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Predictive modelling of the exposure to steviol glycosides in Irish patients aged 1–3 years with phenylketonuria and cow's milk protein allergy

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ABSTRACT

Children with Phenylketonuria (PKU) and severe cow's milk protein allergy (CMPA) consume prescribed, specially formulated, foods for special medical purposes (FSMPs) as well as restricted amounts of normal foods. These patients are exposed to artificial sweeteners from the consumption of a combination of free and prescribed foods. Young patients with PKU and CMPA have a higher risk of exceeding acceptable daily intakes (ADI) for additives than age-matched healthy children. A predictive modelling approach has been adapted successfully to assess the additive exposure of young patients with PKU and CMPA to artificial sweeteners. Steviol glycosides (E960) are at various stages of regulatory approval for the various food categories in the EU but are not as yet permitted for use in products intended for young children. The aim of this study was to predict potential steviol glycoside exposure in young children with PKU and CMPA considering the potential for future provisions for the use of this sweetener. The recent introduction of steviol glycosides means that no exposure data are available for children with CMPA and PKU. Food consumption data were derived from the food consumption survey data of healthy young children in Ireland from the National Preschool and Nutrition Survey (NPNS, 2010–11). Specially formulated amino acid-based FSMPs are used to replace whole or milk protein foods and were included in the exposure model to replace restricted foods. The recommendations to ensure adequate protein intake in these patients were used to determine FSMP intake. Exposure assessment results indicated that the maximum permitted level (MPL) for FSMPs would warrant careful consideration to avoid exposures above the ADI. These data can be used to inform recommendations for the medical nutrition industry.

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Introduction

The diets of patients with Phenylketonuria (PKU) or severe cow's milk protein allergy (CMPA) are managed under close medical supervision from infancy through childhood. This is necessary to avoid serious clinical outcomes of severe, chronic, irreversible mental disability in PKU (Scriver and Clow 2007; Blau et al. 2010) or acute skin, gastrointestinal symptoms and anaphylaxis in CMPA (Vlieg-Boerstra et al. 2006; Fiocchi et al. 2010; De Silva et al. 2014). The approach to dietary management is to avoid normal foods containing whole (PKU) or milk (CMPA) protein completely and to replace these foods with foods for special medical purposes (FSMPs), regulated under European Commission Directive No. 1999/21. These FSMPs contain artificial sweeteners to mask the bitter taste of amino

acids, increase the palatability and maximise dietary adherence of this patient group (European Commission 2008, 2011; O'Sullivan et al. 2016). Young patients with PKU and CMPA are exposed to artificial sweeteners from consumption of both FSMPs and general foods from the normal diet (O'Sullivan et al. 2016, 2017).

Commonly used artificial sweeteners in FSMPs based on amino acids include acesulfame K (E950), aspartame (E951) and sucralose (E955). Aspartame is a source of phenylalanine and not suitable for patients with PKU. The introduction of EU provisions for the use on sucralose and its suitability in UHT liquids had a dramatic impact on the exposures of patients in the UK between 2008 and 2016 (O'Sullivan et al. 2017). The EU provisions for sweeteners such as steviol glycosides (E 960) under the Regulation (EU) No 1131/2011 amending Annex

II of the Regulation on Food Additives mean that an increasing number of patients with PKU and CMPA could be exposed to this sweetener. While there are no provisions in foods specifically intended for young children it is possible that these children could be consuming normal foods containing the sweetener. No data are currently available on the exposure of young patients with PKU and CMPA to steviol glycosides. In addition, given that sucralose (E 955) and aspartame (E 950) are currently being considered by the European Commission it is also plausible that steviol glycosides could be considered for a future extension of additive use application in the EU to FSMPs specifically intended for young children aged 1–3 years in a similar way to sucralose (EFSA 2016a) and acesulfame K (EFSA2016b). Therefore, the current and potential future exposure of these patients to this sweetener warrants further exploration. This also offers an opportunity to consider the applicability of a probabilistic modelling approach to predicting future exposures to steviol glycosides. The approach to calculating exposure is illustrated in Figure 1.

The aim of the present research was to: (i) predict the exposure of PKU and CMPA patients in the Ireland to steviol glycosides using a validated probabilistic model and (ii) determine whether a recommendation could be made on an appropriate future usage level for FSMPs intended for children aged 1–3 years of age. The study hypothesis is that introduction of new provisions for steviol glycosides will not lead to a significant increase in the exposure of these patients to the sweeteners nor increase the risk of exceeding the ADI compared to normal healthy children.

