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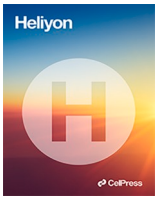

Research article

# Simulated use of thresholds for precautionary allergen labeling: Impact on prevalence and risk

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ABSTRACT

Heterogeneity and overuse of precautionary allergen labelling (PAL) in prepackaged foods have eroded its risk communication efficacy. Experts recommend applying PAL based on allergen concentration thresholds, but adoption remains limited. The aim of this study was to quantitatively assess the potential impact of this approach using Monte Carlo risk simulations. Four allergens and 9 food categories were considered in 2 scenarios: (1) consumption of products currently carrying PAL in Canada where individuals with food allergy (FA) are assumed to consume them, and (2) consumption of products without PAL, in a hypothetical context where PAL is applied based on thresholds that would protect 99 % (ED01) and 95 % (ED05) of individuals with FA, and individuals with FA systematically avoid products with PAL. In scenario (1), although several cases studied would cause <10 reactions/10 000 eating occasions (e.o.), there were also many that would cause >20 reactions/10 000 e.o. Cross-contact milk posed the highest risk (max. 1120 reactions/10 000 e.o.), and peanut, the least (max. 10 reactions/10 000 e.o.). In scenario (2), consumption of products without PAL, when using thresholds for PAL based on ED01, could lead to a maximum of 15 reactions/10 000 e. o. for all studied cases, and based on ED05, to 57 (if excluding dark chocolate with milk PAL). In most cases, the estimated number of reactions per 10 000 e.o. attributed to products with PAL currently on the market would be higher ($p < 0.05$) than that attributed to products without PAL, if PAL is applied based on the simulated thresholds. Thus, a threshold driven approach to adopt PAL on prepackaged foods, while advising consumers to avoid these products, could be beneficial for individuals with FA in Canada, as products without PAL would result in very few and generally mild adverse reactions.

## 1. Introduction

Despite promising results obtained with different forms of immunotherapy [1–3], complete allergen avoidance is currently the primary strategy recommended for individuals with food allergy (FA) to manage their condition [4]. As a result, ingredient declaration and precautionary allergen labelling (PAL) statements, such as “May contain”, may be used by individuals with FA to inform prepackaged food purchasing decisions.

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**Abbreviations**

| | |
|---|---|
| CCHS-2015 | Canadian community health survey – 2015 |
| ED | eliciting dose |
| e.o | eating occasion |
| FA | food allergy |
| FBO | food business operator |
| PARERA | Food risk analysis and regulatory excellence platform |
| LOQ | limit of quantification |
| PAL: | precautionary allergen labelling |

In Canada, mandatory labelling of the 10 Canadian priority allergens has been in place since 2012, such that any intentional addition, without regard to quantity, of an allergen ingredient, all generations included, requires identification within the allergen list or below it, following a "Contains" title [5]. Several other countries adhere to similar requirements, although the allergens for which mandatory declaration is in place may vary [6,7] Comparatively, PAL is considered as a tool to enhance the protection of individuals with FA, with 2 guiding principles: to "prevent the inadvertent consumption of undeclared allergens by sensitive consumers" and "enable a variety of safe and nutritious food choices for the allergic consumer" [8]. Furthermore, PAL is intended to be used only if unintended allergen presence is unavoidable after all reasonable measures are applied, and PAL is not intended to be used to replace good manufacturing practices [9]. More specifically, Food and Drug Regulations include requirements on the formatting of PAL in prepackaged foods, such as placement, color choice and capitalization, and requires that the statement must be truthful and non-ambiguous [5]. Yet, as opposed to obligatory identification of intentionally added priority allergens, there are no regulations dictating when PAL should or should not be used by Food Business Operators (FBOs). Resources and guidance developed by regulatory agencies on the use of PAL are also available [9]. Nevertheless, concerning practices related to the criteria used by FBOs to reach PAL decisions have been documented, such as declaring an allergen ingredient despite it not being intentionally added, or adding a small amount of the allergen to declare it as an ingredient and avoid PAL use [10]. Indeed, the management of cross-contact allergens seems challenging for FBOs, as suggested by the steady prevalence of recalls linked to undeclared allergens (approximately 30 % of all food recalls per year in the last decade) [11,12].

