U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

May 7, 2021

Neal Barnard, M.D.
Physicians Committee for Responsible Medicine
5100 Wisconsin Ave., NW, Suite 400
Washington, DC 20016

Re: Docket Number FDA-2019-P-4643

Dear Dr. Barnard:

This letter is in response to your citizen petition dated October 3, 2019, requesting that the Food and Drug Administration ("FDA" or "we") "require manufacturers to include the following notice on the product packaging and labeling of all dairy cheese products: *Dairy cheese contains reproductive hormones that may increase breast cancer mortality risk.*" (Citizen Petition from Neal Barnard, Physicians Committee for Responsible Medicine, submitted to the Division of Dockets Management, Food and Drug Administration, dated October 3, 2019 ("Petition") at page 1).

We thank you for your concern for the public health. However, your Petition and accompanying documents do not contain facts demonstrating reasonable grounds for requiring the statement that you request.[1] Therefore, in accordance with 21 CFR 10.30(e)(3), we are denying your petition.

DISCUSSION

I. FDA's Authority to Require Warning and Notice Statements in Food Labeling

Your Petition requests that FDA require manufacturers to include a specific notice on the packaging and labeling of all dairy cheese products (Petition at page 1). FDA's authority to require warning and notice statements in the labeling of food generally derives from sections 201(n), 403(a)(1), and 701(a) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") (21 U.S.C. 321(n), 343(a)(1), and 371(a)). Under section 403(a)(1) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular.[2] Section 201(n) of the FD&C Act provides that, in determining whether labeling is misleading, FDA shall take into account not only representations made about the product, but also the extent to which the labeling fails to

[1] *See* 21 CFR 10.40(a)(2)(i).

[2] The term "label" means any written, printed, or graphic matter on the immediate container of an article (section 201(k) of the FD&C Act). The term "labeling" means all labels and other written, printed, or graphic matter either on any article or its containers or wrappers or accompanying such article (section 201(m) of the FD&C Act).

reveal facts material in light of representations made or suggested in the labeling, or facts material as to consequences that may result from use of the product under conditions of use prescribed in the labeling or under customary or usual conditions of use. Section 701(a) of the FD&C Act authorizes FDA to issue regulations for the efficient enforcement of the Act.

In a few instances, FDA has relied on sections 201(n), 403(a)(1), and 701(a) of the FD&C Act to issue rules requiring warning and notice statements in the labeling of food to alert consumers to potential health and safety consequences.[3] We note that where the statements reference a risk of death or serious illness, they have been denoted as warnings, rather than notices, in our regulations and are compelled as such in the labeling.

For instance, in 1998, FDA issued a final rule requiring a warning statement in the labeling of unprocessed juice products to inform consumers of the risk of foodborne illnesses posed by such products.[4] The statement warned about the risk of serious illness in children, the elderly, and persons with weakened immune systems. In support of the language in the statement, the proposed rule provided data on a series of foodborne disease outbreaks traced to the consumption of unprocessed juices.[5]

In 1984, FDA issued a final rule requiring warning and notice statements in the labeling of protein products promoted for weight reduction.[6] The warning pertained to the risk of death or serious illness when protein products are consumed as part of a very low calorie diet. In deciding to compel the warning statement, FDA relied on evidence demonstrating a link between the consumption of protein products, when consumed as part of a diet of less than 400 calories per day, and the risk of death or serious illness.

In sum, FDA has required statements about risks of death or serious illness in the labeling of certain foods based on evidence demonstrating a relationship between the risks and consumption of the foods. Without such evidence, however, FDA does not have a basis to compel warning statements as the absence of material facts from the labeling has not been shown.

II. Scientific Analysis of Your Petition

We carefully reviewed the evidence that you submitted with your petition.[7] Your Petition and accompanying documents do not contain facts demonstrating reasonable grounds for requiring the statement that you request. Specifically, your Petition does not demonstrate that the labeling of dairy cheese products is misleading absent the statement, "*Dairy cheese contains reproductive hormones that may increase breast cancer mortality risk*" (see Petition at page 1).

Your Petition cites 10 publications to support your argument of an increased risk relationship between reproductive hormones contained in dairy cheese and breast cancer mortality. These

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[3] *See* 21 CFR 101.17(a)-(h).

[4] 63 FR 37030, July 8, 1998.

[5] 62 FR 45593, August 28, 1997.

[6] 49 FR 13679, April 6, 1984.

[7] There were no comments submitted to the docket.

publications include one human intervention study,[8] four human observational studies,[9] one meta-analysis,[10] two website printouts of breast cancer statistics,[11] one report,[12] and one economic analysis[13] comparing treatment costs for breast cancer by tumor stage and type of service.

