11%	<0.01 <0.01 0.02	
Wickens et al., 2002 (95)	Children 7–10 yr	Diet under 2 yr: Raw milk never ^c Raw milk ever	38 192	Hay fever Asthma Rhinitis Wheeze SPT ^d AEDS ^e	OR = 1.1 (0.2–5.0) OR = 0.7 (0.2–2.4) OR = 0.3 (0.1–0.1) OR = 0.6 (0.2–0.8) OR = 0.6 (0.2–1.9) OR = 0.2 (0.1–2.2)	<0.1 <0.05	Ethnicity, antibiotic use in first year, mother's smoking, coal and wood fires, history of measles and pertussis

^a OR, odds ratio.^b In addition to age, sex, family history of allergy, farm animal contact, number of siblings^c Referrant.^d SPT, skin prick test.^e AEDS, atopic eczema dermatitis syndrome.

TABLE 6. Population, exposure, outcome, and results of two studies on the effects of raw milk consumption on prevention of cancer and one study on the effects of raw milk consumption on treatment of lactose intolerance

Author	Population assessed	Exposure	Outcome	Measure of association (95% CI)		P value	Confounders controlled for
				I	II		
Donham et al., 1987 (20)	Acute lymphocytic leukemia cases in rural Iowa townships	Raw milk consumption	Acute lymphoid leukemia	No association			
Sellers et al., 2008 (72)	Iowa women ages 55–69	Never consumed raw milk (referent); consumed raw milk only as a child (I); consumed raw milk as an adult with or without consumption as a child (II)	All cancers	0.92 (0.83–1.02)	0.91 (0.79–1.04)	0.24	Age, calories, physical activity, body mass index, smoking status, hormone replacement therapy, family history of breast cancer, residence on a farm, education, and history of diabetes
			Breast cancer	0.86 (0.71–1.03)	0.82 (0.64–1.05)	0.19	
			Hematopoietic cancer	0.79 (0.51–1.22)	1.05 (0.61–1.79)	0.35	
			Lymphoma	0.73 (0.49–1.1)	0.63 (0.36–1.12)	0.21	
			Uterine corpus	1.04 (0.65–1.65)	1.36 (0.78–2.36)	0.43	
			Ovary	0.72 (0.39–1.33)	0.8 (0.35–1.81)	0.58	
			Bronchus, lung	1.07 (0.78–1.48)	1.17 (0.75–1.82)	0.78	
			Pancreatic	1.92 (1–3.67)	1.36 (0.6–3.07)	0.1	
			Colon	1.06 (0.79–1.41)	0.99 (0.64–1.34)	0.68	
			Rectum	0.65 (0.38–1.09)	0.26 (0.1–0.69)	0.02 ^a	
Korpela et al., 2005 (53)	Lactose intolerant adults	Ingestion of 200 ml of raw milk; ingestion of 200 ml of pasteurized milk (72°C for 15 s)	Upper digestive	0.82 (0.46–1.45)	0.56 (0.24–1.32)	0.41	Subjects were not on any medications, were free from acute gastrointestinal disease, and had not taken antibiotics for at least 1 mo
			Proximal colon	1 (0.72–1.39)	0.93 (0.61–1.41)	0.92	
			Distal colon	1.08 (0.59–1.97)	0.83 (0.37–1.83)	0.73	
			Other cancer site	0.99 (0.77–1.27)	1.06 (0.77–1.46)	0.86	
			Evacuation frequency	No significant difference		0.39	
			Abdominal pain				
			Flatulence				
			Nausea				
			Bloating				
			Hardness of feces				

^a Significant result ($P < 0.05$).

considered an important source of vitamin A (32), and because pasteurization appears to increase vitamin A concentrations in milk, the effect of milk heat treatment on this vitamin is not a major public health concern. Results of meta-analyses revealed that pasteurization of milk leads to a significant decrease in vitamin C and folate, but milk also is not an important source of these vitamins (32, 87). However, we did find a significant decrease in vitamin B2 concentrations after pasteurization. Vitamin B2 is typically found in bovine milk at concentrations of 1.83 mg/liter. Because the recommended daily intake for adults is 1.1 mg/day (86), milk consumption greatly contributes to the recommended daily intake of this vitamin (32). With the exception of vitamin B2, pasteurization does not appear to be a concern in diminishing the nutritive value of milk because milk is often not a primary source of these studied vitamins in the North American diet.

