



Probabilistic risk assessment for milk in dark chocolate, cookies and other baked goods with PAL sold in Canada

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ABSTRACT

The risk of having an allergic reaction in milk-allergic individuals consuming products with precautionary allergen labelling (PAL) for milk has been rarely studied in products such as dark chocolate, cookies, and other baked goods. A probabilistic risk assessment model was developed to estimate potential risks. Milk occurrence and contamination levels were reported in a previous article from our group. Dose-response curves for milk were constructed using values ($n = 1078$) from published double-blind placebo-controlled food challenges. Canadian consumption data was extracted from a national survey, and a homemade survey involving food-allergic Canadians. Milk eliciting doses (ED) were 0.23 (ED₀₁), 1.34 (ED₀₅), 3.42 (ED₁₀), and 16.3 (ED₂₅) mg of milk protein (Log-Normal distribution). Average exposures, per eating occasion, were 24 mg (dark chocolate), 3.9 mg (baked goods), and 0.20 mg (cookies) of milk proteins. The estimated risk of having a milk-induced allergic reaction by consuming foods with PAL for milk was higher for dark chocolate (16%; 15,881/100,000) than baked goods (3.8%; 3802/100,000) or cookies (0.6%; 646/100,000) in milk-allergic Canadians. Dark chocolate, cookies, and baked goods with PAL for milk, should be avoided by milk-allergic Canadians (consuming or not products with PAL) to prevent allergic reactions.

1. Introduction

Milk allergy affects 1.1% of the Canadian population, based on a convincing history and/or a physician diagnosis, and its prevalence seems to have increased over time within Canada (Clarke et al., 2020). Avoidance of the foods containing their allergen(s) remains the most effective measure for most allergic individuals to prevent clinical reactions (DunnGalvin et al., 2015; Versluis et al., 2015). To avoid exposure to milk as a food allergen, milk-allergic consumers rely on the labels of pre-packaged food products (DunnGalvin et al., 2015). However, milk can be present in some foods without being listed in the ingredients' section due to potential cross-contamination occurring at the food factory or during raw material transportation and handling (Burndred et al., 2017). Some food manufacturers began using Precautionary

Allergen Labelling (PAL) to warn allergic consumers about the potential risks (Hefle et al., 2007) of cross-contamination and avoid unexpected reactions (Allen et al., 2014). However, PAL should only be used when all efforts to ensure removal or absence of the allergen have been undertaken (Burndred et al., 2017). In Canada, food regulators recommend the use of PAL only when cross-contamination is unavoidable despite following good manufacturing practices (Canadian Food Inspection Agency, 2018). However, specific guidance tools such as action levels remain unavailable (Agence Canadienne d'Inspection des Aliments, 2019). Over time, PAL has become widely used by food industries (Pieretti et al., 2009; Zurzolo et al., 2013), raising concerns about its reliability (DunnGalvin et al., 2015, 2019) and leading to a decrease in foodstuffs available to allergic consumers (Allen and Taylor, 2018).

Facing limited food offerings without PAL, some allergic consumers

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CCHS-2015, Canadian Community Health Survey of 2015; CI, Confidence Interval; DBPCFC, Double-blind placebo-controlled food challenge; ED, Eliciting Dose; LOAEL, Lowest Observed Adverse Effect Level; NOAEL, No Observed Adverse Effect Level; PAL, Precautionary Allergen Labelling; QICSS, Quebec Interuniversity Centre for Social Statistics; USA, United States of America.

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take the risk of eating products with PAL or simply ignore it (Blom et al., 2018). If eating a product with PAL does not trigger an allergic reaction, those allergic consumers might repeat the experience and adopt a risky behaviour, increasing the chances of having an undesired allergic reaction such as anaphylaxis (Versluis et al., 2015; Blom et al., 2018).

Anaphylaxis cases due to consumption of chocolate, cookies and/or baked goods with PAL is not well documented. Miles et al. (2020) reported rates of anaphylaxis in Canada from 2011 to 2017, but the culprit foods and the presence of PAL were not disclosed (Miles et al., 2020). Older articles reported candies, chocolate, cookies, and pastries (baked goods) as foods triggering anaphylaxis, but only one case of a milk reaction to chocolate was explicitly reported (Sampson et al., 1992; Bock et al., 2007). Blom et al. (2018) and Spanjersberg et al. (2010) reported milk in dark chocolate and baked goods as triggering allergic reactions (Blom et al., 2018; Spanjersberg et al., 2010). In the study of Blom and colleagues (2018), within milk-allergic participants, most had mild or moderate symptoms ($n = 4/5$) when exposed to a product containing milk, and one participant experienced a severe reaction with an objective respiratory symptom (cough), but no medication was taken for any of those five patients and it was not specified if anaphylaxis to the culprit foods was observed or not (Blom et al., 2018). In addition, few publications discussing the number of allergic individuals choosing to engage in a risky behaviour related to products with PAL are available. Marchisotto et al. (2017) investigated allergic consumer purchasing habits towards foods with PAL on multiple foods (Marchisotto et al., 2017), but consumption amounts when allergic individuals took the risk were not included. Consumption patterns may be different in allergic individuals compared to the general population (e.g., eat smaller quantities of a product with PAL at first and continue eating if no allergic reaction is observed). Indeed, each allergic individual has their own tolerance to their allergen(s), which makes an additional factor to consider.

There is currently no established clinical threshold for the levels of allergen considered unsafe for consumers allergic to milk in Canada. However, Houben et al. (2020) estimated that 1% of milk-allergic individuals would react to a dose of 0.2 mg or less of milk proteins (Houben et al., 2020). Hence, risk-taking behaviours might not always lead to allergic reactions, depending on the exposure dose (mg). Exposure can vary among foodstuffs, with allergen cross-contamination often being heterogeneous between products from different industrial productions (or production lot) (Manny et al., 2021).