The absence of PAL-specific regulation is also common in other jurisdictions, leading to great variability in its application and consequently, consumer confusion [13,14]. PAL use has increased in the last two decades, reducing food choices for individuals with FA [15,16] and eroding trust in allergen labelling [4,14,17,18]. Reports indicate that as many as 50 % of products per food category use PAL [19–21], with the highest prevalence observed in chocolates, cookies, and cake mixes [19,20,22]. The overabundance, and lack of standardization and clarity of PAL statements, may also result in risk-taking behaviours by individuals with FA. Notably, food-allergic consumers' purchasing decisions related to products with PAL are influenced by the wording of the warning statement, despite there being no evidence of differences in allergen concentration or risk [13,23]. For example, in one study, 41.2 % of participants declared sometimes purchasing products with the warning "Good manufacturing practices used to segregate ingredients in a facility that also processes allergens", while only 11.3 % sometimes purchased products with "May contain" statements [13]. Nevertheless, PAL is now so common that physicians may recommend some allergic patients to consume products with this type of warning, on a case-by-case basis, considering patients's allergic history [24]. This recommendation is aligned with reports of low occurrence and concentration of cross-contact allergens in several prepackaged products with PAL, including in Canada [25–27], – with the exception of dark chocolate, which was found to have high milk cross-contact [28,29], as well as peanuts in various bars in the United States [30,31]. A 2010 Canadian study reported a rate of accidental reactions to PAL foods at about 8 % [32]. However, this study may be outdated as the number of products with PAL has greatly increased in the last decade [33]. In a more recent 2021 U S. study, Gupta et al. reported that about 25 % of individuals with FA that responded to their survey had experienced an allergic reaction after eating products with PAL [23]. It has also been noted that individuals that experienced allergic reactions after eating a product with PAL tend to subsequently avoid these products [13].

Allergen concentration thresholds, derived from risk-based reference doses that would protect the majority of individuals with FA, have been recommended as a regulatory mechanism to standardize the use of PAL among prepackaged food manufacturers [18]. Specifically, eliciting doses (ED) that would trigger a reaction (expected to be mild or moderate) in 1 % (ED01) or 5 % (ED05) of individuals with FA have been estimated for international priority allergens [34], and PAL thresholds based on ED05 have been recommended [18]. Formal tools to calculate the allergen protein concentration in food products, and to compare them to action levels based on allergen reference doses and amounts of food consumed have been proposed as guidance for the use of PAL by FBOs [35]. However, for such a strategy to succeed, education of individuals with FA, FBOs, and health care providers would be critical, as well as the availability of appropriate analytical methods [18]. In particular, changes to individuals with FA's consumption habits and enhanced risk awareness (e.g., understanding of thresholds for PAL, acceptance of a certain level of risk when consuming products with PAL) [17,36] and potentially allergists' education on risk assessment concepts represent major challenges [37]. To date, only three countries regulate PAL through thresholds. Switzerland requires an allergen protein concentration of 1000 ppm before PAL is authorised, while Japan requires allergen declaration at concentrations above 10 ppm but prohibits PAL use [36,38]. Argentina also prohibits PAL use, but other forms of labelling similar to PAL are permitted and function in much the same way [39]. In addition, the Netherlands recently became the first country to adopt a policy for the use of PAL based on ED05, as recommended by FAO/WHO [18],

which is expected to be fully implemented by 2026 [40]. Thus, although there seems to be consensus among stakeholders on the importance of standardizing PAL, uncertainty remains regarding the feasibility and the impact of establishing thresholds for its use [17].

The purpose of this study was therefore to quantitatively assess the impact of the hypothetical use of PAL based on thresholds, in terms of risk for individuals with FA, using Monte Carlo simulations. To do so, the current baseline risk of inducing objective allergic reactions for foods sold in Canada carrying PAL was estimated based on (i) individual consumption data, representative of the Canadian population, (ii) allergen protein occurrence and concentration in products with PAL, compiled in a Canadian database, and (iii) population-based allergen eliciting doses. The use of thresholds for PAL based on doses that would protect 99 % (ED01) and 95 % (ED05) of the allergic population was then simulated, and the associated variation in the number of allergic reactions caused was estimated. This study is expected to provide objective evidence on the impact of potential PAL regulation based on thresholds that could be referred to by regulators and FBOs when considering this strategy. In addition, this study may contribute to individuals with FA's understanding of the variable risk posed by products with PAL currently on the market, the level of consistent protection that can be achieved with a thresholds-based approach for PAL, and its potential impact on the prevalence of products with PAL on the market.

## 2. Materials and methods

### 2.1. Baseline risk

#### 2.1.1. Allergen occurrence and concentration

Data on the occurrence and concentration of cross-contact allergens in prepackaged food products with PAL were extracted from the Food Risk Analysis and Regulatory Excellence Platform's (PARERA, parera.ulaval.ca/en) allergen occurrence database [26,27]. This database compiles results obtained with enzyme-linked immunosorbent assays (R-Biopharm, AG, Darmstadt, Germany; Morinaga, Tokyo, Japan) of samples purchased in Quebec, Canada between 2016 and 2021 for 9 categories of prepackaged food products (i.e., baked goods, baking mixes, candies, cereals, dark chocolates, cookies, crackers, sauces, and snacks) containing PAL for 1 to 4 allergens (i.e., milk, eggs, peanuts, or hazelnuts – samples were tested for more than 1 allergen, when applicable). The entire database (results for 333 products with milk PAL, 258 products with egg PAL, 280 products with peanut PAL, and 285 products with hazelnut PAL) was used in this study (Supplementary Table S1). Between 1 and 4 lots were purchased per product. For more information, please see Manny et al. (2021a; 2021b).