The natural concentrations of vitamins in bovine milk samples can differ significantly as a result of a number of factors, including cow breed, season, country, vitamin concentrations in feed, and frequency of milkings (1, 12, 24, 47). However, changes resulting from pasteurization are likely dependent on the time and temperature of pasteurization conditions. Meta-regression was used to assess the roles of time and temperature in between-study heterogeneity. The duration of pasteurization was positively correlated with folate concentrations, and a direct inverse relationship was found between pasteurization temperature and vitamin C concentrations. Multivariate analysis of time and temperature revealed a significant negative correlation between these variables and vitamin B2 concentrations. These results indicate a likely relationship between time, temperature, and vitamin concentrations in milk; however, further research is needed to tease apart these effects because they appear to differ by vitamin.

Another possible source of heterogeneity among study results is the variation in techniques used to assess vitamin concentrations in milk. HPLC was selected as the “gold standard” method for determination of fat-soluble vitamins by AOAC International (3). No gold standard has been identified for water-soluble vitamins; fluorescence spectroscopy, chromatography, and microbiological methods are all referenced in the AOAC official methods (3). Meta-regression for vitamin B1 and folate studies revealed a significant association between study and method used to quantify vitamins; however, this variable was not significant for other vitamins. Analytic methods must take into consideration separation of vitamins for each vitamin, the methodology used for calibration of external standards, retention of vitamin conformation, and successful recovery (11, 36, 63, 91). The solvents, standards, execution of extraction procedures, and equipment used to carry out these analyses may differ among investigators and can introduce variation among studies (36). Hollman et al. (36) investigated 18 laboratories that were asked to analyze water-soluble vitamin contents in selected foods. These authors reported that in contrast to the fat-soluble vitamins a wider range of methods was used for water-soluble vitamins and

that results from different methods did not always agree for vitamins B2 and C.

Our results also indicate a likely publication bias for studies of vitamins B1 and folate. Possible reasons for this bias include exclusion of those studies not published English and inclusion of only full articles for appraisal and analysis.

Allergy. The collected evidence suggests an association between raw milk consumption and allergy. Epidemiological studies suggest that a number of allergen-independent environmental variables, including lifestyle choices, urban versus rural living (92), diet (68), exposure to human-made pollutants (70), and infectious and noninfectious exposures to microbes (44) influence allergic risk. One of the most consistent findings of these studies was the reduced incidence of allergic hypersensitivities and diseases among children raised on farms (64, 92, 93); however the reasons for this association remain speculative. The hygiene hypothesis states that microbial stimulation during immune development programs host immunity in a manner that prevents hypersensitivity to ambient allergens (84). Farming environments are rich in such microbial content. Results of a meta-analysis of 25 studies reporting associations between farm and/or animal allergens, including raw milk, indicated that “farm living” had a substantial protective influence on the development of allergy (84). However, the authors suggested that the protective influence of farm living on allergic risk is likely to be multifactorial. Thus, although raw milk may contribute to a reduced risk of allergy many other factors must be present to incur protection.

Cancer. The results of this systematic review do not support an association between raw milk consumption and cancer. However, only two studies met the relevance criteria for inclusion in this review. Strengths were found in the design of both studies, e.g., the prospective approach to collecting exposure information before diagnoses, large sample sizes, and controlling for other cancer-related risk factors. The only protective effect of raw milk consumption identified by Sellers et al. (72) was for rectal cancer. However, given the many outcomes that were evaluated in this study, type I error may explain this finding.