Previous studies have shown that only a few products with PAL contained the targeted allergens based on analytical measures (Hefle et al., 2007; Manny et al., 2021; Pele et al., 2007; Ford et al., 2010; Remington et al., 2013; Crotty and Taylor, 2010). However, the presence of milk in products with PAL had a higher occurrence in dark chocolate than other foodstuffs (cookies, baked goods) (Manny et al., 2021; Pele et al., 2007; Crotty and Taylor, 2010). This higher occurrence can be explained by the way chocolate is manufactured, as cross-contamination is difficult to avoid (Crotty and Taylor, 2010; Remington et al., 2015). Without dedicated lines, cross-contamination can occur between milk chocolate and dark chocolate production (Burndred et al., 2017). However, the risk of having an allergic reaction by eating products with PAL remains unknown for cookies and other baked goods, and partially addressed in dark chocolate (Spanjersberg et al., 2010).

This study presents the results of probabilistic risk assessments for milk present as an allergen in dark chocolate, cookies and other baked goods with PAL, using analytical data (Manny et al., 2021) with reported Canadian consumption data for the general population and allergic individuals. Although products without a PAL for milk may also contain unintended milk proteins (Spanjersberg et al., 2010; Blom et al., 2018; Bedford et al., 2017), these products were out of the scope of this study and thus are not discussed; the focus of this risk assessment is on products with PAL and risk-taking milk-allergic individuals.

Based on Spanjersberg et al. (2007), data sources included in the risk

assessment model were: 1) general population consumption data from the Canadian Community Health Survey of 2015 (CCHS-2015) of Statistics Canada; 2) allergic individuals chocolate consumption data and habits acquired through completion of surveys (in collaboration with Food Allergy Canada and *Allergies Québec*); 3) milk occurrence in the targeted foods from the literature (Manny et al., 2021); 4) dose-response curve for milk constructed based on published double-blind placebo-controlled food challenge (DBPCFC) studies (Appendix Table 1).

2. Materials and methods

2.1. Canadian consumption data acquisition

Two surveys were used to acquire and compare consumption data for the general and allergic populations. First, consumption data for chocolate, cookies, and other baked goods (24-h diet recalls) for the general population was extracted from the CCHS-2015 (Statistics Canada, 2015), using SAS software v9.4 (SAS Institute Inc., North Carolina, USA). Raw, confidential data from the survey was extracted with their bootstrapped values to extrapolate them to the whole Canadian population. Distribution parameters were computed for the entire population and for each food involved. Additionally, the serving sizes from the labels' nutritional facts table were recorded for comparison with the CCHS-2015 consumption data.

Second, a survey on chocolate consumption habits in allergic individuals was conducted in collaboration with Food Allergy Canada and *Allergies Québec*, associations representing allergic individuals, health-care providers and other professionals involved in food allergy. Surveys designed with Google Forms were sent to their food-allergic members from April 6th to June 6th, 2020, through their monthly newsletter. French and English versions were available. Their members were invited to answer the survey online, which included information on demographics (sex, age, province of residence), their self-reported/known food allergies, chocolate consumption habits (eating chocolate with PAL for milk?), and the amount consumed (g) when eating chocolate with PAL. Four main chocolate amounts (1.5 g, 5 g, 10 g, 30–40 g) were available on the questionnaire (single choice response), and participants could report another amount if needed using the option "Other". Pictures of chocolate bars and the weight they represented (e.g., one chocolate square = 10 g) were shown with the corresponding choice to help participants recall quantities consumed on one occasion (in general) as close to reality as possible. Reported consumptions were then grouped into ranges (1.5 g or less; 2.5–5 g; 7.4–9.9 g; 10–20 g; 20.1–40 g; >40 g) and the median was used to determine approximate consumption levels (1.5 g; 3.75 g; 8.75 g; 15 g; 30 g; 50 g). Five age groups were considered: children (0–12 years old), teenagers (13–17 years old), young adults (18–25 years old), adults (26–64 years old), and elders (65 and over). Non-parametrical analysis was performed in SAS Studio University Edition v.3.8 (Basic Edition) (SAS Institute Inc., North Carolina, USA), and included Wilcoxon scores with Wilcoxon two-sample test. Differences were considered statistically significant for a p value lower than 0.05 ($p < 0.05$) with 95% confidence intervals (95% CI).

2.2. Probabilistic risk assessment

The probabilistic risk assessment model structure was based on the work of Spanjersberg et al., in 2007 and 2010, and on the methodology followed by Rimbaud et al. (2010). The Model is presented in Fig. 1.

Milk concentration ranges (concentration distribution) and occurrence data from Manny et al., 2021) differed for each food category. Dark chocolate ($n = 159$), cookies ($n = 138$), and baked goods ($n = 117$) had occurrences of 93%, 11%, and 21%, respectively (Manny et al., 2021). Consequently, there were 148 positive samples with PAL (containing milk proteins) used for dark chocolate (range: 0.003–6.471 mg g⁻¹), 17 for cookies (range: 0.003–0.411 mg g⁻¹) and 25 for baked goods (range: 0.007–2.162 mg g⁻¹) in the risk assessment (Manny et al., 2021).