Allergen protein concentrations (mg/g)[1] for each allergen-food category combination, considering samples with concentrations above the method's level of quantification (LOQ) only (2.5 mg/kg for milk, 0.245 mg/kg for eggs, 0.555 mg/kg for peanuts and 0.375 mg/kg for hazelnuts),[2] were fitted to distributions in RStudio version 4.1.2 (RStudio Team, Boston, Massachusetts, USA) using the *fitdistrplus* package [41]. Although the LOQ for the milk enzyme-linked immunosorbent assay used by Manny et al. (2021a) is greater than for other kits, it is deemed suitable for the detection of milk residues in food matrices, and other assays have similar LOQ values [42].

Distributions were selected based on goodness-of-fit statistics and the uncertainty in each distribution's parameters was estimated by bootstrapping. For allergen-food category combinations with less than 8 concentration values > LOQ, distribution fitting was not attempted; instead, the raw data was sampled directly in the risk assessment model, as described in (Touma et al., 2021). For each allergen-food category combination, the occurrence of cross-contact allergens was calculated as the ratio of the number of food products with concentrations of allergen proteins above the LOQ and the total number of food products with PAL tested.

#### 2.1.2. Food consumption

Consumption distribution parameters for the 9 food categories targeted in this study (i.e., baked goods, baking mixes, candies, cereals, dark chocolates, cookies, crackers, sauces, and snacks), calculated by Ref. [44] based on data from the 2015 Canadian Community Health Survey (CCHS-2015) [45], were used in this study. Briefly, CCHS-2015 raw, confidential data from consumers for each food category (general population, all ages, and biological sex; no stratification) was analyzed at the Quebec Inter-University Center for Social Statistics at Université Laval, fitted to distributions and selected based on goodness-of-fit statistics, as described in Ref. [44]. Only the fitted distribution parameters were extracted due to confidentiality restrictions. Since CCHS-2015 is a 24-h dietary recall survey, the estimated consumption for each food category used in this study represents the amount (grams) consumed in one day.

#### 2.1.3. Allergen eliciting doses

Dose-response relationships for each of the 4 allergens targeted in this study were constructed in RStudio using spline functions (Supplementary Figs. S1–S4) based on the discrete eliciting doses (ED) and allergic population responses estimated by Houben et al. [46]. Briefly, interval-censored dose-to-failure raw data from double-blind placebo-controlled food challenges for allergic populations were extracted and analyzed using model averaging methods [47] to estimate the allergen doses (mg) that would trigger an objective reaction in different proportions of the allergic population. The full range of discrete ED values reported for milk, eggs, peanuts, and

[1] Concentration values are presented in mg/g to be consistent with the units of consumption and eliciting dose data use in the risk assessment model.

[2] LOQ values are presented in mg/kg, as indicated in the kits' documentation.

hazelnuts were included in the spline functions developed in this study.

### 2.1.4. Probabilistic risk assessment model

The risk assessment model structure (Fig. 1) for each allergen-food category combination was based on Touma et al., in 2021 and Manny et al. in 2021 [25,43]. The model assumes individuals with FA consume products with PAL and expresses risk as the estimated number of eating occasions (e.o.) that would lead to an allergic reaction for each allergen-food category combination. The model was built in RStudio and follows a Monte Carlo scheme, including 1000 simulations, each representing 10 000 e.o. In each of the 10 000 iterations, allergen occurrence, allergen protein concentration, and the amount of food consumed are randomly selected from the input distributions. These values are used to compute an estimated exposure dose (mg) for each e.o., which is then applied to the dose-response spline function to establish the probability of occurrence of an allergic reaction. For each allergen, the "response" component of the dose-response spline functions was truncated at the maximum percent reported by Houben et al. in 2020 [46] to avoid extrapolations. The model then sums the number of allergic reactions estimated to occur for each simulation of 10 000 e.o.; this output represents the risk attributed to products with PAL for the allergen-food category combinations studied currently on the market (i.e., "baseline"). In addition, among the total number of allergic reactions estimated to occur for each simulation of 10 000 e.o., those attributed to exposure doses below ED01 and ED05 were calculated. The model outline and input distributions for each allergen-food category combination are presented in Supplementary Tables S2–S5.

## 2.2. Simulated use of PAL based on thresholds

In these hypothetical scenarios, individuals with FA do not consume products with PAL. Food products have PAL only if food manufacturers estimate they could carry cross-contact allergen concentrations representing exposure doses higher than a given threshold (i.e., ED01 or ED05). Specifically, for each allergen-food category combination, allergen action levels computed by Manny et al. in 2022 based on the 75th percentile (P75) of the food consumption distribution and the allergen protein dose estimated not to trigger an objective reaction in 95 % (ED05) or 99 % (ED01) of the allergic population were used to establish the need for PAL [44]. For each allergen-food category combination, the allergen occurrence and concentration inputs of the risk assessment model described in 2.1.4 were modified to simulate the use of thresholds for PAL. Data from the PARERA allergen database was filtered to exclude cross-contact allergen concentrations equal to or higher than the respective action level. For instance, the ED01 action level (P75) for peanut in dark chocolate reported by Manny et al. (2022) is 8.2 mg/kg. This value is obtained from equation (1), as described in Manny et al. (2022), using an ED01 of 0.2 mg of peanut protein [46].

