Food and Chemical Toxicology 46 (2008) S61–S69

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

The use of a sweetener substitution method to predict dietary exposures for the intense sweetener rebaudioside A

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ARTICLE INFO

Article history:
Received 4 October 2007
Accepted 7 May 2008

Keywords:
Rebaudioside A
Dietary exposure
Intake assessment
Intense sweetener
Diabetics
Children

ABSTRACT

There are more published dietary exposure data for intense sweeteners than for any other group of food additives. Data are available for countries with different patterns of sweetener approvals and also for population groups with high potential intakes, such as children and diabetic subjects. These data provide a secure basis for predicting the potential intakes of a novel intense sweetener by adjustment of the reported intakes of different sweeteners in mg/kg body weight by their relative sweetness intensities. This approach allows the possibility that a novel sweetener attains the same pattern and extent of use as the existing sweeteners. The intakes by high consumers of other sweeteners allows for possible brand loyalty to the novel sweetener. Using this method, the estimated dietary exposures for rebaudioside A in average and high consumers are predicted to be 1.3 and 3.4 mg/kg body weight per day for the general population, 2.1 and 5.0 mg/kg body weight per day for children and 3.4 and 4.5 mg/kg body weight per day for children with diabetes. The temporary ADI defined by the JECFA for steviol glycosides [JECFA, 2005. Steviol glycosides. In: 63rd Meeting of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization (WHO), Geneva, Switzerland, WHO Technical Report Series 928, pp. 34–39] was set at 0–2 mg/kg body weight (expressed as steviol equivalents); after correction for the difference in molecular weights, these estimated intakes of rebaudioside A are equivalent to daily steviol intakes of less than 2 mg/kg. In consequence, this analysis shows that the intakes of rebaudioside A would not exceed the JECFA temporary ADI set for steviol glycosides.

1. Introduction

The leaves of the plant *Stevia rebaudiana* are sweet tasting and contain a number of active components, the most important of which are stevioside and rebaudioside A. Both compounds are glycosides of steviol and are hydrolysed in the intestinal tract to steviol, which is lipid soluble and absorbed. Stevioside was evaluated by the JECFA (Joint FAO/WHO Expert Committee on Food Additives) in 2005 and a temporary ADI of 0–2 mg/kg body weight was established based on toxicology data on steviol and stevioside (JECFA, 2005). The ADI was expressed as steviol equivalents because the potential for toxicity resides in the steviol moiety, and because many stevioside preparations contain other glycosides in addition to stevioside. The future use of pure rebaudioside A as an intense sweetener requires an assessment of potential intake for comparison with the temporary ADI established by the JECFA (2005).

Various methods have been used to estimate the dietary exposures to food additives, which range in sophistication from simple screening methods to complex and expensive dietary records (Kroes et al., 2002).

Screening methods are normally used prior to the approval of a novel additive and are highly conservative in order to determine if there is any potential for the human dietary exposure to exceed the acceptable daily intake (ADI). A commonly used initial approach is the so-called Danish budget method (Hansen, 1979), which in the worst-case assumes that the compound is present at the maximum permitted concentration and is consumed daily in all foods (100 kcal per kg body weight) and liquids (100 ml per kg body weight). A modified budget method assumes that the compound is present in all food groups for which it is approved and uses high consumption data for the relevant food groups. Such methods overestimate real exposures, but a more sophisticated approach is not necessary if the dietary exposures are below the ADI. An alternative screening method, the sucrose replacement method, has been used in the past for intense sweeteners. As the name implies, this method assumes that the intense sweetener replaces all dietary sucrose. This approach is highly conservative because it ignores the many non-sweetener functions of sucrose.

Abbreviations: ADI, acceptable daily intake; EU, European Union; FDA, Food and Drug Administration; JECFA, Joint FAO/WHO Expert Committee on Food Additives; kg, kilogram; kcal, kilocalorie; mg, milligram; NHANES, National Health and Nutrition Examination Survey; UK, United Kingdom; USA, United States of America.