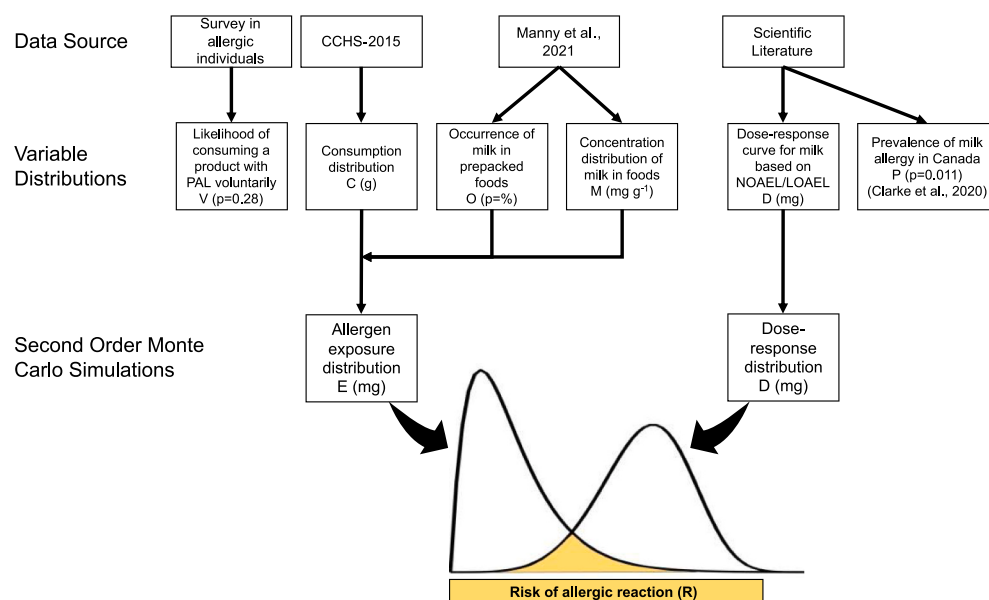


Fig. 1. Probabilistic Risk Assessment Model adapted from Remington et al. (2013) (Remington et al., 2013), and Spanjersberg et al. (2007). The model simulates the amount of pre-packaged food (e.g., dark chocolate, cookies, or baked goods) a milk-allergic consumer would eat, the level of milk contamination, and the likelihood the allergic consumer would consider the PAL, to compute a distribution of estimated exposure doses. As the input of a dose-response relationship, exposure doses allow for the estimation of the population that would exhibit an allergic reaction under this scenario (Risk of allergic reaction).

Distribution fitting of raw occurrence data from positive samples was performed using SAS Studio, and initial analysis of milk occurrence data presented in a previous publication by our research team (Manny et al., 2021) showed milk concentration followed Weibull and Gamma distributions (Table 1).

The distribution of eliciting doses (ED) was based on the No Observed Adverse Effect Levels (NOAEL) and Lowest Observed Adverse Effect Levels (LOAEL) of milk-allergic participants (mostly children) available in milk challenges from the literature (Baehler et al., 1996; Blom et al., 2013; Gushken et al., 2013; Hill et al., 1988; Høst and Samuelsson, 1988; Keet et al., 2012; Lam et al., 2008; Longo et al., 2008; Morisset et al., 2003; Nørgaard and Bindslev-Jensen, 1992; Okada et al., 2015; Orhan et al., 2009; Caminiti et al., 2009; Patriarca et al., 2002;

Rolinck-Werninghaus et al., 2012; Skripak et al., 2008; Staden et al., 2007; Vlieg-Boerstra et al., 2008; Winberg et al., 2015; Dambacher et al., 2013; Ebrahimi et al., 2017; Devenney et al., 2006; Eller et al., 2012; Fiocchi et al., 2003; Flinterman et al., 2006; Goldberg et al., 2015) (Appendix Table 1). Only discrete doses triggering objective symptoms were considered ($n = 1078$). The ED values (mg milk protein) to elicit reactions in 1, 5, 10 and 25% of the allergic population (ED_{01} , ED_{05} , ED_{10} , ED_{25}) were estimated using Weibull, Log Normal & Log Logistic distributions as recommended in previous risk characterization/assessment (Remington et al., 2015; Taylor et al., 2009). The ED obtained (mg) were then compared to published ED (Houben et al., 2020) and the lowest NOAEL-NOAEL values reported in the clinical studies (Baehler et al., 1996; Blom et al., 2013; Okada et al., 2015; Orhan et al., 2009;

Table 1

Distribution parameters of the probabilistic risk assessment.

Variable (unit)	Distribution/Equation (parameters)			Data Source
	Dark chocolate	Cookies	Baked goods	
C Consumption (g)	Log Normal (meanlog = 2.37, sdlog = 1.21)	Burr (shape1 = 1.08, shape2 = 1.93, scale = 21.85)	Burr (shape1 = 2.80, shape2 = 1.63, scale = 128.62)	CCHS-2015, all age groups
M Milk protein concentration (mg milk proteins/g food)	Weibull (shape = 0.67, scale = 0.82)	Gamma (shape = 0.74, rate = 8.72)	Gamma (shape = 0.47, rate = 1.71)	Canadian occurrence data (Manny et al., 2021)
O Milk occurrence (%)	Bernouilli (p = 0.93)	Bernouilli (p = 0.11)	Bernouilli (p = 0.21)	Canadian occurrence data (Manny et al., 2021)
E Exposure (mg)	$E = C \times M \times O$			N/A
D Dose-Response (mg)	Log Normal (meanlog = 4.59, sdlog = 2.52)			NOAEL & LOAEL from literature (Baehler et al., 1996; Blom et al., 2013; Gushken et al., 2013; Hill et al., 1988; Høst and Samuelsson, 1988; Keet et al., 2012; Lam et al., 2008; Longo et al., 2008; Morisset et al., 2003; Nørgaard and Bindslev-Jensen, 1992; Okada et al., 2015; Orhan et al., 2009; Caminiti et al., 2009; Patriarca et al., 2002; Rolinck-Werninghaus et al., 2012; Skripak et al., 2008; Staden et al., 2007; Vlieg-Boerstra et al., 2008; Winberg et al., 2015; Dambacher et al., 2013; Ebrahimi et al., 2017; Devenney et al., 2006; Eller et al., 2012; Fiocchi et al., 2003; Flinterman et al., 2006; Goldberg et al., 2015)
R Risk ^z	$R = D(E)$			N/A
V Likelihood of consuming a product with PAL voluntarily	Bernouilli (p = 0.28)			Food Allergy Canada & Allergies Québec survey
P Prevalence of milk allergy in Canadians	Bernouilli (p = 0.011)			Clarke et al., 2020 (Clarke et al., 2020)

^z: Probability of having an allergic reaction at a given exposure.