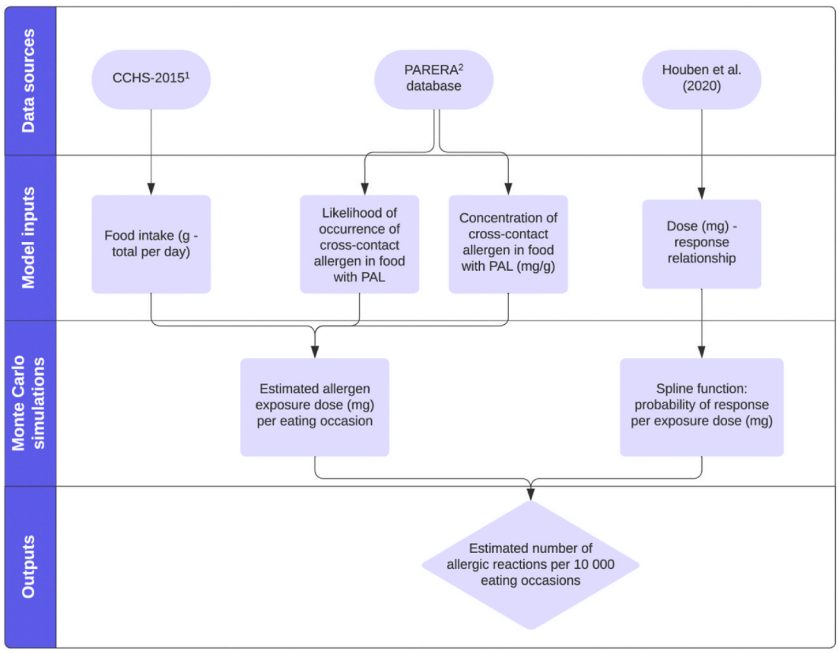


**Fig. 1.** Graphic representation of the risk assessment model indicating data sources, model inputs, steps simulated using Monte Carlo, and outputs.
1. CCHS-2015: Canadian Community Health Survey 20 15
2. PARERA: Food Risk Analysis and Regulatory Excellence Platform.

$$\text{Action level for allergen } \ddot{x} \text{ and food category } \ddot{y}(\ddot{ppm}) = \text{ED01 or ED05 for allergen } \ddot{x}(\text{mg allergen protein}) / \text{P75 of the consumption distribution of food category } \ddot{y}(\text{kg}) \quad (1)$$

Thus, data points representing peanut protein concentrations in dark chocolate ≥8.2 mg/kg were excluded, as food products with such concentrations would require PAL and allergic consumers would avoid their consumption (Supplementary Table S1), and a new concentration distribution and occurrence were generated (Supplementary Table S6), as described in 2.1.1. These new inputs were then used in the risk assessment model described in 2.1.4, using the food consumption and eliciting dose functions described in 2.1.2 and 2.1.3. The same process was followed for all other allergen-food category combinations. The modified models estimated the number of objective allergic reactions per 10 000 e.o. that would occur due to consumption of products without PAL in each simulated scenario.

### 2.3. Statistical analysis

The following comparisons were tested for statistical significance (Table 2).

- Mean baseline number of allergic reactions attributed to products with PAL currently on the market and mean number of allergic reactions attributed to products without PAL, if PAL is applied based on (i) ED05, over a total of 10 000 e.o.
- Mean baseline number of allergic reactions attributed to products with PAL currently on the market and mean number of allergic reactions attributed to products without PAL, if PAL is applied based on (ii) ED01, over a total of 10 000 e.o.
- Mean number of allergic reactions attributed to products without PAL, if PAL is applied based on (i) ED05 and (ii) ED01, over a total of 10 000 e.o.

Differences between proportions were determined using chi-square and Fisher's exact test (for contingency tables with values < 5), based on a p-value of 0.05. Statistical analyses were conducted in RStudio.