FDA considers review articles, meta-analyses, book reviews, letters to the editor, federal reports, and website print-outs as background materials. Although useful for background information, these materials do not sufficiently evaluate dairy cheese containing reproductive hormones and the associated relationship to risk of breast cancer mortality. FDA evaluated the five human studies,[14-15] including critical elements of the study design, data collection, and data analysis, for relationship between dairy cheese containing reproductive hormones and increased risk of breast cancer mortality and found that the human studies did not sufficiently evaluate the relationship between dairy cheese containing reproductive hormones and risk of breast cancer mortality.

Therefore, FDA is unable to draw scientific conclusions from this information to demonstrate that dairy cheese products are misbranded absent the warning statement you suggest.

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[8] Prentice RL, Aragaki AK, Howard BV, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. *J Nutr.* 2019;149:1565-1574.

[9] McCann SE, Hays J, Baumgart CW, et al. Usual consumption of specific dairy foods is associated with breast cancer in the Roswell Park Cancer Institute Databank and BioRepository. *Curr Dev Nutr.* 2017;1:e000422; Brinkman MT, Baglietto L, Krishnan K, et al. Consumption of animal products, their nutrient components and postmenopausal circulating steroid hormone concentrations. *Eur J Clin Nutr.* 2010;64:176-183; Kroenke CH, Kwan ML, Sweeney C, Castillo A, Caan BJ. High- and low-fat dairy intake, recurrence, and mortality after breast cancer diagnosis. *J Natl Cancer Inst.* 2013;105:616-623; Ronco AL, De Stéfani E, Dáttoli R. Dairy foods and risk of breast cancer: a case-control study in Montevideo, Uruguay. *Eur J Cancer Prev.* 2002;11:457-463.

[10] Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst.* 2002;94:606-616.

[11] CDC, Breast Cancer Statistics, https://www.cdc.gov/cancer/breast/statistics/index.htm (May 2019); U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz (June 2019).

[12] World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018, https://www.wcrf.org/dietandcancer.

[13] Blumen H, Fitch K, Polkus V. Comparison of treatment costs for breast cancer, by tumor stage and type of service. *Am Health Drug Benefits.* 2016;9:23-32.

[14] Prentice RL, Aragaki AK, Howard BV, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. *J Nutr.* 2019;149:1565-1574.

[15] McCann SE, Hays J, Baumgart CW, et al. Usual consumption of specific dairy foods is associated with breast cancer in the Roswell Park Cancer Institute Databank and BioRepository. *Curr Dev Nutr.* 2017;1:e000422; Brinkman MT, Baglietto L, Krishnan K, et al. Consumption of animal products, their nutrient components and postmenopausal circulating steroid hormone concentrations. *Eur J Clin Nutr.* 2010;64:176-183; Kroenke CH, Kwan ML, Sweeney C, Castillo A, Caan BJ. High- and low-fat dairy intake, recurrence, and mortality after breast cancer diagnosis. *J Natl Cancer Inst.* 2013;105:616-623; Ronco AL, De Stéfani E, Dáttoli R. Dairy foods and risk of breast cancer: a case-control study in Montevideo, Uruguay. *Eur J Cancer Prev.* 2002;11:457-463.

A. Dairy Cheese Containing Reproductive Hormones

The term "dairy" can refer to milk and milk products from cows, as well as other animals such as goats, sheep, and buffalo.[16] Likewise, "dairy cheese" is a broad term that can encompass a range of varieties, including blue, hard, pasta filata, processed, semi-hard, semi-soft, soft and fresh, and soft-ripened.[17] Between different types of dairy cheeses, there is a wide variation in fat content as well as other nutrients, such as calcium and vitamin D. Individual dairy cheeses containing differing amounts of fat, calcium, vitamin D, or various hormones could confer different effects in the body. When a study refers to a whole food such as "dairy cheese" or the category "dairy products" as an intervention or exposure, it is not possible to accurately determine any independent effect of a particular component in that whole food or category because the specific component (i.e., a specific reproductive hormone) is unknown.

While the Petition suggests that all dairy cheese products contain reproductive hormones, the Petition does not define the term "reproductive hormones" or provide specific evidence regarding the presence of reproductive hormones in dairy cheese. Without specifying which hormones are "reproductive hormones" or the level of hormones that could increase risk of breast cancer mortality, the Petition provides insufficient evidence for FDA to accurately determine an independent effect of "reproductive hormones" because any putative effect could be due to one of many hormones. Under these circumstances, FDA cannot draw scientific conclusions from the studies cited in the Petition to support a causal relationship between dairy cheese containing reproductive hormones and a disease.