N/A: Not applicable.

Caminiti et al., 2009; Patriarca et al., 2002; Rolinck-Werninghaus et al., 2012; Skripak et al., 2008; Staden et al., 2007; Vlieg-Boerstra et al., 2008; Winberg et al., 2015; Dambacher et al., 2013; Gushken et al., 2013; Ebrahimi et al., 2017; Devenney et al., 2006; Eller et al., 2012; Fiocchi et al., 2003; Flinterman et al., 2006; Goldberg et al., 2015; Hill et al., 1988; Høst and Samuelsson, 1988; Keet et al., 2012; Lam et al., 2008; Longo et al., 2008; Morisset et al., 2003; Nørgaard and Bindeslev-Jensen, 1992).

The *fitdistrplus* (v1.1-1) and *survival* (Birot et al., 2017) (v2.42-3) packages with goodness of fit statistics in RStudio v1.1.456 (RStudio Team, Boston, Massachusetts, USA) were used 1) to fit distributions for each food category (i.e. dark chocolate, cookies, baked goods), 2) to build the cumulative distribution functions for the clinical ED data, and 3) to run probabilistic risk assessments using second-order Monte Carlo simulations (1000 runs of 100,000 iterations (Remington et al., 2013)) to simulate the exposure to milk (as an allergen) of a milk-allergic consumer adopting a risky behaviour.

Distribution parameters used in the risk assessment are presented in Table 1.

3. Results

3.1. Consumption data

3.1.1. Canadian consumption survey CCHS-2015 nutrition

Consumption data from the CCHS-2015 for dark chocolate, cookies, and baked goods differed: dark chocolate was consumed in lower amounts (mean = 22.4 g; median = 10.8 g) than cookies (mean = 32.0 g; median = 20.6 g) and baked goods (mean = 75.0 g; median = 58.9 g). Baked goods were consumed in quantities two to three times higher than the other foods investigated and mean consumptions of all foods were 1.5–2 times higher than their median values.

The serving sizes displayed on the products' labels also differed from the CCHS-2015 consumption data. According to the labels, baked goods had the highest serving sizes (mean = 58.2 g; median = 54 g) followed by dark chocolate (mean = 36.8 g; median = 40 g) then cookies (mean = 29.6 g; median = 30 g). Compared to the CCHS-2015, cookies had a similar mean serving size declared on the label, which was not the case of dark chocolate nor baked goods (higher or lower serving sizes).

3.1.2. Chocolate consumption survey in allergic individuals

A total of 825 allergic individuals took part in the survey conducted by Food Allergy Canada and *Allergies Québec*. Most respondents lived in Ontario (51.9%), followed by the Prairies (Alberta, Saskatchewan, Manitoba; 16.0%), *Québec* (15.0%), British Columbia (10.2%), Maritimes (Nova Scotia, New Brunswick, Prince Edward Island; 5.7%), and Newfoundland and Labrador (1.2%). No participants lived in Northern Canada (Yukon, Northwest Territories, Nunavut). The number of participants per age group are presented in Appendix Table 2 and 56% were female. Most participants (n = 618; 75%) self-reported multiple allergies. Peanut (n = 633; 77%) and tree nut-allergies (n = 552; 67%) were the most reported, followed by milk, (n = 162; 20%), egg (n = 161; 20%), and other allergies (n = 41; 5%). Among participants, 28% (228/825) reported eating chocolate with PAL regardless of their allergy. Additionally, 28% of those who reported being milk-allergic (42/152) ate chocolate with a PAL for milk (Appendix Table 2). The median chocolate consumption among all or milk-allergic participants eating chocolate with PAL was estimated to be around 8.8 g (Appendix Table 3), with no reported consumption over 40 g. In open questions, some allergic participants eating products with PAL specified they would try a small amount and stop if they experienced any symptoms. When asked why they were eating products with PAL (multiple choices), the majority (68%) answered they thought PAL was used by food industries to protect themselves from liability, 64% trusted certain brands, 41% never experienced an allergic reaction, 10% had minor symptoms, and 7% believed they had a good tolerance to their allergen(s). There

were no significant differences in chocolate consumption between participants who were allergic to milk and those who were allergic to other foods excluding milk, except between young adults (milk allergic vs. allergic to other foods than milk; $p = 0.04$). A higher amount of chocolate was consumed in non-milk allergic young adults. In addition, there were no significant differences between chocolate consumption of the different age groups ($p = 0.06$).

3.2. Risk assessment

3.2.1. Dose-response relationship using eliciting doses (NOAEL & LOAEL)

The ED distributions built using discrete milk doses (NOAEL-LOAEL; Appendix Table 1) for Weibull, Log Normal and Log Logistic are presented in Fig. 2.

Overall, Weibull had the best fit according to the Akaike Information Criterion (AIC; AIC = 4178) and Bayesian Information Criterion (BIC; BIC = 4188). However, the Log Normal distribution (AIC = 4314; BIC = 4324) fitted lower values (i.e., <25 mg) better than Weibull or Log Logistic (AIC = 4362; BIC = 4372) (Fig. 2, and Appendix Fig. 1). The ED values (ED₀₁, ED₀₅, ED₁₀, ED₂₅) obtained with each distribution are presented and compared with thresholds estimated by Houben et al. (2020) in Table 2.

The Weibull distribution's estimated ED values were lower than those obtained with the two other distributions, except for ED₂₅, and had very conservative values for the ED₀₁ (Table 2). Estimated ED₀₁ and ED₀₅ obtained with the Log Normal distribution were in close agreement with those recommended as reference doses (Houben et al., 2020) (Table 2), and was selected for subsequent analysis.