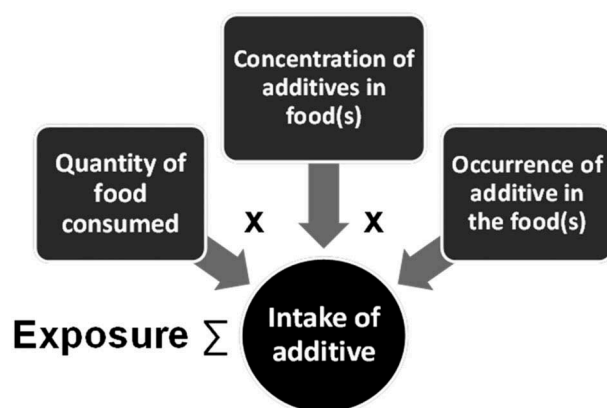


Figure 1. Model of total dietary exposure to food additives.

Materials and methods

Selection of the target population

Young children aged between one and three years were selected as the target population for this study (European Commission 2006, 2013). Healthy young children consume foods readily available to older children and adults as well as food specifically intended for them such as processed cereal-based foods and baby food regulated under Commission Directive 2006/125/EC. In Ireland, young patients with PKU and CMPA who consume specially formulated FSMP protein substitutes containing artificial sweeteners have been demonstrated to have intakes which differ from normal age-matched healthy children (O'Sullivan et al. 2016, 2017). Therefore young patients with PKU and CPMA were chosen as the population for further study.

Construction of reference databases for foods consumed by patients

No food consumption database is available for young Irish patients with PKU and CMPA. The data used for the predictive modelling were based on that available from Irish National Preschool and Nutrition Survey (NPNS) (Irish Universities Nutrition Alliance, 2012; Walton and Flynn 2013). This study was designed to assess the diet, nutrient intake and nutritional status of healthy children aged 1–4 years and data collected in Ireland between 2010 and 2011. A 4-day weighted food diary was used as the means of collecting NPNS food consumption data of children (50:50 male/female) in Ireland aged 12–59 months of age ($n = 500$) from both rural and urban background. The population of interest in the NPNS representative sample is that which is regulated as 'Young Children' under EU legislation and aged from 1 year to 3 years (376 subjects).

As previously described (O'Sullivan et al. 2016, 2017), the methodological limitations of gathering representative data for small populations of PKU and CMPA patients currently limit the feasibility of direct sampling. Therefore the data used for the present analysis are derived from the NPNS using healthy young children as a baseline. As described in (O'Sullivan et al. 2016, 2017), the diets of patients were divided into two portions: (i) 'free' portion

Table 1. Model for replacement of food groups in PKU and CMPA.

Group numbers and names of replaced foods in PKU	Group numbers and names of replaced foods in CMPA
(1) Dairy products and analogues	(1) Dairy products and analogues
(8) Meat	-
(9) Fish and fisheries products	-
(10) Eggs and egg products	-
(13) Infant Formula, Follow-on Formula, Processed cereal-based foods and baby foods, Other foods for young children	(13) Infant Formula, Follow-on Formula, Processed cereal-based foods and baby foods, Other foods for young children

represented by unrestricted foods which may be consumed freely and (ii) 'restricted' protein containing foods which must be eliminated from the diet. The 'free' portion of the diet was assumed the same as the age-matched normal healthy NPNS children surveyed. Restricted foods were selected for exclusion and replacement with prescribed FSMPs containing artificial sweeteners, [Table 1](#).

The food groups used for data collection in this study are the 17 EU food categories cited in Regulation (EU) No. 1129/2011. The restricted food groups were eliminated based on the clinical recommendations for the dietary management of PKU (Medical Research Council Working Party on Phenylketonuria 1993; MacDonald et al. 2006, 2010), [Table 1](#). A replacement file was created to represent the same food amount of FSMP product in each case for the specific food codes consumed within NPNS. This was based on recommendations for adequate protein intake and dietary adherence data. New food tables were created to represent a range of predicted steviol glycoside sweetened FSMP products. The replacement of all 'high' protein containing foods with FSMPs was done on a 1-to-1 basis. This highly conservative approach leads to protein equivalent intakes in the region of 3g/kg bw/day or greater based on the best-fit to the clinical recommendations (Department of Health, 1991).