B. Breast Cancer Mortality

Your Petition refers to "breast cancer mortality" in the proposed warning statement (Petition at page 1). "Breast cancer mortality" is death resulting from breast cancer, a disease characterized by the uncontrolled growth and spread of abnormal cells that starts in the breast.[18] Both genetic and environmental factors may affect the risk of different types of cancers. Risk factors for breast cancer may include inheriting certain genes, age, history of cancer(s), alcohol consumption, being overweight, lack of physical activity, not having children, not breastfeeding, use of birth control, and hormone therapy after menopause.[19]

Breast cancer statistics report the incidence of breast cancer and rate of breast cancer death. The cancer mortality statistics cited in the Center for Disease Control's (CDC) Data Visualizations Tool come from the underlying cause of death on a death certificate.[20] Cause of death determined by autopsy combined with clinical data is considered the best estimate of the true cause of death.[21] The percentage of cancers coded as the underlying cause of death on the death certificate that agree with the cancer diagnosis in the medical record is an indication of the

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[16] 21 CFR 1240.3(j).

[17] Fox, Patrick F.; Guinee, Timothy P.; Cogan, Timothy M.; McSweeney, Paul L. H. "Principal Families of Cheese," *Fundamentals of Cheese Science*, p. 388 (Aspen Publishers, 2000).

[18] https://www.cancer.org/cancer/breast-cancer/about/what-is-breast-cancer.html (last visited Oct. 20, 2020).

[19] https://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm (last visited Nov. 9, 2020).

[20] https://www.cdc.gov/cancer/uscs/technical_notes/interpreting/mortality.htm (last visited Dec. 8, 2020).

[21] Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. *New England Journal of Medicine* 1985;313(20):1263–1269.

reliability with which the underlying cause of death can be determined from the death certificate. Therefore, for the purposes of this evaluation, we consider "breast cancer mortality" to be death resulting from breast cancer, confirmed by death certificates that report breast cancer as the underlying cause of death.

With this backdrop in mind, we evaluate your points, along with each of the studies that they reference, below.

C. Scientific Evaluation of Petition's Statement of Grounds

1. *Assertion One*: "*High-fat dairy products, such as cheese, are associated with an increased risk for breast cancer . . . . Components in dairy such as insulin-like growth factor (IGF-1) and other growth hormones may be among the reasons for the increased risk for cancer.*"[22]

Your Petition refers to a study by McCann et al. to support the position that dairy cheese is associated with increased risk for breast cancer and that increased risk may be due to insulin-like growth factor 1 (IGF-1) and other growth hormones contained in dairy products.

We disagree that the case-control study by McCann et al. supports the relationship between dairy cheese containing reproductive hormones and increased risk of breast cancer mortality. The study did not report consumption of any hormones in dairy cheese nor the outcome of breast cancer mortality. Hence, we could not draw scientific conclusions from this study about the relationship between reproductive hormones contained in dairy cheese and breast cancer mortality.

The McCann et al. study was a retrospective case-control study[23] that examined associations between the types and quantity of dairy foods consumed and the risk of breast cancer incidence among women registered in a cancer databank[24] between 2003 and 2014. The study did not report the outcome of breast cancer mortality. The study collected information on diet intake using a self-administered food-frequency questionnaire ("FFQ") from 1,941 breast cancer cases and 1,237 controls. Intakes of dairy foods were queried and grouped into monthly intakes of total dairy, milk, yogurt, low-fat cheese, other cheese, and sweet dairy. Low fat cheese was not defined, and "other cheese" included American, cheddar, and cream cheese. The FFQ did not collect information on consumption of foods by fat content nor did the study report the amount of dairy cheese containing reproductive hormones consumed. The study Included only a

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[22] Petition at page 1 (citing McCann SE, Hays J, Baumgart CW, et al. Usual consumption of specific dairy foods is associated with breast cancer in the Roswell Park Cancer Institute Databank and BioRepository. *Curr Dev Nutr.* 2017;1:e000422).

[23] A case-control study is an observational study designed to determine if an exposure is associated with an outcome (i.e., disease or condition of interest). Case-control studies, due to their typically retrospective nature, can be used to establish a correlation between exposures and outcomes, but cannot establish *causation.* Another weakness of the case-control study is recall bias, when a participant who has been diagnosed with a disease (case) may recall the foods consumed differently than a healthy individual (control). Recall bias may lead to concluding that there are associations between the exposure and disease that do not, in fact, exist. (Szklo M., Nieto FJ. Epidemiology Beyond the Basics, Aspen Publishing, 2000).