## 3. Results

### 3.1. Baseline risk

The baseline number of allergic reactions with objective symptoms estimated to occur if products currently on the market with PAL for the targeted allergens are consumed by individuals with FA is presented in Table 1. Milk was the cross-contact allergen estimated to cause the most reactions per e.o., mainly when present in dark chocolate (1120/10 000 e.o.) and baked goods (243/10 000 e.o.). Cross-contact peanut was estimated to cause the lowest number of reactions, with an estimated mean ≥ 10/10 000 e.o. only in dark chocolate. The highest number of reactions attributed to cross-contact egg was linked to baked goods (55/10 000 e.o.). For hazelnut, dark chocolate represented the highest risk food category (74/10 000 e.o.). Candy was the only food category with no estimated allergic reactions for any of the allergens studied. Baking mix was identified as a low risk (<10 mean estimated reactions/10 000 e.o.) food category with respect to the 4 cross-contact allergens studied. Cereal, crackers, and snacks posed low risk (<10 mean estimated reactions/10 000 e.o.) for cross-contact egg, peanut, and hazelnut. The last two columns of Table 1 represent the number of baseline

**Table 1**
Mean estimated number of allergic reactions [95 % confidence interval] per 10 000 eating occasions attributed to consumption of products with PAL currently on the market ("baseline").

| Allergen | Food category | Mean baseline total number of allergic reactions[a] | Mean number of allergic reactions, out of the baseline total, attributed to exposure doses below: | |
|---|---|---|---|---|
| | | | ED01 | ED05 |
| **Milk**[b] | Baked goods | 243 [205–273] | 1 [0–1] | 21 [17–24] |
| | Cereal | 186 [155–213] | 3 [2–4] | 32 [28–36] |
| | Cookies | 48 [38–57] | 1 [0–2] | 18 [14–21] |
| | Crackers | 108 [67–139] | 1 [0–2] | 11 [8–13] |
| | Dark chocolate | 1120 [1068–1171] | 4 [2–5] | 68 [62–74] |
| | Sauce | 21 [17–23] | 9 [7–11] | 18 [15–21] |
| | Snacks | 12 [10–15] | 2 [1–3] | 6 [4–7] |
| **Egg**[c] | Baked goods | 55 [31–72] | 1 [0–1] | 8 [6–10] |
| | Cookies | 29 [19–38] | 2 [1–3] | 9 [7–12] |
| **Peanut**[d] | Dark chocolate | 10 [7–12] | 4 [2–5] | 9 [7–11] |
| **Hazelnut**[e] | Baked goods | 27 [20–32] | 1 [0–1] | 16 [13–18] |
| | Dark chocolate | 74 [65–82] | 6 [4–7] | 52 [47–57] |

[a] Only allergen-food category combinations with mean estimates ≥10 reactions/10 000 e.o. are shown.
[b] Food categories <10 reactions/10 000 e.o.: baking mix, candy.
[c] Food categories <10 reactions/10 000 e.o.: baking mix, candy, cereal, crackers, dark chocolate, snacks.
[d] Food categories <10 reactions/10 000 e.o.: baked goods, baking mix, candy, cereal, cookies, crackers, snacks.
[e] Food categories <10 reactions/10 000 e.o.: baking mix, candy, cereal, cookies, crackers, snacks.

**Table 2**
Estimated number of allergic reactions per 10 000 eating occasions [95 % confidence interval] attributed to consumption of products without PAL in simulated scenarios where allergic consumers avoid products with PAL, and PAL is applied based on exposure dose thresholds (ED01 or ED05) and 75th percentile of the food consumption distribution[a].

| Allergen | Food category | Baseline allergic reactions[b] | Allergic reactions attributed to products without PAL, when PAL is applied based on: | |
|---|---|---|---|---|
| | | | ED01 | ED05 |
| **Milk** | Baked goods | 243[a] | NA[c] | 8[b] [5–13] |
| | Cereal | 186[a] | 2[b] [1–4] | 34[c] [21–56] |
| | Cookies | 48[a] | 1[b] [<1-1] | 19[c] [12–31] |
| | Crackers | 108[a] | 2[b] [1–4] | 8[b] [5–14] |
| | Dark chocolate | 1120[a] | 10[b] [6–17] | 105[c] [63−170] |
| | Sauce | 21[a] | 15[a] [8–25] | Equivalent to baseline[d] |
| | Snacks | 12[a] | 2[b] [1–3] | 4[b] [2–7] |
| **Egg** | Baked goods | 55[a] | 1[b] [<1-1] | 6[b] [4–12] |
| | Cookies | 29[a] | 3[b] [2–5] | 3[b] [2–6] |
| **Peanut** | Dark chocolate | 10[a] | 3[b] [1–4] | Equivalent to baseline[d] |
| **Hazelnut** | Baked goods | 27[a] | 1[b] [<1–2] | Equivalent to baseline[d] |
| | Dark chocolate | 74[a] | 4[b] [10–13] | 57[a] [23–77] |

[a] Significant differences are shown with superscript letters and represent comparisons per row (i.e., within each allergen-food category combination).
[b] Current scenario (i.e., products with PAL currently on the market) as presented in Table 1. Repeated here for comparison purposes. Only allergen-food category combinations with mean estimates ≥10 reactions/10 000 e.o.
[c] No change compared to baseline allergen occurrence and concentration inputs. All concentration values > LOQ were higher than the action level. All products in the database would have PAL in this hypothetical scenario.
[d] All baseline allergen concentration values > LOQ were below the action level. None of the products in the database would have PAL in this hypothetical scenario.

allergic reactions that are attributed to products with PAL currently on the market due to allergen doses that are equal or below to ED01 or ED05.