3.2.2. Risk assessment

RStudio was used to run the Monte Carlo simulations based on the model (Fig. 1) and determine the exposure based on the distribution parameters of each variable (Table 1). Cookies resulted in the lowest estimated average exposure (0.20 [0–1.87] mg of milk proteins) based on the results of the risk assessment. Baked goods had an average exposure of 3.9 [0–44.1] mg, and dark chocolate had an average exposure six times higher than baked goods (24.2 [0–179.3] mg). The average number of allergic reactions out of 100,000 milk-allergic individuals from 1000 simulations were estimated to be 15,881 (2.5%: 13,728; 97.5%: 18,825) for dark chocolate, 3802 (2.5%: 2677; 97.5%: 4990) for baked goods, and 646 (2.5%: 385; 97.5%: 948) for cookies. When considering 28% of milk-allergic individuals consumed chocolate with PAL for milk, the estimated average number of reactions decreased (4447/100,000). When applying the Canadian probable prevalence for milk allergy (1.1%), 49 out of 100,000 Canadians would be estimated to have an allergic reaction from eating dark chocolate with a PAL for milk.

4. Discussion

To the authors' knowledge, this is the first study to perform a probabilistic risk assessment based on collected Canadian occurrence and consumption data from a Canadian national survey (CCHS-2015), for the milk allergen in three different foods.

The lowest average exposure estimated by the model was 0.20 mg of milk proteins in cookies, slightly lower than the proposed ED₀₁ established through this article's dose-response model (0.23 mg) but similar to the literature's recommendation (0.2 mg) (Houben et al., 2020). Baked goods had an average exposure of 3.9 mg, which was slightly higher than the proposed ED₁₀, but under the ED₂₅ (16.3 mg). Dark chocolate presented the highest average exposure (24.2 mg) and was 1.5 times higher than the ED₂₅ (Table 2). Thus, the results of this risk assessment estimate that, on average, more than 25% of the milk-allergic individuals in Canada could experience objective symptoms after eating dark chocolate with a PAL for milk.

Probabilistic risk assessments involving allergens often chose chocolate as a matrix of interest (Spanjersberg et al., 2010; Kruizinga et al.,

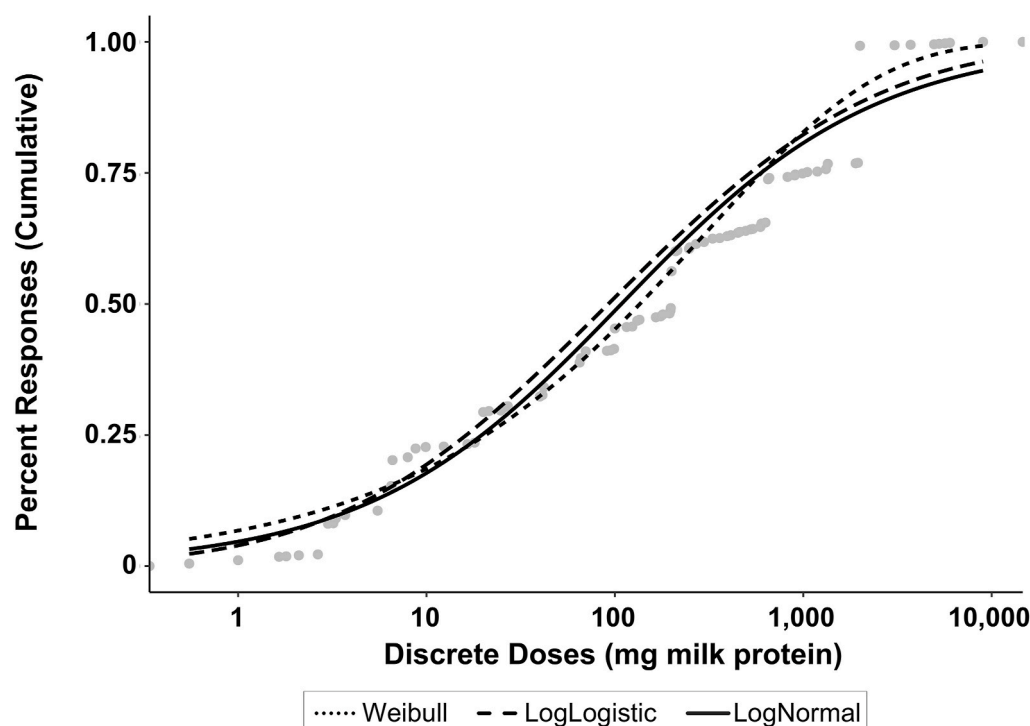


Fig. 2. Cumulative distribution function of milk protein discrete doses triggering allergic reactions in allergic individuals. The scatter points represent the mean of the NOAEL-LOAEL interval for interval-censored data, and the reported value for censored data (i.e., NOAEL for right censored and LOAEL for left-censored data).

Table 2

Milk protein ED values estimated in this study with three distributions (Weibull, Log Normal, Log Logistic), compared to recommended reference doses (Houben et al., 2020).

	Weibull	Log Normal	Log Logistic	Published Reference Thresholds
ED ₀₁ (mg) [95% CI]	0.016 [0.009–0.028]	0.233 [0.164–0.332]	0.086 [0.055–0.135]	0.2 [0.1–0.5]
ED ₀₅ (mg) [95% CI]	0.51 [0.34–0.78]	1.34 [1.02–1.77]	1.12 [0.81–1.54]	2.4 [1.3–5.0]
ED ₁₀ (mg) [95% CI]	2.40 [1.71–3.35]	3.42 [2.69–4.35]	3.57 [2.73–4.67]	7.1 [3.8–14.2]
ED ₂₅ (mg) [95% CI]	20.6 [16.3–26.0]	16.3 [13.5–19.7]	19.7 [16.0–24.1]	32.7 [18.2–61.8]