Chemical concentration data for steviol glycosides

Only foods identified as permitted to contain steviol glycosides were considered to contain them. Food codes were used in accordance with the NPNS food consumption database. Chemical concentration tables for artificial sweeteners were created for the relevant foods consumed in NDNS using data available from: (i) the maximum permitted levels (MPLs) in the Regulation (EU) No 1131/2011 amending Annex II of the Regulation on Food Additives, and (ii) considering a range of possible usage levels for

FSMPs for the purposes of this study. To account for steviol glycosides in normal foods model chemical concentration input for normal foods was created based on a % of the MPL for the purposes of modelling refined concentrations and determining the impact of various possible 'baseline' scenarios for exposures in healthy young children. The assumption of the contribution of non-alcoholic beverages to the intake of artificial sweeteners in children observed elsewhere was also considered in the setting of an appropriate baseline (Garnier-Sagne et al. 2001; Illback et al. 2003; Devitt et al. 2004; [FSAI] Food Safety Authority of Ireland 2005, 2009; Huvaere et al. 2012; Vin et al. 2013; Martyn et al. 2016). To model baseline intake for steviol glycoside consumption in children the data of Dewinter et al. (2016) were considered. No specific exposure data were gathered for children aged 1–3 years in this study. However, the exposure in children aged 4–6 years currently represent the only data available on this sweetener.

Estimating exposures of PKU and CMPA patients to steviol glycosides

The adapted validated probabilistic model using Monte Carlo simulation has been successfully used to assess patient exposure to artificial sweeteners (O'Sullivan et al. 2016, 2017) using a web-based software application, Creme Food Safety® (Creme Global 2016). This approach to modelling exposures was previously validated as a viable means to estimate dietary exposures in patients consuming FSMPs as well as a restricted number of normal foods (O'Sullivan et al. 2016, 2017). Additive exposure assessment for the general population including young children have also previously been conducted using the model (Lambe 2002; Gibney and Van Der Voet 2003; Gilsenan et al. 2003; Vin et al. 2013; Martyn et al. 2016). An assumption of the assessment model was that the incidence of PKU and CMPA is 100% in the subjects included from the NPNS study.

This does not reflect true incidence of these diseases but the assumption was made to ensure that the available Irish food consumption data were utilised fully to closely reflect 'real-life' weight matched food intakes for young children. The impact of this assumption is that the food consumption patterns of the free portion of the diet in PKU and CMPA patients are assumed the same as age-matched healthy children.

Modelling of dietary adherence in patients

The level of adherence to prescribed FSMPs containing sweeteners (the subject of this study is Steviol Glycosides) and therefore intake, is a key factor in determining the overall exposure to sweeteners. Limited data are available on level of dietary adherence by PKU patients to the prescribed diet based on clinical recommendations and these data are based on blood phenylalanine concentrations (control) rather than consumption (Walter et al. 2002; Ahring et al. 2009; Garcia et al. 2017). Therefore, the necessary assumption that control is directly reflective of the level of dietary adherence was made. The data available indicate that control and adherence in patients aged 1–3 years is tightest of all years outside infancy but may range from 47% to 80% (Burgard et al. 1996; Walter et al. 2002; Ahring et al. 2009; MacDonald et al. 2010; Garcia et al. 2017). While data available from World Health Organization (WHO) estimates overall that of patients with chronic disease have only 50% adherence to the dietary recommendations ([WHO] World Health Organization 2003). These data were used as the basis for the modelled exposure scenarios of: 0.0 (0%), 0.5 (50%), and 0.75 (75%) of

patient adherence. There are no data available to indicate the plausibility of 100% dietary adherence for patients aged 1–3 years and therefore this scenario was not included in the final estimations of exposure. Neophobia, food avoidance and refusal are characteristic behaviours in young children. The model for 0% (complete non-adherence to diet) is the baseline reflective of normal healthy age-matched children consuming artificial sweeteners. Where a food sweetened with steviol glycosides is available it was assumed as always consumed (probability of occurrence = 1.0). This led to three FSMP replacement scenarios:

- Scenario 1: high adherence (75% replacement probability), artificially sweetened products always consumed.
- Scenario 2: moderate adherence (50% replacement probability), artificially sweetened products always consumed.
- Scenario 3: non-adherent to prescribed medical nutrition (FSMPs), artificially sweetened products always consumed (baseline).

These FSMP replacement scenarios were then built into up into a number of different modelled exposure scenarios for steviol glycosides based on the hypothesised product usage levels and occurrence in general foods and FSMPs. The exposure estimates = sweetener usage (general foods & FSMPs) $\times$ occurrence $\times$ adherence to diet. This provides six scenarios of predictive model exposure estimates from patients with PKU and CMPA, see Table 2. The FSMP replacement Scenario 3 forms the baseline for the modelled exposure scenarios.