### *3.2. Simulated use of PAL based on thresholds*

The use of PAL based on eliciting dose thresholds ED01 and ED05 was simulated for allergen-food category combinations with baseline mean risk estimates ≥10 reactions/10 000 e.o. (Table 2). The use of PAL based on ED05 was not simulated for milk in sauce, peanut in dark chocolate and hazelnut in baked goods because all concentration values > LOQ for these allergen-food categories reported in the PARERA allergen database were already below the corresponding action level reported in Manny et al. in 2022 [44]. Therefore, they would not carry PAL and the results of the simulation would be equivalent to the baseline. The use of thresholds for PAL based on ED01 was not simulated for milk in baked goods; all concentration values > LOQ for this allergen-food category reported in the PARERA allergen database were higher than the corresponding action level reported in Manny et al. in 2022 [44]. Therefore, all products that carried PAL in the baseline scenario would also carry PAL if action levels based on ED01 were used; simulations for products without PAL could not be conducted.

For most allergen-food category combinations, simulations showed that the estimated number of allergic reactions per 10 000 e.o. attributed to products with PAL currently on the market ("baseline") would be significantly higher than that attributed to products without PAL, if PAL is applied based on thresholds (Table 2). No differences were noted only for milk in sauces (baseline versus the use of ED01 and ED05 thresholds for PAL) and hazelnut in dark chocolate (baseline versus the use of ED05 threshold for PAL). The estimated number of reactions attributed to products without PAL per 10 000 e.o., when the simulated use of PAL was based on ED01 vs. ED05, was significantly different only for milk in cereal, cookies, and dark chocolate, and for hazelnut in dark chocolate. In these cases, as expected, the simulated use of PAL based on ED01, compared to ED05, resulted in significantly fewer estimated reactions attributed to products without PAL. Overall, when using thresholds for PAL based on ED01, products without PAL were estimated to trigger 10 or fewer reactions per 10 000 e.o. in all cases studied, except milk in sauces. When using thresholds for PAL based on ED05, products without PAL were estimated to trigger 10 or fewer reactions per 10 000 e.o. in five allergen-food category combinations (i.e., milk in baked goods, crackers and snacks; egg in baked goods and cookies).

## 4. Discussion

This study estimates the number of allergic reactions that consumption of certain food products with PAL sold in Canada could cause, and compares it to hypothetical scenarios where PAL is applied using thresholds based on ED01 and ED05. This comparative assessment is intended to provide objective evidence on the impact of a potential implementation of the recommendations of the FAO/WHO Expert Consultation on Risk assessment of Food Allergens on this matter [18,34].

Currently, several of the allergen-food category combinations studied could cause <10 allergic reactions per 10 000 e.o. In some

instances, PAL could be poorly protecting individuals with FA and could instead be hindering allergic consumers diets by greatly limiting the number of food products available on the market without PAL. These results concur with studies that demonstrate the low frequency of allergen contamination in North American food products with PAL, except dark chocolate with PAL for milk [15,26,27,30,31,48–51]. Products with PAL for hazelnut have the greatest number of food categories with 0 (per 10 000 e.o.) baseline allergic reactions, followed by products with PAL for peanuts, and then egg and milk. This means that PAL for hazelnut could be the most overused or the least effective of the allergens tested at protecting allergic consumers in Canada.

Dark chocolate and baked goods are the food product categories that could currently cause the most allergic reactions for the 4 allergens studied. This indicates that these food categories present the greatest number of products with current exposures sufficient to induce allergic reactions. Several factors could explain it. Dark chocolate with PAL for milk has been shown to frequently carry milk contamination [26,48,49] and to have a high likelihood of causing allergic reactions [52]. Dark chocolate production often shares equipment with other chocolate products that use milk as an ingredient and the equipment is difficult to properly clean, which could be due to the nature of milk ingredients and the viscosity of chocolate [15]. Taylor et al. have also shown that all studied confectionary manufacturers, including chocolate manufacturers, use milk as an ingredient in their facilities [53]. Regarding baked goods, high allergen exposure may be in part explained by their consumption pattern, characterized by greater quantities per e.o. than other studied food categories [44]. Furthermore, baked goods manufacturers use milk, eggs, tree nuts, and peanuts as ingredients at higher rates than most other food category manufacturers [53].