2008; Remington et al., 2013; Rimbaud et al., 2010). Only one probabilistic risk assessment focused on the presence of milk in nine chocolate products, all containing milk, with and without PAL (Spanjersberg et al., 2010). Their study estimated that 0.6–1.0% milk-allergic individuals would experience objective symptoms after consuming dark chocolate (Spanjersberg et al., 2010), which is lower than the average risk observed in this study for milk-allergic Canadians consuming voluntarily products with PAL (4.4%; 4447/100,000). However, this risk was associated with products who did not have a PAL for milk, and the dose-response distribution was built based on a single DBPCFC paper which involved ten adults (Lam et al., 2008), while 26 different studies were used in this article (Appendix Table 1). Blom et al., 2018 estimated ranges of risk of an allergic reaction based on the allergen concentrations

measured in products responsible of allergic reactions in food-allergic individuals who took part in their study. Two dark chocolate products with a PAL for milk contained respectively 4.388 and 0.702 mg g⁻¹ (intakes of 123 and 3.3 mg milk proteins), and their ranges of estimated risk were respectively 41.9–46.4% and 18.6–22.4% (Blom et al., 2018). After applying our dose-response model (i.e., Log Normal distribution for ED values) to those milk protein concentrations, we found lower but similar ranges of estimated risk (35–40% and 16–19%). Since Blom et al. (2018) applied two distributions (Log Normal, Log Logistic) from different clinical data on milk eliciting doses to estimate the risk (Blom et al., 2018), differences were expected.

In the present study, individual thresholds of milk-allergic patients subject to food challenges were pooled from published data to determine the ED for milk proteins. To the authors' knowledge, this is the first study to build a dose-response relationship for milk with >1000 clinical data points. According to AIC and BIC values, Weibull best fitted the clinical thresholds, but the estimated ED values were the most conservative. From the 26 studies, the lowest NOAEL and LOAEL were reported by Keet et al., 2012) (0.1 mg and 1 mg milk protein respectively) (Keet et al., 2012) and would only be covered by the ED₀₅ and ED₁₀ of the Weibull distribution. Since the Log Normal distribution closely fitted lower threshold doses (as determined in Fig. 2 and Appendix Fig. 1), included the lowest reported NOAEL and LOAEL for ED₀₁–ED₀₅ values better than Weibull (Weibull having more conservative ED estimates), and was in closer agreement with recommended reference doses (Houben et al., 2020), it was selected for further analysis. Although these criteria are not purely statistical, selection based on the quality of the fit in low dose ranges is relevant in food allergen dose-response modelling, as very low doses can lead to severe reactions and pose a risk to allergic consumers (Remington et al., 2013; Crevel et al., 2007). The differences between the ED values for milk protein presented in this study versus the recommended reference doses (Houben et al., 2020) may be attributed to differences in data sources and modelling techniques. Additionally, in our study as well as in most previously published allergen risk assessments, dose-response modelling integrates clinical data from heterogeneous challenge studies. For example, some trials used raw milk instead

of milk powder, and it is known that milk-allergic children seem to tolerate baked milk better than raw milk (Bartnikas et al., 2012). Thus, this may introduce a bias in the results and explain why higher doses were experienced in certain trials and why ED values differed. Furthermore, the oral food challenges selected for the study ($n = 26$) did not always follow the same protocol, with different time lapses between doses (e.g., 15 min to 2 h), different terms used to determine “objective symptoms”, and the milk protein content was not always provided. In studies where there was no indication of doses’ milk protein concentration, a conversion factor of 3.3% for liquid milk was used (Hill et al., 1988; Høst and Samuelsson, 1988; Longo et al., 2008; Nørgaard and Bindslev-Jensen, 1992; Orhan et al., 2009; Caminiti et al., 2009; Patriarca et al., 2002; Ebrahimi et al., 2017; Devenney et al., 2006; Fiocchi et al., 2003) to ensure the collection of uniform discrete doses from DBPCFC. Despite these limitations, notably related to data inputs and model selection, overall, the dose-response relationship developed for this risk assessment agrees with recognized published thresholds (Houben et al., 2020), further consolidating these results. Amounts consumed per eating occasion reported in the CCHS-2015 were different than the suggested serving sizes on the products’ labels and varied by food category. Extracted consumption data from the CCHS-2015 for chocolate showed 50% of observations were ≤ 11 g (median) on a 24-h recall, which is lower than the average serving size (36.8 g) appearing on the chocolates’ labels. As the CCHS-2015 survey uses computing tools (Automated Multiple-Pass Method), consumption data might be misrepresented. Chocolate could be reported in the survey as a basic food (e.g., entire chocolate bar), or part of a recipe (e.g., a teaspoon of chocolate candies on an ice cream). Thus, chocolate ingredients as part of a recipe would correspond to a lower intake on a single occasion. Statistics Canada investigated and reported that some participants might have underreported the amount of food they consumed (Garriguet, 2018). Nevertheless, such conclusion might not apply to other foods like cookies and baked goods, since the opposite of chocolate was seen in baked goods, and the average CCHS-2015 and serving size amounts on products’ labels were similar in cookies. Since serving sizes are suggestions rather than consumed amounts, they are not recommended for risk assessment purposes if national consumption data is available. Consumption sizes from the CCHS-2015 for cookies and baked goods were higher than for chocolate. As opposed to chocolate which can be part of a recipe (e.g., chocolate chips ingredient in a cookie), cookies and baked goods are considered as basic foods (e.g., oatmeal, raisin, or chocolate chip cookies; croissants, muffins, etc.) and may weigh more. They can also be eaten as part of a meal (e.g., ham croissant) or a dessert (e.g., piece of cake). An article on 24 h consumption recalls of food-allergic individuals found no significant differences between the food intake of allergic vs. non-allergic individuals and suggested use of national surveys for risk assessments (Blom et al., 2020). However, the results of Blom et al. (2020) were based on a survey of only 73 allergic individuals and did not consider the presence of PAL on food labels, meaning that allergic individuals may still have different eating habits regarding the information provided through PAL.