[24] Roswell Park Cancer Institute Data Bank and BioRepository.

single qualitative question that asked what types of milk were usually consumed. The question allowed participants to record multiple choices but did not capture the proportion of each type of milk consumed. The authors used $p< 0.05$ to determine statistical significance of results.

The authors also reported that higher intakes of yogurt were associated with reduced risk of breast cancer (odds ratio (OR): 0.61; 95% confidence interval (CI): 0.46, 0.82) and higher intakes of "other cheeses" were associated with a marginally increased risk of breast cancer (OR: 1.53; 95% CI: 0.99, 2.34; $p = 0.05$). FDA does not view the association between other cheeses and increased risk of breast cancer as significant because the p value is not less than 0.05 and the confidence interval of 0.99 to 2.32 spans 1.[25] Accordingly, we cannot determine whether the exposure of "other cheeses" increases or decreases the odds of the event happening with our specified level of confidence.[26]

The Petition asserts, "High-fat dairy products, such as cheese, are associated with an increased risk for breast cancer. . . . The results showed that those who consumed the most American, cheddar, and cream cheeses had a 53 percent increased risk for breast cancer" (Petition at page 1). However, the study authors do not define "high-fat dairy products" in their methods. In fact, they stated that a limitation of their study was that they were unable to examine dairy consumption according to fat content because the FFQ was not designed to query this level of detail. High-fat dairy products could include food other than cheese, therefore, FDA cannot draw conclusions from the study cited to support this statement as it does not show an independent effect of cheese.

The Petition further notes, "Components in dairy such as insulin-like growth factor (IGF-1) and other growth hormones may be among the reasons for the increased risk for cancer" (Petition at page 1). However, the study did not measure IGF-1, other growth hormones, or any hormones at all in dairy products or cheese, nor did it measure reproductive hormones in cases with breast cancer. FDA cannot draw scientific conclusions from this statement because we cannot draw conclusions from the study cited to support it. For the reasons stated above, FDA cannot draw scientific conclusions to support the relationship between reproductive hormones and increased risk of breast cancer mortality from the McCann et al. study.

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[25] The p value is the probability of an event or outcome in a statistical experiment. "P value." *Merriam-Webster.com Dictionary*, Merriam-Webster, www.merriam-webster.com/dictionary/P%20value (last visited Feb. 4, 2021). *See also* Rosner, Bernard. Fundamentals of biostatistics, 2011.

[26] The odds ratio (OR) is a measure of how strongly an event is associated with exposure. The larger the odds ratio, the higher odds that the event will occur with exposure. Odds ratios smaller than one imply the event has fewer odds of happening with the exposure. If the confidence interval for the odds ratio includes the number 1, then the calculated odds ratio would not be considered statistically significant. An odds ratio greater than 1 implies there are greater odds of the event happening in the exposed versus the non-exposed group. An odds ratio of less than 1 implies the odds of the event happening in the exposed group are less than in the non-exposed group. An odds ratio of exactly 1 means the odds of the event happening are the exact same in the exposed versus the non-exposed group. Thus, if the confidence interval includes 1 (e.g., [0.01, 2], [0.99, 1.01], or [0.99, 100] all include 1 in the confidence interval), then the expected true population odds ratio may be above or below 1, so it is uncertain whether the exposure increases or decreases the odds of the event happening with our specified level of confidence. (Szklo M., Nieto FJ. Epidemiology Beyond the Basics, Aspen Publishing, 2000).

2. *Assertion Two: "Australian researchers who measured hormone levels in 766 postmenopausal women found that those who consumed the most dairy products had 15 percent more estradiol in their bloodstreams, compared with women consuming little or no dairy products."*[27]

Your Petition also cites Brinkman et al. in support of your position. We disagree that the cross-sectional study by Brinkman et al. supports a relationship between dairy cheese containing reproductive hormones and increased risk of breast cancer mortality. The study did not report consumption of dairy cheese containing reproductive hormones nor the outcome of breast cancer mortality. Hence, we could not draw scientific conclusions about the relationship between reproductive hormones contained in dairy cheese and breast cancer mortality from this study.

Brinkman et al. conducted an Australian cross-sectional study that examined the association between estimated dietary intake (including quartiles of dairy products) and plasma concentrations of steroid hormones and sex hormone binding globulin (SHBG) of postmenopausal women. This study did not investigate the association between consumption of dairy cheese (containing reproductive hormone) and breast cancer mortality. Dietary intake was assessed with an FFQ. Dairy products included cheese; ice cream; custards; cream; yogurt; milk consumed with cereal, tea, and coffee; and milk drinks. The study did not report dietary intake of reproductive hormones contained in dairy cheese, nor did it report the outcome of breast cancer mortality.