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doi:10.1016/j.fct.2008.05.009

Table 1
Average intakes by consumers of different intense sweeteners (means or medians if means were not given in the publication)

Date	Country	Number	Average daily intake by consumers in mg/kg body weight/day						References
			Acesulfame	Alitame	Aspartame	Cyclamate	Saccharin	Sucralose	
1977	USA	1135	–	–	–	–	2.0*	–	Morgan et al. (1982)
1980	*Finland*	*National data*	–	–	–	*0.2*	*0.1*	–	Pentilla et al. (1988)
1987	Canada	10416	–	–	1.3	–	–	–	Heybach and Ross (1989)
1987	UK	681	0.7*	–	1.0*	–	0.9*	–	MAFF (1987)
1988	UK	647	0.6	–	0.4	–	0.4	–	Hinson and Nicol (1992)
1988	Germany	2291	–	–	1.2	3.0	0.3	–	Bär and Biermann (1992)
1990–1991	Brazil	673	–	–	1.2	1.7	0.8	–	Toledo and Ioshi (1995)
1991	Denmark (all ages plus diabetics)	1233	0.5	–	0.7	2.0	0.3	–	Renwick (1999)
1992	Netherlands	6218	0.2	–	1.5	1.1	0.2	–	Hulshof et al. (1995)
1992	Spain	2450	–	–	–	2.4	–	–	Serra-Majem et al. (1996)
1993	*Norway*	*National data for children*	*1.7**	–	*3.4**	*4.3**	*0.4**	–	Bergsten (1996)
1994	Australia	128	0.2	–	2.8	2.5	0.5	–	NFA (1995)
1994–1996	Spain – men	784	–	–	–	0.6	–	–	Serra-Majem et al. (2003)
1995	Denmark	3098	0.1		0.8	0.1	0.01		Leth et al. (2007)
1996	Italy – teenagers	212	0.02	–	0.03	0.24	0.21	–	Leclercq et al. (1999)
1997	France – diabetics aged 2–20 years	227	1.1	–	2.4	–	0.4	–	Garnier-Sagne et al. (2001)
1997–1998	Netherlands	National Food Survey	0.0	–	0.1	0.1	0.02	–	van Rooij-van den Bos et al. (2004)
Not stated	UK – various ages	188	0.7	–	–	–	0.5	–	Wilson et al. (1999)
1998	Korea	11525	–	–	0.14	–	0.03	–	Chung et al. (2005)
1999	*Sweden – worst-case in diabetics*	*243 children, +547 adults*	*4*	–	*8*	*5*	*1*	–	Ilback et al. (2003)
2000–2001	Italy – teenagers including high consumers	362	0.02	–	0.05	0.25	0.03	–	Arcella et al. (2004)
2001	UK – children aged 1.5–4.5 years	1110	0.9	–	3.4	4.5	1.2	–	Food Standards Agency UK (2001)
2001–2002	USA – NHANES database	9701	–	–	4.9	–	–	–	Magnuson et al. (2007)
Not stated	Canada – diabetic children	56	0.6	–	4.1	0.0	–	0.2	Devitt et al. (2004)
2002–2003	Australia and New Zealand – consumers	400 high consumers	0.51	–	2.42	2.93	0.46	0.52	Food Standards Australia New Zealand (2004)

Data shown in italics are theoretical worst-case analyses based on national food intake data and maximum permitted use levels; data from these studies are excluded from further analyses.
* The study subdivided the data into various groups; the value given is the highest reported value.

Usually a tiered approach is used and more sophisticated and complex methods are employed when screening methods indicate the need for a more refined dietary exposure assessment (Gibney and Lambe, 1996). More sophisticated methods use food diaries combined with either permitted use levels or measured concentrations in different foods and beverages. The long-term average dietary exposures of consumers are most relevant for risk assessment purposes, but in reality, food diaries become increasingly unreliable with increase in duration, so that detailed food diaries are usually less than two-weeks duration.