A cross-sectional study design that included self-reported mail surveys to assess raw milk consumption was the most common methodology used in studies examining allergy and cancer outcomes. Self-reporting of food consumption involves a high level of respondent burden and associated nonresponse bias, and this method is prone to underreporting and Hawthorne effects (5, 57). Long-term recall of dietary intake and events reported by the same individuals in the distant past (20 to 30 years ago) are not closely correlated (21). Individuals may be unable to accurately recall the frequency of raw milk consumption many years earlier and in some cases may not have been aware whether the milk consumed during childhood was raw or pasteurized. Similar response bias also may apply to recall of allergy and associated diseases. Variation also can

occur between those individuals who drank raw milk a few times during childhood and those who drank raw milk regularly for extensive periods. To evaluate potential associations between raw milk and outcomes such as allergy and cancer, future research should include the quantity and frequency of raw milk consumption at different life stages.

Lactose intolerance. Lactose intolerance associated with dairy products is common among many populations, affecting up to 75% of people worldwide (48). Raw milk has been cited as a “cure” for lactose intolerance because this milk contains natural lactase enzymes and beneficial bacteria such as *Lactobacillus acidophilus* that produce these enzymes, which are otherwise destroyed during pasteurization (59, 69, 94). We identified only one study (50) in which lactose intolerance and raw milk were evaluated, but the authors did not find a significant association. Kim and Gilliland (50) did find that addition of *L. acidophilus* cultures to milk products aided the digestion of milk among lactose intolerant individuals. Thus, although raw milk does not appear to benefit individuals who are lactose intolerant, further research may be warranted.

Limitations. Trials included in systematic reviews and meta-analyses should ideally be of high methodological quality and free of bias so that the observed changes can be confidently attributed to the treatment (22). Many articles in this review did not include standard deviations, standard errors of the mean, or other measures of data dispersion that may have allowed imputation of the standard error. Moreover, many articles did not include *P* values or 95% confidence intervals and indications of statistical significance. In the quality appraisal and data extraction step, difficulties in the interpretation of sample size were encountered because many articles did not include clear descriptions of sample size. In several articles, the length of time for which milk samples were heated was not reported, thereby limiting the interpretation of the results. In several articles, the type of pasteurization was reported without describing the associated time and temperature; these are major limitations of the results reported here. Nine studies were observational, in that the investigators did not control the allocation to pasteurization treatments but rather utilized milk samples that were pasteurized by an external source. These articles often did not include specific time and temperature conditions. Moreover, the primary objective of many studies evaluated herein was not to assess an association between raw milk consumption and cancer, allergy, or lactose intolerance. Further research particular to raw milk consumption and these diseases is needed and should address optimal study design, accurate assessment of exposure and outcomes as it pertains to sociodemographic characteristics, and control of confounding factors.

For this review, the published literature was searched to evaluate scientific evidence for potential health benefits associated with raw milk consumption. Vitamin B2 concentrations in milk appear to be significantly decreased

by pasteurization, and although pasteurization was associated with a decrease in most other vitamins, milk is not considered an important dietary source of these vitamins and is fortified after pasteurization with those vitamins of public health importance. Overall, the results of this review revealed that high quality scientific evidence to support potential benefits of raw milk consumption is generally lacking, and the public should interpret any claims with caution. The results of this review also indicate that better reporting of methods, sample size, and statistical analysis is required to provide quality evidence and allow effective interpretation.

ACKNOWLEDGMENTS

Funding for this project was obtained from the Canadian Institutes of Health Research, Institute of Population and Public Health, and Public Health Agency of Canada Applied Public Health Chair. Many thanks are given to Jennifer Georgieff, Derek Nichols, Amber Reed, Sarah Totton, and Ashley Whiteman for their help in abstract screening and quality appraisal.