### *4.1. Baseline risk*

Milk is the allergen that could currently cause the most allergic reactions, and dark chocolate cross-contaminated with milk is the combination that could cause the most allergic reactions out of all allergen-food product combinations studied (1120 [1068–1171] per 10 000 e.o.). Four milk allergen-food product combinations could currently cause more than 100 allergic reactions per 10 000 e. o. (dark chocolate, baked goods, cereal, and crackers), as shown in Table 1. After milk, baseline allergic reactions are caused, in decreasing number, by hazelnuts, eggs, and peanuts. These results align with research that demonstrates that milk is the most used allergen by food manufacturers, followed by egg, tree nuts, and peanuts in decreasing order of frequency [53]. Overall, milk is generally recognized as the allergen causing the most reactions due to unintended allergen presence [54] and was the allergen responsible for most food recalls related to undeclared allergen presence in Canada between 2017 and 2021 [55]. Milk has also been demonstrated to contaminate food products in the United States and Canada at high frequencies [25,26,48,49].

Egg and hazelnut allergens have similar patterns in the number of allergic reactions estimated for the baseline (i.e., current) scenario, with most combinations leading to $< 1$ allergic reaction, and 2 allergen-food category combinations causing $<100$ allergic reactions per 10 000 e. o. (Table 1). This aligns with international studies reporting that egg and hazelnut are not frequently found as contaminants in products with PAL [29,50,51,56]. It has also been demonstrated, in European products, that hazelnut presence in products with PAL was most frequent in chocolates [19], which is also reflected in our results.

Peanut is currently the lowest threat as its allergen-food product combinations cause between 0 and 10 allergic reactions per 10 000 e.o. (Table 1). These results concur with previous research in the United States indicating that unintended presence of peanut in products with PAL is rare [30,31,50].

For food products with PAL for milk, most allergic reactions are caused by exposure doses above both ED01 and ED05, more so than for egg, peanut, and hazelnut (Table 1). This suggests that unintended presence of milk occurs at higher concentrations than with other studied allergens. Similarly, for food products with PAL for egg, most allergic reactions are caused by exposure doses above both ED01 and ED05 (Table 1). However, most allergic reactions are caused at exposure doses between ED01 and ED05 for products with PAL for peanut and hazelnut (Table 1).

### *4.2. Simulated use of PAL based on thresholds*

The use of PAL thresholds based on ED01 could lead to a maximum of 15 allergic reactions per 10 000 e. o. for all studied allergen-food category combinations. The use of exposure dose thresholds based on ED05, as suggested by the FAO/WHO Expert Consultation on Risk assessment of Food Allergens [18,34], could lead to a maximum of 105 allergic reactions per 10 000 e. o., or 57 allergic reactions, if excluding dark chocolate with milk PAL. The use of PAL based on either of these thresholds could greatly reduce the allergic risk posed by these products to individuals with FA in Canada, especially for products with PAL for milk and egg, which present the largest reduction in the number of estimated allergic reactions (Table 2).

However, the use of thresholds based on ED05 would not impact products with PAL for peanuts, as there is no variation in the number of allergic reactions caused in this simulated scenario compared to the baseline. This demonstrates that these allergic reactions would be caused by allergen exposure doses lower than ED05, suggesting that peanut unintended presence is very low and that food manufacturers using peanut have a certain control over its presence and contamination. This could suggest that peanut is the allergen best controlled by FBOs, as the concentration of unintended allergen is low, leading to low exposures. However, for products with PAL for milk, these results could suggest that this allergen is less effectively managed by FBOs, leading to higher concentrations of unintended allergen in final food products. Although milk has been a declared allergen for a long time, the poorer management of this allergen in facilities may be caused by a lack of understanding by FBOs of the severity of milk allergy and confusion between milk allergy and lactose intolerance, as has been reported for parents of children with FA and physicians [57–60]. If milk allergy is not taken as seriously as other allergies, like peanuts, preventive controls may be less strict. Moreover, milk, as an ingredient, is used very differently from peanuts. It is available in many forms, is used for different technical functions, and is used more often and in larger

quantities by manufacturers in many food categories as opposed to peanut, such as in the baking industry [61–64]. It is also often used as a powder, which can be more difficult to control in terms of cross-contamination than larger solids or liquids, as it can be dispersed through the air [62,65–67]. Furthermore, of the 4 studied allergens, milk is the most commonly used ingredient by medium and large Canadian FBOs [10]. On the contrary, peanuts are often used as a particulate [15,48,54,68,69]. For both egg and hazelnut, it has been demonstrated that unintended allergen presence can occur at higher frequencies, but generally in very specific products, such as products containing spent fowl, and chocolate or cookies, respectively [19,27,70].