Table 2. Model of assumptions in exposure scenarios for Steviol Glycosides in patients with CMPA and PKU.

Scenario	Baseline usage level of Steviol Glycosides in General Foods in relation to MPL*	Predicted usage of Steviol Glycosides in FSMPs 1–3 years and relationship to the MPL for FSMPs for 3+ years onwards	Occurrence Probability in General Foods	Replacement Probability/Dietary Adherence to FSMPs
Scenario 1 a	100%	100%	1	75%
b			1	50%
Scenario 2 a	75%	75%	1	75%
b			1	50%
Scenario 3 a	50%	50%	1	75%
b			1	50%
Scenario 4 a	50%	40%	1	75%
b			1	50%
Scenario 5 a	50%	30%	1	75%
b			1	50%
Scenario 6 a	50%	20%	1	75%
b			1	50%

* MPL = Maximum Permitted level according to Regulation (EC) No. 1169/2011

Exposure assessment

Exposure to steviol glycosides was calculated using Creme Food Safety® (see <http://www.cremeglobal.com>). The functionality of this tool is similar to that which was developed as part of the FACET project and utilising Monte Carlo simulations to assess exposure (Lambe 2002; Gibney and Van Der Voet 2003; Gilsenan et al. 2003; McNamara et al. 2003; FACET 2012; Vin et al. 2013; O'Sullivan et al. 2016, 2017). Using the adaptations described in the previous section the exposure was calculated for each individual eating occasion by combining the amount of food consumed (FSMPs and normal foods containing the sweetener) with the distribution of the concentration for the sweetener in the food category. Brand loyalty was assumed for FSMPs.

The initial assumption applied at Tier 2 in the step-wise approach is to assume that the sweetener was always used where it is permitted according to legislation in the EU (European Commission 2008, 2011). This represents a semi-conservative approach. High consumers were considered as the 97.5th percentile given the sample size of the population (>320). This is in line with the EFSA recommendations (EFSA, 2009). The P95 of intake was included in the assessment to allow for comparison with the data generated using the FAIM screening tool in (O'Sullivan et al. 2016, 2017). This is the basis for exposure for patients with PKU and CMPA across scenarios 2–6 presented in the Results section of this paper. Whereas Scenario 1 is the baseline free portion of the diet in PKU and CMPA equivalent to intake for children of the same age in the general population. Data are available on the typical contribution of artificially sweetened non-alcoholic beverages to exposure in children from the years 1994–2011 (Garnier-Sagne et al. 2001; Illback et al. 2003; Devitt et al. 2004; [FSAI] Food Safety Authority of Ireland 2005, 2009; Huvaere et al. 2012; Vin et al. 2013; Martyn et al. 2016). These data were taken into consideration to establish a more representative and refined baseline for exposure from normal foods. Exposure scenarios for FSMPs were calculated by combining available consumption data with the hypothesised usage levels as a % MPL for the sweetener (O'Sullivan et al. 2016, 2017).

Statistical methods

Each dietary exposure to steviol glycosides in PKU and CMPA patients based on assumed relative levels

of adherence (0.0, 0.5, 0.75) was run through the Creme Food Safety® Software v3.6. These assessments were conducted for the NPNS sampling period 2010–2011. Assessments were run to calculate the daily average exposure for each subject in the data set and subsequently weighted statistical distributions of exposure for the total population. Presence probabilities, representing the probability of a sweetener being present in the food, and replacement probability, representing the adherence of a low protein diet, were accounted for in the probabilistic exposure assessment. The mean, P95 and P97.5 additive exposures (mg/kg/day) were used to compare the results of the average exposure and highest exposure between the sampling periods. The results for exposure estimates were compared against the relevant ADI for the sweetener ([EFSA] European Food Safety Authority 2010).

Results

FSMP survey

The survey of FSMPs intended for patients with PKU and CMPA did not identify any use of steviol glycosides in these products available on the Irish market. Our previous study identified three artificial sweeteners, acesulfame K, aspartame and sucralose as those most commonly used in the survey of FSMPs (O'Sullivan et al. 2016). In addition, neutral FSMPs which do not contain colours, flavourings and sweeteners were also identified as available for consumption by these patients with PKU and CMPA. It is not expected that steviol glycosides would be suitable for use in these products now or in the future. The maximum permitted level (MPL) of 330 mg/kg currently set for the use of steviol glycosides in FSMP intended for older children aged above 3 years and adults. The scenarios below for FSMPs intended for children with PKU and CMPA consider usage levels of 100, 75, 50, 40, 30 and 20% of the current MPL.