REFERENCES

1. Agabriel, C., A. Cornu, C. Journal, C. Sibra, P. Grolier, and B. Martin. 2007. Tanker milk variability according to farm feeding practices: vitamins A and E, carotenoids, color and terpenoids. *J. Dairy Sci.* 90:4884–4896.
2. Andersson, I., and R. Oste. 1994. Nutritional quality of pasteurized milk, vitamin B12, folate and ascorbic acid content during storage. *Int. Dairy J.* 4:161–172.
3. AOAC International. 1995. Official methods of analysis, 16th ed., vol. II. AOAC International, Arlington, VA.
4. Barnes, M., P. Cullinan, P. Athanasaki, S. Macneill, A. M. Hole, J. Harris, S. Kalogeraki, M. Chatzinikolaou, N. Drakonakis, V. Bibaki-Liakou, A. J. Newman Taylor, and I. Bibakis. 2001. Crete: does farming explain urban and rural differences in atopy? *Clin. Exp. Allergy* 31:1822–1828.
5. Baxter, S. D., A. F. Smith, C. H. Guinn, W. O. Thompson, M. S. Litaker, M. L. Baglio, N. M. Shaffer, and F. H. A. Frye. 2003. Interview format influences the accuracy of children's dietary recalls validated with observations. *Nutr. Res.* 23:1537–1546.
6. Bector, B. S., and S. Rani. 1998. A methodology to fortify low fat milk with vitamin A without using a homogenizer. *Indian J. Dairy Sci.* 51(1):69–72.
7. Bendicho, S., A. Espachs, J. Arantegui, and O. Martin. 2002. Effect of high intensity pulsed electric fields and heat treatments on vitamins of milk. *J. Dairy Res.* 69:113–123.
8. Boudonck, K. J., M. W. Mitchell, J. Wulff, and J. A. Ryals. 2009. Characterization of the biochemical variability of bovine milk using metabolomics. *Metabolomics* 5:375–386.
9. Burton, H., J. E. Ford, J. G. Franklin, and J. W. G. Porter. 1967. Effects of repeated heat treatments on the levels of some vitamins of the B-complex in milk. *J. Dairy Res.* 34:193–197.
10. Burton, H., J. E. Ford, A. G. Perkin, J. W. G. Porter, K. J. Scott, S. Y. Thompson, J. Toothill, and J. D. Edwards-Webb. 1970. Comparison of milks processed by the direct and indirect methods of ultra-high-temperature sterilization. *J. Dairy Res.* 37:529–533.
11. Byrdwell, W. C. 2009. Comparison of analysis of vitamin D3 in foods using ultraviolet and mass spectrometric detection. *J. Agric. Food Chem.* 57:2135–2146.
12. Calderón, F., B. Chauveau-Duriot, B. Martin, B. Graulet, M. Doreau, and P. Nozière. 2007. Variations in carotenoids, vitamins A and E, and color in cow's plasma and milk during late pregnancy and the first three months of lactation. *J. Dairy Sci.* 90:2335–2346.
13. Callieri, D. A. 1959. Studies on the vitamin B12, cyanocobalamin-binding capacity, desoxyribosides, and methionine in some commercial milk products and cheese. *Acta Chem. Scand.* 13:737–749.
14. Calvo, M. S., S. J. Whiting, and C. N. Barton. 2004. Vitamin D fortification in the United States and Canada: current status and data needs. *Am. J. Clin. Nutr.* 80:1710S–1716S.