A large number of intake surveys have been undertaken on intense sweeteners since 1977 (reviewed in Renwick, 1999, 2006), and there is a more extensive database available for intense sweeteners than for any other type of food additive. In this paper published data on dietary exposures to approved intense sweeteners have been used to predict the maximum likely intake of rebaudioside A. The method is equally applicable to other novel or recently approved intense sweeteners for which specific intake data are lacking.

2. Method[1]

The method is based on published intake data for approved intense sweeteners. The amount of sucrose replaced by an intense sweetener equals the dietary exposure for that sweetener multiplied by its relative sweetness intensity compared with sucrose. The intake of a novel intense sweetener is then calculated by dividing the estimated sucrose equivalent intakes by the relative sweetness of the novel sweetener.

There have been many published studies performed in a number of different countries with different patterns of sweetener approval. Approval scenarios range from the USA in the late 1970s and Canada in the 1990s, when saccharin or aspartame, respectively were the only sweeteners used in foods and beverages, to recent data for Australia and New Zealand, where six intense sweeteners are permitted. The various studies represent a massive database covering many thousands of individuals in different countries.

Many papers reported the average intakes for the whole population and also for consumers only; inclusion of data for non-consumers lowers the intake estimates and is not useful for risk assessment purposes; the intake data used in this paper are for "consumers only".

The "ideal" dietary exposure assessment would use a two-weeks prospective brand-specific questionnaire with accurate measurement of the amount of each food/beverage consumed on each eating occasion. Such a study would be complex and costly and few such data exist for any additive. In practice, most intake surveys on intense sweeteners have included conservative assumptions to some degree (see Renwick, 2006). Realistic estimation of dietary exposure requires exclusion of data from studies where the intake estimates were based on modified budget methods, or the dietary records did not differentiate between low-calorie and regular products. The data used in the present analysis were mostly from studies that used specifically-designed food diaries combined with actual use levels or approved levels in different foods and beverages. Some studies were based on the intakes of categories of foods, rather than diary records of specific products; the extent to which such studies would overestimate exposure would depend on how broad the categories were, and whether they grouped together products sweetened with sucrose or with an intense sweetener.

A number of studies given in Table 1 were excluded from further analysis. The studies of Pentilla et al. (1988), Bergsten (1996) and Ilback et al. (2003) were theoretical screening analyses using national food intake data combined with maximum permitted use levels. The study of Chung et al. (2005) analyzed the concentrations of aspartame, saccharin and stevioside in different food products in Korea and

[1] The FDA has used a similar method to predict the intakes in the USA of acesulfame-K (http://frwebgate.access.gpo.gov/cgi-bin/getpage.cgi?dbname=1998_register&position=all&page=36345) and sucralose (http://frwebgate.access.gpo.gov/cgi-bin/getpage.cgi?dbname=1998_register&position=all&page=16418) (M.J. Dinovi – personal communication).

Table 2
Intakes by high consumers of different intense sweeteners (90th, 95th or 97.5th percentiles as given in the publication)

Date	Country	Number	Daily intake by high consumers in mg/kg body weight/day						References
			Acesulfame	Alitame	Aspartame	Cyclamate	Saccharin	Sucralose	
1984–1992	USA	MRCA data	–	–	2.3	–	–	–	Butchko et al. (2002) (90th percentile)
1987	Canada	10416	–	–	5.7/7.25	–	–	–	Heybach and Ross (1989) (90th/95th percentiles)
1987	UK	681	–	–	1.7*	–	2.6*	–	MAFF (1987) (97.5th percentile)
1988	UK	647	1.8	–	1.6	–	1.3	–	Hinson and Nicol (1992) (90th percentile)
1988	Germany	2291	–	–	2.8	6.4	0.6	–	Bär and Biermann (1992) (90th percentile)
1991	Denmark (all ages plus diabetics)	1233	1.4/2.0/2.4	–	1.5/3.2/6.1	4.5/8.2/10.5	1.0/1.4/2.7	–	Renwick (1999) (90th/95th/97.5th percentiles)
1992	Netherlands	6218	0.8	–	5.2	4.9	1.0	–	Hulshof et al. (1995) (90th percentile)
1994	Australia	128	0.45	–	9.2	11.8	2.8	–	NFA (1995) (90th percentile)
1995	Denmark	3098	0.7		4.0	1.8	0.2		Leth et al. (2007)
1997	France –diabetics aged 2–20 years	227	4.0	–	7.8	–	1.3	–	Garnier-Sagne et al. (2001) (97.5th percentile)
1997–1998	Netherlands	National Food Survey	0.1	–	0.5	0.4	0.01	–	van Rooij-van den Bos et al. (2004) (95th percentile)
2001	UK – children aged 1.5–4.5 years	1110	3.7	–	12.0	14.1	3.8	–	Food Standards Agency UK (2001) (97.5th percentile)
2001–2002	USA – NHANES database	9701	–	–	10.4/13.3	–	–	–	Magnuson et al. (2007) (90th/95th percentiles)
Not stated	Canada – diabetic children	56	1.9	–	7.8	0.0	–	0.9	Devitt et al. (2004) (90th percentile)
2002–2003	Australia and New Zealand	400 high consumers	0.92/1.39	–	5.02/6.98	7.80/9.32	1.28/2.35	1.32/2.31	Food Standards Australia New Zealand (2004) (90th/95th percentiles)