Modelled exposure assessments for young patients

Steviol glycosides intake PKU patients

Table 3 shows that the mean intake of steviol glycosides using a range of scenarios of predictive

Table 3. Intake for Steviol Glycosides in PKU and CMPA patients.

Population	Scenario	Mean intake (mg kg ⁻¹ bw day ⁻¹)	High consumers P95 (mg kg ⁻¹ bw day ⁻¹)	High consumers P97.5 (mg kg ⁻¹ bw day ⁻¹)	% ADI (mean)	% ADI (P95)	% ADI (P97.5)
Baseline		1.2	9.3	11.6	30.0	232.8	290.0
PKU	S1a	10.4	20.7	24.0	260.0	517.5	600.0
PKU	S1b	7.2	16.2	19.0	181.0	405.8	475.0
PKU	S2a	7.8	17.2	18.5	195.0	430.0	462.5
PKU	S2b	5.5	12.2	13.9	137.5	305.0	347.5
PKU	S3a	5.2	11.4	12.6	130.0	285.0	315.0
PKU	S3b	3.7	8.1	9.8	92.5	202.5	245.0
PKU	S4a	4.3	9.1	10.0	107.5	227.5	250.0
PKU	S4b	3.1	7.1	8.5	77.5	177.5	212.5
PKU	S5a	3.3	7.5	8.7	82.5	187.5	217.5
PKU	S5b	3.3	7.6	9.0	82.5	190.0	225.0
PKU	S6a	2.4	6.1	7.5	60.0	152.5	187.5
PKU	S6b	1.8	5.7	6.7	45.0	142.5	167.5
CMPA	S1a	8.5	17.9	21.8	212.5	447.5	545.0
CMPA	S1b	6.0	14.1	18.0	150.0	352.5	450.0
CMPA	S2a	0.9	6.8	8.7	22.0	170.0	217.5
CMPA	S2b	0.9	6.8	8.7	22.0	170.0	217.5
CMPA	S3a	0.9	7.0	8.7	22.0	175.0	217.5
CMPA	S3b	0.9	7.0	8.7	22.0	175.0	217.5
CMPA	S4a	0.6	4.8	5.8	15.0	120.0	145.0
CMPA	S4b	0.6	4.8	5.8	15.0	120.0	145.0

modelling for PKU patients ranged between 1.8 and 10.4 mg/kg bw/day. The intake for P95 and P97.5 high consumers ranges between 5.7–20.7 mg/kg bw/day and 6.7–24.0 mg/kg bw/day, respectively. The table shows that intake of steviol glycosides exceeded the ADI of 4.0 mg/kg/day for PKU patients who are high consumers (P95 and P97.5) across all the predicted scenarios of intake including non-adherence to diet (baseline). The intake of steviol glycosides exceeded the ADI in patients with mean intakes and high and moderate adherence to diet for scenarios 1 and 2. For scenarios 3 and 4 the ADI is exceeded for patients with mean intake and high adherence to diet, but is not exceeded in those patients with moderate adherence to diet. The ADI is not exceeded in patients with mean intake and high or moderate adherence to diet in scenarios 5 and 6. The table shows that the exposure of high consumers (P95 and P97.5) with PKU is predicted to be lower than that of normal healthy children (baseline).

Steviol glycosides intakes in CMPA patients

Table 3 shows that the mean intake of steviol glycosides using Scenarios 2–4 predictive modelling for CMPA patients ranges between 0.6 mg/kg and 8.5 mg/kg bw/day. The intake for P95 and P97.5 high consumers ranges between 4.8–17.9 mg/kg bw/day and 5.8–21.8 mg/kg bw/day, respectively. The table shows that for CMPA patients the mean intake of steviol glycosides did not exceed the ADI of

4.0 mg/kg/day in Scenario 2, 3 or 4 for any of the adherence scenarios investigated. The table shows that intake of steviol glycosides exceeded the ADI of 4.0 mg/kg/day for CMPA patients who are high consumers (P95 and P97.5) across all the predicted scenarios of intake including non-adherence to diet (baseline).