15. Canada Department of Justice. 2009. Food and drug regulations, part B, division 8. Dairy products. Available at: http://laws.justice.gc.ca/eng/C.R.C.-c.870/page-1.html#anchorbo-ga:l_B-gb:l_8. Accessed 21 October 2009.
16. Canada Department of Justice. 2010. Food and drug regulations, part D, division 3. Addition of vitamins, mineral nutrients or amino acids to foods. Available at: http://laws.justice.gc.ca/eng/C.R.C.-c.870/page-2.html#anchorbo-ga:l_D-gb:l_3. Accessed 17 April 2010.
17. Canadian Food Inspection Agency. 2005. National dairy code, 4th ed. Available at: http://www.cfis.agr.ca/english/regcode/ndrc/amdmt_jul_and_oct2005/2005_ppr_e.pdf. Accessed 12 October 2009.
18. Denny, J., M. Bhat, and K. Eckmann. 2008. Outbreak of *Escherichia coli* O157:H7 associated with raw milk consumption in the Pacific Northwest. *Foodborne Pathog. Dis.* 5:321–328.
19. DerSimonian, R., and N. Laird. 1986. Meta-analysis in clinical trials. *Control Clin. Trials* 7:177–188.
20. Donham, K. J., L. F. Burneister, S. F. VanLier, and T. C. Greiner. 1987. Relationships of bovine leukemia virus prevalence in dairy herds and density of dairy cattle to human lymphocytic leukemia. *Am. J. Vet. Res.* 48:235–238.
21. Dwyer, J. T., J. Gardner, K. Halvorsen, E. A. Krall, A. Cohen, and I. Valadian. 1989. Memory of food intake in the distant past. *Am. J. Epidemiol.* 130:1033–1046.
22. Egger, M., G. D. Smith, and D. G. Altman (ed.). 2001. Systematic reviews in health care: meta-analysis in context, 2nd ed. BMJ Publishing Group, London.
23. Egger, M., G. D. Smith, M. Schneider, and C. Minder. 1997. Bias in meta-analysis detected by a simple, graphical test. *Br. Med. J.* 315: 629–634.
24. Ellis, K. A., A. Monteiro, G. T. Innocent, D. Grove-White, P. Cripps, W. Graham McLean, C. V. Howard, and M. Mihm. 2007. Investigation of the vitamins A and E and β -carotene content in milk from UK organic and conventional dairy farms. *J. Dairy Res.* 74:484–491.
25. Food Standards Australia. 2008. Primary production and processing standard for dairy products. Available at: <http://www.foodstandards.gov.au/thecode/primaryproductionprocessingstandards/dairystandards.cfm>. Accessed 12 October 2009.
26. Ford, J. E., S. K. Kon, and S. Y. Thompson. 1959. Effects of processing on vitamins of the B-complex in milk. *Proc. 15th Int. Dairy Congr.* 1:429–434.
27. Ford, J. E., J. W. G. Porter, S. Y. Thompson, J. Toothill, and J. Edwards-Webb. 1969. Effects of ultra-high temperature processing and of subsequent storage on the vitamin content of milk. *J. Dairy Res.* 36:447–454.
28. Gregory, M. E., and H. Burton. 1965. The effect of ultra-high temperature heat treatment on the content of thiamine, vitamin B6 and vitamin B12 of milk. *J. Dairy Res.* 32:13–17.
29. Haddad, G. S., and M. Lowenstein. 1981. Effect of several heat treatments and frozen storage on thiamine, riboflavin, and ascorbic acid content of milk. *J. Dairy Sci.* 66:1601–1606.
30. Hand, D. B. 1943. Reduced and total vitamin C in milk. *J. Dairy Sci.* 26:7–12.
31. Harris, L. J., and S. N. Ray. 1935. Diagnosis of vitamin C subnutrition by urine analysis. *Lancet* 25(5811):71–77.
32. Haug, A., A. T. Høstmark, and O. M. Harstad. 2007. Bovine milk in human nutrition—a review. *Lipids Health Dis.* 6:1–16 (article 25).
33. Hawley, E. E. 1938. Vitamin C content of milks: raw, pasteurized, and baby formulae. *J. Am. Diet. Assoc.* 14:275–277.
34. Headrick, M. L., S. Korangy, N. H. Bean, F. Angulo, S. F. Altekruze, M. E. Potter, and K. Klontz. 1998. The epidemiology of raw milk—associated foodborne disease outbreaks reported in the United States, 1973 through 1992. *Am. J. Public Health* 88:1219–1221.
35. Henry, K. M., and S. K. Kon. 1938. The effect of commercial sterilization on the nutritive value of milk. *J. Dairy Res.* 9:185–187.
36. Hollman, P. C., J. H. Slangen, P. J. Wagstaffe, U. Faure, D. A. Southgate, and P. M. Finglas. 1993. Intercomparison of methods for determination of vitamins in foods, part 2. Water-soluble vitamins. *Analyst* 118:481–488.