* Calculated assuming an average body weight of 65 kg.

estimated dietary exposures by multiplying the overall average concentration (including non-detects as zero) by the average and high percentile intakes for each food product, based on a 1998 national survey of the intakes of different food categories. The study of Leth et al. (2007) estimated intakes from beverages alone; only the data for children from this study were retained because beverages are the single most important source of dietary exposure for children (Hinson and Nicol, 1992).

The intakes reported in the different papers have been converted to sucrose equivalents, by multiplying the daily intakes, expressed in mg specific sweetener/kg body weight into mg sucrose/kg body weight. The sweetness potencies, relative to sucrose, have been taken as acesulfame-K = 200, alitame = 2000, aspartame = 180, cyclamate = 30, saccharin = 300, sucralose = 600 (Food Standards Australia New Zealand, 2004). The use of sucrose as a "common currency" allows the data from the different studies to be compared. The predicted intake of a novel intense sweetener can then be calculated by dividing the estimated sucrose equivalent intakes by the relative sweetness for that intense sweetener.

The data in the publications were reported in a variety of ways. For example, most studies gave the intakes as mg/kg body weight per day, although some reported the data as mg/day and others as the % of the relevant ADI per day. Where necessary, the data have been converted to mg/kg body weight per day using the reported intake data for consumers of each sweetener and assuming a body weight of 65 kg.

The dietary exposures of individuals with higher than average intake of a particular sweetener (high consumers) are likely to reflect some degree of brand loyalty. Therefore, analysis of the published data for high consumers of an approved sweetener provides important information for assessing the potential dietary exposure to a novel sweetener. Different studies used different percentiles of the population (90th, 95th or 97.5th percentile of intakes) to define the intakes by "high consumers". Such data have been used as published, because it is not possible from the available information to use a consistent percentile. The 90th percentile has been used when available as it is an indicator of the intake by high consumers.

In addition, there was variation in the degree to which the data for the study population were subdivided into subgroups, such as by gender and different age bands. In consequence, the data have been analyzed for the whole study population, as reported. Where possible, data for children and patients with diabetes have been analyzed separately since these subgroups are expected to have higher than average dietary exposures when expressed on a body weight basis.

In order to provide a realistic but conservative dietary exposure assessment, studies that reported unusually low intakes of intense sweeteners have been excluded from calculation of the predicted intake of rebaudioside A. Uncharacteristically low average intakes were reported in two studies on Italian teenagers (Leclercq et al., 1999 and Arcella et al., 2004) and in studies on the general populations of the Netherlands (van Rooij-van den Bos et al., 2004); data from these studies were not used in subsequent analyses. These studies are given in Table 1 for completeness but the data were not used in the analyses.

In contrast, some of the earlier studies were at a time when only a limited number of sweeteners were approved; these studies have been retained, because although this could result in higher average intakes for the whole population, it would not greatly affect the intakes by consumers who show brand loyalty.