The authors reported that mean concentrations of total and free estradiol were 15 and 14% higher for women in the highest quartile of dairy product consumption than for those in the lowest quartile, respectively. However, the study reported no statistical test to assess significance between quartile comparisons (i.e., quartile 1 versus 4). The study reported only p for trend (0.02 and 0.03, respectively). Risk statistics (e.g., hazard ratios (HR) and 95% CIs) were also not conducted to show significant differences between quartiles. While this trend may be significant ($P < 0.05$), the difference in risk between subjects at various levels of intake may not be statistically significant (CI includes 1). When a study does not perform statistical analyses between the highest and lowest quartiles, one cannot determine if the result comparing the two quartiles is real or due to chance. Thus, we cannot draw scientific conclusions about the role of the dairy products assessed and the outcome measured.

The Petition refers to these results as evidence to support the warning statement (Petition at page 1). While the study included cheese in the category of dairy products, it did not report intake of dairy cheese containing reproductive hormones, nor did it measure reproductive hormones in cheese. Further, the study population was postmenopausal women who had not had breast cancer before baseline and were not taking hormone replacement therapy. The outcome measure did not include breast cancer mortality. Hence, one cannot draw scientific conclusions from this study about the relationship between reproductive hormones contained in dairy cheese and breast cancer mortality.

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[27] Petition at page 1 (citing Brinkman MT, Baglietto L, Krishnan K, et al. Consumption of animal products, their nutrient components and postmenopausal circulating steroid hormone concentrations. *Eur J Clin Nutr.* 2010;64:176-183).

3. *Assertion Three: "Postmenopausal women with higher levels of estradiol in their bloodstreams have more than double the cancer risk, compared with women with lower levels."*[28]

In support of your assertion that postmenopausal women with higher levels of estradiol in their bloodstreams have more than double the cancer risk, compared with women with lower levels, you cite a study by the Endogenous Hormones and Breast Cancer Collaborative Group ("EHBCCG") (Petition at page 1).

We disagree that the EHBCCG's meta-analysis that you cite supports the relationship between dairy cheese containing reproductive hormones and increased risk of breast cancer mortality. Specifically, we could not draw scientific conclusions about the relationship between the reproductive hormones contained in dairy cheese and breast cancer mortality because the meta-analysis did not report consumption of hormones in dairy cheese nor the outcome of breast cancer mortality.

The EHBCCG analyzed worldwide data pooled from nine prospective cohort studies. It examined the relationship between the levels of endogenous sex hormones and breast cancer risk in 663 postmenopausal women who developed breast cancer and 1,765 women who did not. The analysis reported neither dietary intakes (including cheese products) of participants nor the outcome of breast cancer mortality. It found that the risk for breast cancer increased statistically significantly with increasing concentrations of all sex hormones examined. However, a meta-analysis such as this does not provide sufficient information on the individual studies included for FDA to determine critical elements, such as the study population characteristics and the composition of the products consumed. Similarly, the lack of detailed information on studies summarized in review articles prevents FDA from determining whether the studies are flawed in critical elements, such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether scientific conclusions can be drawn from it—something that we were unable to do with the meta-analysis your Petition cites.

In addition, the EHBCCG's meta-analysis only measured plasma sex hormones in women and did not evaluate the relationship between dairy cheese (containing reproductive hormones) and breast cancer mortality. Hence, we could not draw scientific conclusions from this study about the relationship between the reproductive hormones contained in dairy cheese and breast cancer mortality to support the notice statement that you request.

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[28] Petition at page 1 (citing Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst.* 2002;94:606-616).

4. *Assertion Four: "Among women previously diagnosed with breast cancer, consumption of high-fat dairy products is associated with increased mortality risk. The Life After Cancer Epidemiology study included 1,893 women previously diagnosed with early-stage invasive breast cancer. After a median follow-up of 11.8 years, those consuming one or more servings of high-fat dairy products (e.g., cheese, ice cream, whole milk) daily had a 49 percent higher breast cancer mortality, compared with those consuming less than one-half serving daily."*[29]

Your Petition cites Kroenke et al. in support of your argument. We disagree that the prospective cohort study by Kroenke et al. supports a causal relationship between dairy cheese containing reproductive hormones and increased risk of breast cancer mortality. While the study did measure breast cancer mortality as an outcome, it did not report consumption of hormones in dairy cheese. Hence, we could not draw scientific conclusions from this study about the relationship between the reproductive hormones contained in dairy cheese and breast cancer mortality.