The homemade survey designed with Food Allergy Canada and *Allergies Québec* as part of our study led to better understanding of how many food-allergic individuals would consume chocolate with PAL, and in what amount. Twenty-eight percent (28%) of all allergic individuals who participated in the survey reported eating chocolate with a PAL including the allergen(s) they are allergic to. This is higher than the observation made in a 2010 Canadian survey where 8% of participants were ignoring PAL (Sheth et al., 2010), but lower than the 40% reported by a 2017 North American survey (Marchisotto et al., 2017). Because the homemade survey conducted as part of our study focused on chocolate, which had the highest milk occurrence among the products investigated by Manny et al. (2021), the reported percentage of allergic individuals eating products with PAL for all foods might be closer to the 2010 Canadian survey (8%) where food categories were not mentioned (Sheth et al., 2010), but this would need to be further investigated and

confirmed. As seen with the CCHS-2015, consumption amounts vary by food category: the probability to voluntarily consume a product with PAL might also vary depending on the food involved. Thus, this home-made survey conducted with food-allergic individuals cannot be used to determine consumption data with precision and in a manner that is representative for the targeted consumers, nor be comparable to the CCHS-2015 national data. The amounts of cookies and other baked goods consumed may be higher and the likelihood of consuming a product with PAL might be different.

The median amount of chocolate consumed was lower (8.8 g) in the Food Allergy Canada and *Allergies Québec* survey than the CCHS-2015 (10.8 g), but no differences could be assumed because the consumption amounts were not calculated using the same method. Additionally, Blom et al. (2020) did not report any differences between food intakes of the general and allergic populations, and recommended the use of national dietary survey consumption data for the allergic population (Blom et al., 2020). Between participants of the homemade, food-allergic survey, no significant differences were found between age groups (Appendix Table 3), so the general allergic population was chosen (all participants). The only difference resided in chocolate consumption of young adults. Milk-allergic young adults ate less chocolate than other young adults allergic to other foods, excluding milk ($p = 0.04$). However, this significant difference has a low statistical power because of the limited sample size ($n = 8$ young adults eating chocolate with PAL) and might be explained by the higher occurrence of milk contamination in dark chocolate than other allergens. Bedford et al. (2017) reported that milk contamination in dark chocolate was 77%, higher than peanuts with 8% of contaminated products (Bedford et al., 2017), which might make milk-allergic individuals more cautious than non-milk allergic individuals. Some surveyed participants who were taking risks (i.e., eating chocolate with PAL) also shared that when trying new products, they would eat small quantities first, a previously documented behaviour (Monks et al., 2010). In those cases, if a reaction occurs, the participant would stop eating the product, supporting the hypothesis that the amount of chocolate with PAL eaten per single occasion could be lower for allergic individuals than for the general population. Nevertheless, some participants also answered that they would still eat entire chocolate bars (~ 30 – 40 g) despite the presence of PAL. This can be explained by the allergen tolerance that differs between each allergic individual.

It is likely that the allergic individuals identified in our survey who ignore PAL predominantly have higher individual thresholds and less severe symptoms when they do have allergic reactions. This allows them to take chances on products with PAL on a regular basis and rarely, if ever, have an allergic reaction. If it is true that consumers ignoring PAL come from a specific (less sensitive) subset of allergic consumers, the likelihood of allergic reactions when those individuals consume products with PAL may be lower than predicted by the model used in this study. Nevertheless, even if the risk may seem low in some specific cases, milk-allergic Canadians should avoid eating products (especially chocolate) with a PAL for milk regardless of their threshold level, since milk protein concentrations previously reported are heterogeneous (Manny et al., 2021) and products with >1000 mg g⁻¹ milk proteins are not uncommon in the Canadian market.

The results of this risk assessment lead to the conclusion that risk-based PAL used by food industries could help protect a part of the allergic population. To protect a maximum of individuals, the ED₀₁ should be selected as some clinical studies excluded highly sensitive participants (Gushken et al., 2013; Keet et al., 2012; Caminiti et al., 2009; Skripak et al., 2008; Winberg et al., 2015; Fiocchi et al., 2003) (i.e., at a higher risk of anaphylactic shock) and thus limit the number of allergic reactions. The risk assessment model relied on previously reported milk occurrence in Canadian food products (Manny et al., 2021). This dataset included 148 positive results for milk in dark chocolate, 25 in baked goods and 17 in cookies. The risk assessment simulation could have integrated other sources of data for milk contamination, instead of

only using the study published by our research team, which included few results ($n < 20$) for cookies (Manny et al., 2021). However, the authors did not have access to raw datasets of other publications to achieve a larger sample number for the three foods analysed in this study. As new data becomes available, model predictions could be readily updated.

Further occurrence-based probabilistic risk assessments should be performed to determine exposure levels for all priority allergens in Canada. As this study proposes, these risk assessments should be based on up-to-date country-specific data such as the CCHS-2015 instead of using serving sizes on the products' labels. In addition, "single dose" challenges, such as the one conducted by Hourihane et al. (2017) on peanuts, could be achieved for milk and help validate ED thresholds, which in turn would help establish action levels in real-life settings before their possible implementation in food industries (Hourihane et al., 2017).

CRedit authorship contribution statement

Emilie Manny: Writing – original draft, Writing – review & editing, Investigation, Formal analysis, Validation, Conceptualization. **Sébastien La Vieille:** Validation, Writing – review & editing, Supervision, Conceptualization. **Silvia A. Dominguez:** Data curation, Formal analysis, Writing – review & editing, Validation. **Gregor Kos:** Resources, Software, Validation, Writing – review & editing. **Virginie Barrère:** Supervision, Writing – review & editing. **Jérémy Théolier:** Supervision, Writing – review & editing. **Joseph Touma:** Writing – review & editing, Resources. **Samuel Benrejebe Godefroy:** Supervision, Writing – review & editing, Project administration, Funding acquisition, Conceptualization, Resources.