In pooling the data from different studies, the averages are not weighted by the numbers of subjects in each study because each study is representative of a particular population/country at a particular time. A large study population will reduce errors but will not greatly alter the mean or high consumer intake estimates. In addition, weighting by the numbers in the study population would result in disproportionate weight being given to the study in Canada by Heybach and Ross (1989), for which aspartame was the only approved sweetener, and the study in the USA by Magnuson et al. (2007), which was based on categories of foods consumed rather than a brand-specific consumption and concentration data.

The studies used to calculate the intakes by average and high consumers involved food diaries that allowed analysis of foods containing intense sweeteners, although many used the maximum permitted levels rather than analytical data. Most were studies in the general population although some identified potential consumers from a preliminary screen.

3. Results

3.1. Daily intakes of approved intense sweeteners expressed as mg/kg body weight of each sweetener

Table 1 presents the data for the average daily intake by consumers of products containing each sweetener.

It is clear from the data in Table 1 that the main intense sweeteners used in food products were acesulfame-K, aspartame, cyclamate and saccharin, while sucralose did not have high market penetration at the time of the studies. Although alitame was approved at the time of some of the studies, none of the publications reported any intake of alitame. (The sucrose equivalents data in this paper could be used to predict possible future intakes of alitame.). Furthermore, some of the studies concentrated on children and/or on subjects with diabetes, since they would have higher potential intakes than the general population (specific studies on these groups are analyzed separately in Tables 5 and 6). The highest intakes were for saccharin and aspartame, because of their wide usage, and for cyclamate, because of its lower sweetness intensity.

Table 2 presents the data for the daily intake by high consumers of each sweetener. Not all studies determined the intakes by high consumers and therefore, not all studies in Table 1 are included in Table 2 (or in Table 4 – see below). Data in Table 2 are given for those studies that reported different percentiles of the distribution of intakes, but not those that simply reported the maximum intake observed in the study population or data reported for a separate subgroup of high consumers. An exception to this is the data from Australia and New Zealand (Food Standards Australia New Zealand, 2004) where the main study was undertaken in a group of 400 subjects identified in a preliminary screen as likely to have higher than average intakes. The 90th percentile exposure of consumers in this group would have overestimated the 90th percentile in the original consumer population, but the data were retained as this was one of the most comprehensive studies available.

3.2. Daily intakes of approved intense sweeteners expressed as mg/kg body weight of sucrose substituted by each sweetener

Table 3 presents the data for the average daily intakes of the different sweeteners adjusted for sweetness intensity and expressed as sucrose equivalents.

The intakes of acesulfame-K, alitame and sucralose were generally lower than those of aspartame and saccharin, and most data for these sweeteners were not included in calculation of the overall average sucrose substitution because this would underestimate the possible intakes. The intakes of cyclamate were equivalent to the replacement of less than 150 mg of sucrose/kg body weight/day, which probably reflects the more restricted use profile of this sweetener, and the data for this sweetener were not used to predict the intake of rebaudioside A.

The data show that the average intakes of aspartame, saccharin and sucralose (using the 2004 data for Australia and New Zealand) were equivalent to the replacement of about 100–300 mg of sucrose/kg body weight/day. The average daily intake for the general population (mostly non-diabetic adults, because data specific to children and diabetic subjects were not used) expressed as sucrose equivalents is 255 mg/kg body weight (using values of 234, 180, 72, 216, 216, 126, 270, 504, 882 and 436 for aspartame, 600, 270, 120, 90, 240, 90, 60, 150, 150, 138 for saccharin and 312 for sucralose – shown in bold font in Table 3).

Table 4 presents the data for the daily intake by high consumers of each sweetener adjusted for sweetness intensity. Data are given for the studies identified in Table 2. The daily intakes by high consumers were calculated using the 90th percentile intakes where possible, and a higher percentile when the 90th percentile was not reported.