The study by Kroenke et al. analyzed data from a prospective cohort study that examined the relationship of high- versus low-fat dairy products and risk of breast cancer recurrence and mortality in 1,893 postmenopausal women diagnosed with invasive breast cancer. The study collected dietary intake data using a validated FFQ. Dairy products queried included one or more options of full fat, low-fat, skim, and non-fat milk; cheese, including low-fat cottage cheese, non-fat cheese, part-skim or reduced fat cheese, and other cheese; dairy desserts; and yogurts. Breast cancer-specific death included death attributable to breast cancer as a primary or underlying cause on the death certificate. The authors used $p \leq 0.05$ to determine the statistical significance of results.

The authors reported that the sample size was not large enough to assess the relationship between an individual dairy food, e.g., cheese, with breast cancer mortality. In multivariable adjusted analyses, those consuming average intake (0.5 – 1.0 servings/day) of high-fat dairy did not show a significant association with breast cancer mortality (HR = 1.20, 95% CI = 0.82 to 1.77) compared with the reference intake group (0 to <0.5 servings/day). The authors reported a minor, but significant, increase in breast cancer mortality in those consuming the highest dairy intake (≥1.0 servings/day; HR = 1.49, 95% CI = 1.00 to 2.24 using $p = .05$ for trend). While this trend may be significant ($P \leq 0.05$), the difference in risk between groups at the lowest and highest intake levels was not statistically tested. When a test for statistical significance is not performed between the highest and lowest intake groups, one cannot determine if the result comparing those consuming high versus low-fat dairy products is real or due to chance. Therefore, we could not draw scientific conclusions about the role of the high-fat dairy products and the risk of breast cancer mortality from this study.

The Petition asserts, "Among women previously diagnosed with breast cancer, consumption of high-fat dairy products is associated with increased mortality risk. . . Those consuming one or more servings of high-fat dairy products (e.g., cheese, ice cream, whole milk) daily had a 49 percent higher breast cancer mortality, compared with those consuming less than one-half

[29] Petition at page 2 (citing Kroenke CH, Kwan ML, Sweeney C, Castillo A, Caan BJ. High- and low-fat dairy intake, recurrence, and mortality after breast cancer diagnosis. *J Natl Cancer Inst.* 2013;105:616-623).

serving daily" (Petition at page 2). FDA does not consider these general statements to accurately reflect the Kroenke et al. study results because the study did not statistically analyze the comparisons between the high and low intake groups. In addition, the authors reported on high-fat dairy products, not specifically dairy cheese. Thus, we could not draw conclusions about dairy cheese. The study did not report on measurements of reproductive hormones contained in dairy cheese, which is the subject of the notice that your Petition requests. Hence, we could not draw scientific conclusions from this study about the relationship between the reproductive hormones contained in dairy cheese and risk of breast cancer mortality.

5. *Assertion Five: "Among women previously diagnosed with breast cancer, consumption of high-fat dairy products is associated with increased mortality risk. . . . This is in keeping with an earlier case-control study including 111 women diagnosed with breast cancer."*[30]

To support this assertion, the Petition cites Kroenke et al.[31] and Ronco et al.[32] Kroenke et al. measured breast cancer mortality as an outcome, whereas Ronco et al. measured breast cancer incidence.

We disagree that the case-control study by Ronco et al. supports the Petition's assertion that consumption of high-fat dairy products is associated with increased mortality risk. We further disagree that the Ronco et al. study supports the relationship between dairy cheese containing reproductive hormones and increased risk of breast cancer mortality. The study did not report consumption of hormones in dairy cheese nor did it measure the outcome of breast cancer mortality. Hence, we could not draw scientific conclusions about the relationship between the reproductive hormones contained in dairy cheese and risk of breast cancer mortality.

Ronco et al. was a case control study that evaluated associations of milk and dairy products and the risk of breast cancer in Montevideo, Uruguay, from 1999-2001. The study collected dietary intake data with an unvalidated food frequency questionnaire from 111 cases of breast cancer and 222 healthy age and residence matched controls. Dairy products analyzed included varying fat versions of milks and yogurts, chocolate milk, ricotta cheese, mozzarella cheese, danbo cheese, parmesan cheese, Gruyere cheese, butter, chantilly cream, and ice cream.

The multivariate adjusted analysis found that the highest tertiles of intakes of whole milk [OR, (95% CI) 2.84 (1.38–5.84)], chocolate milk 2.85 (1.06–7.69), total milk 1.99 (1.04–3.83), ice cream 1.98 (1.07–3.66) and Gruyere cheese 1.93 (1.05–3.55) were associated with significant increased risk of breast cancer. However, the authors reported a *p* for trend value lacking statistical significance and did not statistically test the difference in risk between tertiles. Other dairy products with similar or higher fat content, such as parmesan cheese, total cheese, chantilly cream, total dairy, and butter had no significant associations. Similarly, ricotta cheese and skim yogurt were associated with significant decreased risks, whereas skim milk was not.