Discussion

The predictive approach to modelling offers the opportunity to anticipate future exposure scenarios in young Irish patients with PKU and CMPA aged from 1 year to –3 years who consume FSMPs. The exposure assessment model reported here has shown that young patients aged from 1 year to 3 years who consume FSMPs used in the dietary management of PKU and CMPA containing steviol glycosides would have higher mean exposures to these sweeteners than healthy age-matched children. Patients with PKU have a higher risk of exceeding the ADI for steviol glycosides than children with CMPA. Similar observations have been made in previous studies estimating exposure of patients to other sweeteners (O’Sullivan et al. 2016). This is reflective of the greater number of protein containing foods which are restricted for PKU patients and the replacement with FSMPs which may contain the sweetener. However, the data in this study indicate that high consumers (P95 and P97.5) of steviol glycosides in both patients and healthy children

have a risk of exceeding the ADI across multiple scenarios of sweetener usage and intake. The low numerical ADI of steviol glycosides (4 mg/kg bw/day) and rapid rise in usage relative to other artificial sweeteners such as acesulfame K (9 mg/kg bw/day), sucralose (15 mg/kg bw/day) and aspartame (40 mg/kg bw/day) also may increase the likelihood of exceeding the ADI.

These results represent the first estimates of exposure of these young patients with PKU and CMPA who could consume steviol glycoside sweetened FSMPs in addition to general foods from the normal diet. The predictive modelling and availability of baseline food consumption data available for normal healthy children in Ireland through the NPNS allowed for the testing of a variety of plausible future consumption scenarios. While the approach retains some conservative assumptions for occurrence the model allows a more refined screening of potential intakes than other methods currently available such as EFSA's Food Additive Intake Model (FAIM). EFSA has acknowledged the limitations of the FAIM tool make it unsuitable for use in reliably estimating patient intakes (EFSA, 2016a; 2016b; 2016c; 2016d). As a result, a different approach is necessary for assessing the exposure to sweeteners in patients with PKU and CMPA. The predictive model assumed that steviol glycosides always occur in foods where the sweetener is permitted to do so and always consumed by the patients where it is available in these foods (occurrence probability = 1). There are a variety of FSMPs currently available to patients in either powder or liquid form and these contain various artificial sweeteners as well as unsweetened, unflavoured varieties. Therefore the occurrence probability of the sweetener is expected to be < 1. As a result, patients are less likely to consume products that exclusively contain a single artificial sweetener, now and in the future irrespective of their loyalty to a single brand. Loyalty to a single product was assumed in the current model. This is a conservative assumption within the assessments. It would be more likely that patients consuming FSMPs that were to contain steviol glycosides would consume a number of different available products with different sweeteners or without sweeteners during the day. This could reduce exposure and is a limitation of the current model which could

lead to an overestimation of intake of steviol glycosides.

Nevertheless, the predictive approach provides the opportunity for a measured initial consideration of the impact of a future provision for steviol glycosides in FSMPs intended for children aged 1–3 years of age on exposure. The data provided in this study indicate that the current MPL of 330 mg/kg or mg/l for FSMPs intended for older children and adults would not be suitable to be directly applied for those FSMPs intended for the young children with PKU. The scenarios which utilised this level of usage for FSMPs indicated that the ADI would be exceeded for those PKU patients with both mean and high intakes of FSMPs. The predicted exposure indicates that a maximum usage range of 165–200 mg/kg or mg/l would be appropriate in order to minimise the risk of exceeding the ADI for patients with PKU consuming steviol glycoside sweetened FSMPs in addition to normal foods. The possibility that higher usage levels of the sweetener in FSMPs would not lead to the ADI being exceeded cannot be discounted.

Conclusion

Data on the impact of the introduction of new provisions for sweeteners on the overall exposure of patients are very limited (Devitt et al. 2004; Dewinter et al. 2016; O'Sullivan et al. 2017). There is the possibility that a future provision for steviol glycosides in FSMPs intended for young children aged 1–3 years could lead to a reduction in the exposure to other artificial sweeteners and increased selective innovation with steviol glycosides. The recent longitudinal study of exposure of UK PKU patients over the 20 years from 1992 to 2012 observed a decline in the overall exposure and the risk of exceeding the ADI for acesulfame K and significant increase in exposure to sucralose for all PKU children (O'Sullivan et al. 2017). The authors recommended that if steviol glycosides are considered for an extension of additive use in the EU towards FSMPs intended for children aged 1–3 years that a maximum permitted level (MPL) of no greater than 200 mg/kg or mg/l be considered. This study demonstrates an additional application of probabilistic modelling as a viable means to predict

patient exposure and formulate practical recommendations for future innovation by the medical nutrition industry.

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