37. Holmes, A. D. 1944. Effect of pasteurization on the riboflavin content of milk. *J. Am. Diet. Assoc.* 20:226–227.
38. Holmes, A. D. 1950. Rate of destruction of reduced ascorbic acid in riboflavin-fortified pasteurized milk. *Food Technol.* 4(3):92–93.
39. Holmes, A. D. 1952. Stability of ascorbic acid in milk at different stages of processing. *J. Pediatr.* 40:91–95.
40. Holmes, A. D., C. P. Jones, J. W. Kuzmeski, and A. E. Wertz. 1943. The ratio of ascorbic acid, riboflavin and thiamine in raw and pasteurized milk. *J. Nutr.* 26:337–345.
41. Holmes, A. D., C. P. Jones, H. G. Lindquist, and A. W. Wertz. 1945. Effect of high-temperature-short-time pasteurization on the ascorbic acid, riboflavin and thiamin content of milk. *J. Dairy Sci.* 28:29–33.
42. Holmes, A. D., G. H. Satterfield, F. Tripp, and E. A. Woelffer. 1939. The influence of pasteurization on the ascorbic acid (vitamin C) content of certified milk. *J. Am. Diet. Assoc.* 15:363–368.
43. Holt, D. L., R. L. Wehling, and M. G. Zeece. 1988. Determination of native folates in milk and other dairy products by high-performance liquid chromatography. *J. Chromatogr.* 449:271–279.
44. Horner, A. A. 2006. Toll-like receptor ligands and atopy: a coin with at least two sides. *J. Allergy Clin. Immunol.* 117:1133–1140.
45. Host, A., and E. G. Samuelsson. 1988. Allergic reactions to raw, pasteurized and homogenized/pasteurized cow milk: a comparison. *Allergy* 43:113–118.
46. Houston, J., S. K. Kon, and S. Y. Thompson. 1940. The effect of commercial pasteurization and sterilization on the vitamin B1 and riboflavin content of milk as measured by chemical methods. *J. Dairy Res.* 11:67–70.
47. Indyk, H. E., and D. C. Woollard. 1995. The endogenous vitamin K1 content of bovine milk: temporal influence of season and lactation. *Food Chem.* 54:403–407.
48. Insel, P., R. E. Turner, and D. Ross. 2004. Nutrition, 2nd ed. American Dietetic Association, Jones and Bartlett Publishers, Sudbury, MA.
49. Jensen, R. G. 1995. Handbook of milk composition. Academic Press, San Diego, CA.
50. Kim, H. S., and S. E. Gilliland. 1983. *Lactobacillus acidophilus* as a dietary adjunct for milk to aid lactose digestion in humans. *J. Dairy Sci.* 66:959–966.
51. Kon, S. K., and M. B. Watson. 1936. The effect of light on the vitamin C of milk. *Biochem. J.* 30:2273–2290.
52. Kon, S. K., and M. B. Watson. 1937. The effect of commercial pasteurization on the vitamin C content of milk, p. 52–56. In Milk and nutrition: new experiments reported to the Milk Nutrition Committee. National Institute for Research in Dairying, University of Reading, Berkshire, UK.
53. Korpela, R., L. Paajenen, and T. Tuure. 2005. Homogenization of milk has no effect on the gastrointestinal symptoms of lactose intolerant subjects. *Milchwissenschaft* 60(1):3–6.
54. Lauritsen, J. M. 2008. EpiData data entry, data management and basic statistical analysis system, ed. 3.1. EpiData Association, Odense, Denmark.
55. LeJeune, J. T., and P. J. Rajala-Schultz. 2009. Unpasteurized milk: a continued public health threat. *Clin. Infect. Dis.* 48:93–100.
56. Lind, I., J. Reeser, K. Stayman, M. Deasy, M. Moll, A. Weltman, V. Urdaneta, S. Ostroff, W. Chiridon, E. Campagnolo, and J. Chen. 2007. *Salmonella typhimurium* infection associated with raw milk and cheese consumption—Pennsylvania 2007. *Morb. Mortal. Wkly. Rep.* 56:1161–1164.
57. Macdiarmid, J., and J. Blundell. 1998. Assessing dietary intake: who, what and why of underreporting. *Nutr. Res. Rev.* 11:231–253.
58. Millar, K. R., and A. D. Sheppard. 1972. α -Tocopherol and selenium levels in human and cow's milk. *N. Z. J. Dairy Sci.* 15:3–15.
59. NaturalMilk.org. 2003. The case for untreated milk. Available at: <http://naturalmilk.org/>. Accessed 11 November 2009.
60. Neujahr, H. Y., M. Jonasson, and H. Lundin. 1960. On vitamin B12 and its occurrence in milk. *Milk Dairy Res.* 59:1–22.
61. Oamen, E. E., A. P. Hansen, and K. R. Swartzel. 1989. Effect of ultra-high temperature steam injection processing and aseptic storage on labile water-soluble vitamins in milk. *J. Dairy Sci.* 72: 614–619.