Declaration of competing interest

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Canada; the Ministry of Science, Technology, and Innovation, Government of Quebec; Canada's Innovation Foundation; the U.S. Department of Agriculture Foreign Agriculture Service; R-Biopharm GmbH; and R-Biopharm Canada Inc. Samuel Benrejebe Godefroy acts as an expert advisor for members of the food and beverage industry, international organizations (the Food and Agriculture Organization of the United Nations, the United Nations Industrial Development Organization, and the World Bank), and international food regulators such as the China National Centre for Food Safety Risk Assessment and consumer organizations such as Food Allergy Canada. The other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2021.112196>.

Appendix

Appendix Table 1

Censoring attributes of milk DBPCFC studies used for dose-response modelling in this risk assessment

Authors	NOAEL (mg)*	NOAEL (n)	LOAEL (n)	Left Censored (n)	Interval Censored (n)	Right Censored (n)
Baehler et al., 1996	1.8	7	9	2	7	0
Blom et al., 2013	0.2	82	82	0	82	0
Caminiti et al., 2009	3.3	11	11	0	11	0
Dambacher et al., 2013	18	18	21	3	18	0
Devenney et al., 2006	3.3	2	3	1	2	0
Ebrahimi et al., 2017	16.5	12	13	1	12	0
Eller et al., 2012	175	0	2	2	0	0
Fiocchi et al., 2003	198	7	12	5	7	0
Flinterman et al., 2006	180	8	11	3	8	0
Goldberg et al., 2015	2.1	13	15	2	13	0
Gushken et al., 2013	26.3	20	39	19	20	0
Hill et al., 1988	1.65	5	30	25	5	0
Høst and Samuelsson, 1988	165	3	5	2	3	0
Keet et al., 2012	0.1	30	30	0	30	0
Lam et al., 2008	90	8	6	0	6	2
Longo et al., 2008	3.3	51	9	9	0	51
Morisset et al., 2003	3.2	0	1	1	0	0
Nørgaard and Bindslev-Jensen, 1992	165	3	3	0	3	0
Okada et al., 2015	100	0	42	42	0	0
Orhan et al., 2009	330	4	4	0	4	0
Patriarca et al., 2002	0.3	8	8	0	8	0
Rolinck-Werninghaus et al., 2012	3	571	634	63	571	0

(continued on next page)

Appendix Table 1 (continued)

Authors	NOAEL (mg)*	NOAEL (n)	LOAEL (n)	Left Censored (n)	Interval Censored (n)	Right Censored (n)
Skrupak et al., 2008	40	6	26	20	6	0
Staden et al., 2007	11.5	3	3	0	3	0
Vlieg-Boerstra et al., 2008	3.5	5	5	0	5	0
Winberg et al., 2015	300	1	1	0	1	0
Total		878	1025	1078		

*mg milk proteins.

Appendix Table 2

Survey results - Reported frequency of consumption of chocolate with PAL by age group and type of allergy

Age Group	All participants	Milk allergic	All allergic participants eating chocolate with a PAL containing their allergen	Milk allergic Participants eating chocolate with PAL for milk
	n (%)	n/N (%)	n/N (%)	n/N (%)
All age groups	825 (100)	152/825 (18.4)	228/825 (27.6)	42/152 (27.6)
Children (0–12 years old)	272 (33.0)	59/152 (38.8)	62/228 (27.2)	11/42 (26.2)
Teenagers (13–17 years old)	191 (23.2)	28/152 (18.4)	44/228 (19.3)	4/42 (9.5)
Young adults (18–25 years old)	131 (15.9)	29/152 (19.1)	31/228 (13.6)	8/42 (19.0)
Adults (26–64 years old)	212 (25.7)	34/152 (22.4)	85/228 (37.3)	18/42 (42.9)
Elders (65 and over)	19 (2.3)	2/152 (1.3)	6/228 (2.6)	1/42 (2.4)

Appendix Table 3

Survey results - Reported consumption of chocolate with PAL by age group and type of allergy

Age Group	Quantity of chocolate with PAL consumed, in grams (g)						p value ^z
	All allergic participants (n = 228)		Non-Milk-allergic participants (n = 186)		Milk-allergic participants (n = 42)		
	Mean ± SD [95%CI]	Median	Mean ± SD [95%CI]	Median	Mean ± SD [95%CI]	Median	
All age groups	16.7 ± 11.8 [15.2–18.3]	8.8	17.6 ± 12.0 [15.9–19.4]	8.8	12.8 ± 10.0 [9.7–15.9]	8.8	0.06
Children (0–12 years old)	13.1 ± 11.2 [10.3–16.0]	8.8	13.1 ± 11.4 [9.9–16.3]	8.8	13.4 ± 10.9 [6.1–20.8]	8.8	0.73
Teenagers (13–17 years old)	18.3 ± 12.1 [14.6–21.9]	19.4	19.3 ± 12.1 [15.5–23.2]	30.0	7.5 ± 2.5 [3.5–11.5]	8.8	0.11
Young adults (18–25 years old)	19.0 ± 11.7 [14.7–23.3]	30.0	21.5 ± 11.0 [16.8–26.3]	30.0	11.9 ± 11.5 [2.3–21.5]	8.8	0.04
Adults (26–64 years old)	17.9 ± 11.6 [15.4–20.4]	8.8	18.9 ± 11.8 [16.0–21.8]	30.0	14.2 ± 10.2 [9.1–19.3]	8.8	0.27
Elders (65 and over)	13.8 ± 12.9 [0.3–27.3]	8.8	14.8 ± 14.0 [0 [†] – 32.3]	8.8	8.8 [†]	8.8	NA [†]

^z Difference between milk-allergic and non-milk-allergic participants eating chocolate with a PAL containing their allergen(s).[†] Lower 95%CI value was negative (–2.7) but was adjusted to zero because consumption values cannot be negative.[†] Result not available (could not be calculated because only one observation was available for the milk-allergic participants).

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