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[30] Petition at page 2 (citing Ronco AL, De Stéfani E, Dáttoli R. Dairy foods and risk of breast cancer: a case-control study in Montevideo, Uruguay. *Eur J Cancer Prev.* 2002;11:457-463).

[31] Kroenke CH, Kwan ML, Sweeney C, Castillo A, Caan BJ. High- and low-fat dairy intake, recurrence, and mortality after breast cancer diagnosis. *J Natl Cancer Inst.* 2013;105:616-623.

[32] Ronco AL, De Stéfani E, Dáttoli R. Dairy foods and risk of breast cancer: a case-control study in Montevideo, Uruguay. *Eur J Cancer Prev.* 2002;11:457-463.

We could not draw scientific conclusions from this study for several reasons. The study collected dietary intake data with an unvalidated food frequency questionnaire. Validation of the food frequency questionnaire method to assess food intake is essential in order to be able to draw conclusions from the scientific data, as the failure to validate may lead to false associations between dietary factors and diseases or disease-related markers.

In addition, the study did not statistically compare differences in risk between tertiles. When a test for statistical significance is not performed between the highest and lowest intake groups, one cannot determine if the result comparing those consuming high versus low-fat dairy products is real or due to chance. Further, if a level of statistical significance is not reported, one cannot determine if the result is significant (i.e., $p < 0.05$). Thus, one cannot draw scientific conclusions about the role of the high-fat dairy products and the risk of breast cancer mortality. Most importantly, the study did not report analysis of dairy cheese containing reproductive hormones nor the outcome of breast cancer mortality associated with intake of dairy cheese. Hence, we could not draw scientific conclusions from this study about the relationship between the reproductive hormones contained in dairy cheese and risk of breast cancer mortality.

6. *Assertion Six: "New data from the Women's Health Initiative show that a lower-fat, higher-carbohydrate diet emphasizing fruits, vegetables, and grains resulted in long-term health benefits. Compared with women who made no diet changes, the dietary intervention group had 15 percent lower long-term risk of breast cancer mortality, a 30 percent reduction in heart disease, and 13 percent lower risk of developing insulin-requiring diabetes. Possible mechanisms for these results include increased fiber intake, reductions in hormones associated with breast cancer, and improvements in LDL cholesterol, blood pressure, insulin, and glucose levels."*[33]

We disagree that the randomized controlled trial by Prentice et al. that the Petition cites supports the relationship between dairy cheese containing reproductive hormones and increased risk of breast cancer mortality. In general, this study was not designed to investigate the association between consumption of dairy cheese containing reproductive hormones and breast cancer mortality. It did not report consumption of dairy cheese containing reproductive hormones, nor did it report confirmed breast cancer mortality. Hence, we could not draw scientific conclusions from this study about the relationship between the reproductive hormones contained in dairy cheese and risk of breast cancer mortality.

The study by Prentice et al. was a multi-center, randomized, controlled trial that assigned a low-fat dietary pattern or a usual diet comparison to 48,835 postmenopausal women aged 50–79 years old with no prior history of breast cancer. The low-fat or usual diet patterns reported on only fruit, vegetable, and total grain consumption. Dietary intake of dairy products, dairy cheese, or dairy cheese containing reproductive hormones was not reported.

The study measured a primary outcome of invasive breast cancer incidence, and secondary outcomes of coronary heart disease, diabetes, death from any other cause, and total mortality.

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[33] Petition at page 2 (citing Prentice RL, Aragaki AK, Howard BV, et al. Low-fat dietary pattern among postmenopausal women influences long-term cancer, cardiovascular disease, and diabetes outcomes. *J Nutr.* 2019;149:1565-1574.

Breast cancer mortality was not reported. The study did report on "breast cancer followed by death from any other cause;" however, the study lacked confirmation that the primary or underlying cause of death was due to breast cancer. Thus, the study was unable to assess mortality from breast cancer. Results showed a benefit from reduction in dietary fat with increase in vegetables, fruits, and grains, and lower risk of breast cancer followed by death from any cause over a 19.6-year (median) follow-up period (HR = 0.84, 95% CI = 0.74 to 0.96).