62. Panfili, G., P. Manzi, and L. Pizzoferrato. 1998. Influence of thermal and other manufacturing stresses on retinol isomerization in milk and dairy products. *J. Dairy Res.* 65:253–260.
63. Perales, S., A. Alegria, R. Barbera, and R. Farre. 2005. Review: determination of vitamin D in dairy products by high performance liquid chromatography. *Food Sci. Technol. Int.* 11:451–462.
64. Perkin, M. R., and D. P. Strachan. 2006. Which aspects of the farming lifestyle explain the inverse association of childhood allergy. *J. Allergy Clin. Immunol.* 117:1374–1381.
65. Pizzoferrato, L. 1992. Examples of direct and indirect effects of technological treatments on ascorbic acid, folate and thiamine. *Food Chem.* 44:49–52.
66. ProQuest. 2008. RefWorks-COS. ProQuest, Ann Arbor, MI.
67. Radon, K., D. Windstetter, J. Eckart, H. Dressel, L. Leitz, J. Reichert, M. Schmid, G. Praml, M. Schosser, E. Von Mutius, and D. Nowak. 2004. Farming exposure in childhood, exposure to markers of infections and the development of atopy in rural subjects. *Clin. Exp. Allergy* 34:1178–1183.
68. Rautava, S., M. Kalliomaki, and E. Isolauri. 2005. New therapeutic strategy for combating the increasing burden of allergic disease: probiotics—a nutrition, allergy, mucosal immunology and intestinal microbiota (NAMI) research group report. *J. Allergy Clin. Immunol.* 116:31–37.
69. Raw-Milk-Facts.com. 2009. Raw medicine. Available at: <http://www.raw-milk-facts.com/raw-medicine.html>. Accessed 11 November 2009.
70. Saxon, A., and D. Diaz-Sanchez. 2005. Air pollution and allergy: you are what you breathe. *Nat. Immunol.* 6:223–226.
71. Schone, F., M. Leiterer, H. Hartung, C. Kinast, A. Greiling, V. Bohm, and G. Jahreis. 2003. Trace elements and further nutrition-related constituents of milk and cheese. *Milchwissenschaft* 58(9–10):486–490.
72. Sellers, T. A., R. A. Vierkant, J. Djeu, E. Celis, A. H. Wang, N. Kumar, and J. R. Cerhan. 2008. Unpasteurized milk consumption and subsequent risk of cancer. *Cancer Causes Control* 19:805–811.
73. Sharma, R., and L. Darshan. 1998. Influence of various heat processing treatments on some B-vitamins in buffalo and cow's milks. *J. Food Sci. Technol.* 35:524–526.
74. Sharp, J. C., G. M. Paterson, and N. J. Barrett. 1985. Pasteurization and the control of milkborne infection in Britain. *Br. Med. J.* 291:463–464.
75. Sharp, P. F., E. S. Guthrie, and D. B. Hand. 1940. Deaeration as a means of retarding oxidized flavors and preserving the vitamin C of milk. *Annu. Rep. N. Y. State Assoc. Dairy Milk Inspect.* 14:63–76.
76. Sierra, I., and C. Vidal-Valverde. 2000. Effect of storage on the vitamin B1 content of microwave- and conventionally treated milk. *Milchwissenschaft* 55:253–255.
77. Sierra, I., and C. Vidal-Valverde. 2001. Vitamin B1 and B6 retention in milk after continuous-flow microwave and conventional heating at high temperatures. *J. Food Prot.* 64:890–894.
78. Sierra, I., C. Vidal-Valverde, and A. Olano. 1999. The effects of continuous flow microwave treatment and conventional heating on the nutritional value of milk as shown by influence on vitamin B1 retention. *Eur. Food Res. Technol.* 209:352–354.
79. Singh, R., and A. D. Deodhar. 1993. Quantitative assessment of total, bound and free forms of thiamine and riboflavin in cow milk and curd. *Indian J. Dairy Sci.* 46(11):525–528.
80. Sutton, A. J., K. R. Abrams, D. R. Jones, T. A. Sheldon, and F. Song. 2000. Methods for meta-analysis in medical research. John Wiley and Sons Ltd., Chichester, UK.