Overall, the results of this study suggest that consumption of products without PAL, when using thresholds for PAL based on ED01 or ED05, would result in very few and generally mild to moderate adverse reactions [34]. The FAO/WHO Expert Consultation on Risk assessment of Food Allergens has recommended the use of PAL based on ED05, as it could meet their safety objective ("to minimise, to a point where further refinement does not meaningfully reduce health impact, the probability of any clinically relevant objective allergic response, as defined by dose distribution modelling of minimum eliciting doses and supported by data regarding severity of symptoms in the likely range of envisioned Reference Doses"), and is easier to apply for FBOs, and to quantify with commercially available analytical methods [18,34]. The use of thresholds for PAL would help standardize the application and meaning of this type of labelling in Canada, currently used by food manufacturers on a voluntary basis and following a variety of disparate practices [10]. Current Canadian regulations only limit the formatting of PAL and do not require previous analyses or evaluations to determine the pertinence of this warning (Food and Drug Regulations, 2023). Finally, our results suggest that in Quebec, in most cases – except for dark chocolate with PAL for milk, PAL may be overused and may not fully accomplish its 2 functions, as defined by Health Canada [9], i.e., "prevent inadvertent consumption of undeclared allergens by sensitive consumers" and "enable a variety of safe and nutritious choices for the allergic consumer". Although purchased in Quebec, given that most products included in this study are sold throughout Canada, estimates for other provinces or nationwide are likely to be similar.

This study has certain limitations. For the scenarios simulating the use of thresholds for PAL, this study assumes full consumer compliance, i.e., individuals with FA do not consume any products with PAL. Currently, and as assumed in baseline scenarios (Tables 1 and 2), individuals with FA regularly engage in risk-taking behaviours by consuming products with PAL [30,54]. For this important change in behaviour to occur, consumer education would be necessary. Beneficial effects of using threshold-based PAL will only be achieved if individuals with FA do not consume products with PAL for the allergens they are allergic to. Another important limitation of this study is the use of nutritional surveys for consumption data. Although this is common practice in most allergen risk assessments [31,52,71], these surveys provide information on daily food consumption, and not on individual eating occasions, which is important in the case of allergic reactions, as they are acute and can occur within minutes of consumption. Daily nutritional surveys may overestimate consumption of some products such as baked goods that may be eaten several times a day on different eating occasions, which could overestimate allergen exposure and the resulting number of allergic reactions caused. In addition, nutritional surveys, like the one used in this study, address the general population and not specifically individuals with FA; however, it has been reported that these populations do not follow different consumption patterns [72]. Individual overconsumption could also skew exposure values, but the effect of specific eating behaviours is out of the scope of this research. In fact, the choice of action levels calculated by Manny et al. in 2022based on P75 of the consumption distribution to simulate PAL use, recommended by Blom et al., in 2019, excludes extreme intakes without resulting in overly conservative estimates [44,73]. Further studies could also consider using action levels calculated based on the median or the mean of the consumption distribution – values that are usually more readily available and that are deemed adequate for deterministic allergen risk assessment [74]. Other than food intake considerations, food allergen oral challenge studies that were the basis of ED models developed in 2020 by Houben et al. [46] often exclude the most sensitive food allergic patients, and could also skew EDs and the associated values used in this study. Likewise, potential tolerance to denatured proteins is not captured in the ED models developed in 2020 by Houben et al. [46], and could have resulted in an overestimation of the number of reactions we calculated for individuals with egg and/or milk allergy consuming baked goods. Finally, this study addresses 9 categories of products available in Quebec, for 4 Canadian priority allergens, and is not necessarily representative of the allergic risk of different products, different allergens, or different regions. In addition, the allergens database reflects products on the market in Quebec between 2016 and 2021, and does not include market variations or inclusions after 2021.

## 5. Conclusions

According to our simulations, PAL thresholds based on ED05 would provide, in most cases, an adequate level of protection. Implementing this kind of approach may also increase the number of safe options for individuals with FA, and may facilitate interpretation of PAL in terms of risk. Nevertheless, for this strategy to succeed, individuals with FA's avoidance of products with PAL is crucial, and would require significant consumer education efforts. Furthermore, an accurate quantitative assessment requires representative food consumption data, which is not always accessible to food manufacturers. However, a probabilistic assessment like the one presented here is unlikely to be relevant or feasible in a manufacturing setting, where "worst-case" deterministic assessments could fulfill regulatory requirements. Finally, our simulations revealed that, currently, several allergen-food category combinations may be unnecessarily using PAL (Table 1). In these cases, a qualitative risk assessment, rather than a quantitative one, could adequately justify the need or not for this warning.

## Data availability statement

Data will be made available upon request and is also available at parera.ulaval.ca/en.

## CRediT authorship contribution statement

**Kamila Lizée:** Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Silvia Dominguez:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Conceptualization. **Jérémie Théolier:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Sébastien La Vieille:** Writing – review & editing, Supervision, Conceptualization. **Samuel B. Godefroy:** Writing – review & editing, Funding acquisition, Conceptualization.

## Declaration of competing interest

Samuel B. Godefroy's research activities are funded by the Natural Sciences and Engineering Research Council of Canada; the U.S. Department of Agriculture Foreign Agriculture Service; R-Biopharm GmbH; and R-Biopharm Canada Inc. Samuel B. 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. Samuel Benrejeb Godefroy is the Board President of the Global Food Regulatory Science Society (GFoRSS). The other authors declare no competing 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.heliyon.2024.e33316.

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