The Petition asserts, "Compared with women who made no diet changes, the dietary intervention group had 15 percent lower long-term risk of breast cancer mortality" (Petition at page 2). However, the study assessed "breast cancer followed by death from any cause" not breast cancer mortality. FDA does not consider breast cancer followed by death from any cause equal to breast cancer mortality. FDA views breast cancer mortality as death resulting from breast cancer, where it is confirmed by death certificates that report breast cancer as the underlying cause of death. By assessing breast cancer followed by death from any cause, the study makes it impossible to independently evaluate a diet and breast cancer mortality relationship because mortality could have been due to reasons other than breast cancer.

The Petition also cites Prentice et. al to assert, "Possible mechanisms for these results include increased fiber intake, reductions in hormones associated with breast cancer, and improvements in LDL cholesterol, blood pressure, insulin, and glucose levels" (Petition at page 2). However, the Prentice et. al study was not designed to evaluate the mechanism or relationship of reductions in hormones associated with breast cancer nor dairy cheese containing reproductive hormones and breast cancer mortality. For these several reasons, we could not draw scientific conclusions from this study about the relationship between the reproductive hormones contained in dairy cheese and risk of breast cancer mortality.

7. *Assertion Seven: "It should be noted that limited evidence suggests that dairy intake in general (that is, not specifically, high-fat dairy products) is associated with a lower risk of breast cancer."*[34]

As previously noted, the Petition refers to a report by the World Cancer Research Fund that summarizes current research on *Diet, Nutrition, Physical Activity and Cancer* (Petition at page 2). Although useful for background information, this report does not contain sufficient information on the individual studies reviewed, nor does it present data on the relationship between dairy cheese containing reproductive hormones and risk of breast cancer mortality.

In this same paragraph, the Petition asserts that high-fat dairy products contain higher concentrations of estrogenic hormones; however, the Petition provides no citation for this assertion (Petition at page 2). Of the studies that did assess high-fat dairy product intake, none reported measurement of estrogenic hormones and/or reproductive hormones in high-fat dairy products or specifically dairy cheese. Hence, we could not draw scientific conclusions from this report about the relationship between the reproductive hormones contained in dairy cheese and breast cancer mortality.

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[34] Petition at page 2 (citing Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst.* 2002;94:606-616).

D. Scientific Conclusions

We reviewed each individual human study for the evaluation of dairy cheese containing reproductive hormones and increased risk of breast cancer mortality, including critical elements of the study design, data collection, and data analysis. We considered one intervention study and four observational studies to not be credible evidence for the evaluation of the relationship between dairy cheese containing reproductive hormones and risk of breast cancer mortality. We could not draw scientific conclusions from those studies for the following reasons.

- Four of five studies assessed some sort of dairy cheese(s) (McCann et al. 2005; Brinkman et al. 2010; Kroenke et al. 2013; Ronco et al. 2002), while one study did not report any dietary intake information (Prentice et al. 2019). Of the four studies that did assess dairy cheese, none of the studies measured the reproductive hormones contained in dairy cheese. Thus, none of the five studies evaluated dairy cheese containing reproductive hormones.

- Four of five studies did not measure breast cancer mortality (McCann et al. 2005; Brinkman et al. 2010; Ronco et al. 2002; Prentice et al. 2019). One study evaluated breast cancer mortality, however, it did not measure reproductive hormones contained in dairy cheese (Kroenke et al. 2013). Thus, none of the five studies evaluated dairy cheese containing reproductive hormones and breast cancer mortality.

In summary, none of the studies that the Petition cites evaluated dairy cheese containing reproductive hormones and breast cancer mortality. The studies did not specify and measure reproductive hormones contained in dairy cheese, which is the subject of the proposed notice. Likewise, they did not appropriately measure the specific disease, breast cancer mortality, that is in the proposed notice.

Without evidence demonstrating a relationship between consumption of dairy cheese and an increased risk of breast cancer mortality, we cannot conclude that the absence of this information from the labeling of dairy cheese constitutes an omission of material fact and misleads consumers under sections 201(n) and 403(a)(1) of the FD&C Act. Therefore, we do not have a basis to compel the proposed statement in the labeling of dairy cheese.

III. Conclusion

Based on our consideration of the scientific evidence and other information submitted with your Petition, we conclude that the evidence is insufficient to support that the labeling of dairy cheese is misleading in the absence of the requested notice statement. Your Petition does not contain

facts demonstrating any reasonable grounds to require the notice, "*Dairy cheese contains reproductive hormones that may increase breast cancer mortality risk*," on all dairy cheese products, as you request. Therefore, in accordance with 21 CFR 10.30(e)(3), we are denying your petition.

Sincerely,

Claudine Kavanaugh, Ph.D., M.P.H., R.D.
Director
Office of Nutrition
and Food Labeling
Center for Food Safety
and Applied Nutrition