81. Syvaaja, E. L., V. Piironen, P. Varo, P. Koivistoinen, and K. Salminen. 1985. Tocopherols and tocotrienols in Finnish foods: dairy products and eggs. *Milchwissenschaft* 40:467–469.
82. Theophilus, D. R., and O. E. Stamborg. 1945. The influence of breed, feed and processing on the riboflavin content of milk. *J. Dairy Sci.* 28:259–268.
83. Tobias, J., and E. O. Herreid. 1959. Determination of degradation products of ascorbic acid. *J. Dairy Sci.* 42:428–440.
84. Tse, K., and A. A. Horner. 2008. Allergen tolerance versus the allergic march: the hygiene hypothesis revisited. *Curr. Allergy Asthma Rep.* 8:475–483.
85. UK Legislation. 2006. Food hygiene (England) regulations, no. 14. Available at: <http://www.opsi.gov.uk/si/si2006/20060014.htm>. Accessed 11 November 2009.
86. U.S. Department of Agriculture. 2001. Dietary reference intakes—recommended intakes for individuals. National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. Available at: http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=3&tax_subject=256&topic_id=1342&level3_id=5140. Accessed 12 November 2009.
87. U.S. Department of Agriculture. 2009. “What’s in the foods you eat” search tool. Available at: <http://www.ars.usda.gov/services/docs.htm?docid=7783>. Accessed 12 November 2009.
88. U.S. Food and Drug Administration. 2007. Pasteurized milk ordinance. Available at: <http://www.fda.gov/Food/FoodSafety/Product-SpecificInformation/MilkSafety/NationalConferenceonInterstateMilkShipmentsNCIMSModelDocuments/PasteurizedMilkOrdinance2007/default.htm>. Accessed 11 November 2009.
89. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. 2005. Grade “A” pasteurized milk ordinance revision. 25 March 2005. Available at: <http://www.cfsan.fda.gov/~ear/pmo05toc.html>. Accessed 12 October 2009.
90. Varadharaju, N., S. Prasad, and S. Prasad. 1988. Flexible polypropylene (pp) pouches for sterilization of milk. *Indian J. Dairy Sci.* 41(4):478–481.
91. Vinas, P., N. Balsalobre, C. Lopez-Erroz, and N. Hernandez-Cordoba. 2004. Liquid chromatographic analysis of riboflavin vitamers in foods using fluorescence detection. *J. Agric. Food Chem.* 52:1789–1794.
92. von Mutius E. 2000. The environmental predictors of allergic disease. *J. Allergy Clin. Immunol.* 105:9–19.
93. von Mutius, E. 2002. Environmental factors influencing the development and progression of pediatric asthma. *J. Allergy Clin. Immunol.* 109:S525–S532.
94. Westin A. Price Foundation. 2009. A campaign for real milk. Available at: <http://www.realmilk.com>. Accessed 11 November 2009.
95. Wickens, K., J. M. Lane, P. Fitzharris, R. Siebers, G. Riley, J. Douwes, T. Smith, and J. Crane. 2002. Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy* 57:1171–1179.
96. Wigertz, K., I. Hansen, M. Hoier-Madsen, J. Holm, and M. Jagerstad. 1996. Effect of milk processing on the concentration of folate-binding protein (FBP), folate-binding capacity and retention of 5-methyltetrahydrofolate. *Int. J. Food Sci. Nutr.* 47:315–322.
97. Woessner, W. W., H. A. Schuette, and K. G. Weckel. 1940. The effect of commercial practices on ascorbic acid and dehydroascorbic acid (vitamin C) in milk. *J. Dairy Sci.* 23:1131–1141.
98. Ziegler, J. A., and N. B. Keevil. 1944. Photochemical destruction of riboflavin in milk and losses during processing. *J. Biol. Chem.* 155:605–606.

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