The data show that the intakes of aspartame and saccharin by high consumers were equivalent to the replacement of up to 1872 mg of sucrose/kg body weight/day for adults. The average daily intake for high consumers in the general population (mostly non-diabetic adults) expressed as sucrose equivalents is 675 mg/kg body weight (using values of 414, 1026, 306, 288, 504, 270, 936, 1656, 1872 and 904 for aspartame, 780, 390, 180, 300, 300, 840 and 384 for saccharin and 792 for sucralose).

3.3. Daily dietary exposures to approved sweeteners by population groups with high potential intakes (children and diabetics)

3.3.1. Data on dietary exposure assessment of approved sweeteners in children

Studies that provided useful data for exposure assessment for children (Table 5) were:

Butchko et al. (2002) – The paper summarized a number of studies on aspartame intake in the USA that used 14-day food intake data from the MRCA survey; limited details are provided and the total numbers in different subgroups were not reported.

Heybach and Ross (1989) – The study was performed in Canada and included two cohorts of 5544 subjects (February/April) and 4872 subjects (July/September); data were presented for different

Table 3
Average intakes of different intense sweeteners expressed as sucrose equivalents

Date	Country	Number	Average daily intake by consumers expressed as sucrose equivalents in mg/kg body weight/day						References
			Acesulfame	Alitame	Aspartame	Cyclamate	Saccharin	Sucralose	
1977	USA	1135	–	–	–	–	**600**	–	Morgan et al. (1982)
1987	Canada	10416	–	–	**234**	–	–	–	Heybach and Ross (1989)
1987	UK	681	140	–	**180**	–	**270**	–	MAFF (1987)
1988	UK	647	120	–	**72**	–	**120**	–	Hinson and Nicol (1992)
1988	Germany	2291	–	–	**216**	90	**90**	–	Bär and Biermann (1992)
1990–1991	Brazil	673	–	–	**216**	51	**240**	–	Toledo and Ioshi (1995)
1991	Denmark (all ages plus diabetics)	1233	100	–	**126**	60	**90**	–	Renwick (1999)
1992	Netherlands	6218	40	–	**270**	33	**60**	–	Hulshof et al. (1995)
1992	Spain	2450	–	–	–	72	–	–	Serra-Majem et al. (1996)
1994	Australia	128	40	–	**504**	75	**150**	–	NFA (1995)
1994–1996	Spain – men	784	–	–	–	18	–	–	Serra-Majem et al. (2003)
1996	Italy – teenagers	212	4	–	5	7	63	–	Leclercq et al. (1999)
1997	France – diabetics aged 2–20 years	227	220	–	432	–	120	–	Garnier-Sagne et al. (2001)
1997–1998	Netherlands	National Food Survey	0	–	18	3	6	–	van Rooij-van den Bos et al. (2004)
Not stated	UK – various ages	188	140	–	–	–	**150**	–	Wilson et al. (1999)
2000–2001	Italy – teenagers including high consumers	362	4	–	9	8	9	–	Arcella et al. (2004)
2001	UK – children aged 1.5–4.5 years	1110	180	–	612	135	360	–	Food Standards Agency UK (2001)
2001–2002	USA – NHANES database	9701	–	–	**882**	–	–	–	Magnuson et al. (2007)
Not stated	Canada – diabetic children	56	120	–	738	0	–	120	Devitt et al. (2004)
2002–2003	Australia and New Zealand – consumers	400 high consumers	102	–	**436**	88	**138**	**312**	Food Standards Australia New Zealand (2004)

Values shown in bold font are those used to estimate the average sucrose replacement in the general population adults.

Table 4
Intakes of different intense sweeteners by high consumers (90th, 95th or 97.5 percentiles as given in the publication) expressed as sucrose equivalents

Date	Country	Number	Daily intake by high consumers expressed as sucrose equivalents in mg/kg body weight/day						References
			Acesulfame	Alitame	Aspartame	Cyclamate	Saccharin	Sucralose	
1984–1992	USA	MRCA data	–	–	**414**	–	–	–	Butchko et al. (2002) (90th percentile)
1987	Canada	10416	–	–	**1026**/1305	–	–	–	Heybach and Ross (1989) (90th/95th percentiles)
1987	UK	681	–	–	**306**	–	**780**	–	MAFF (1987) (97.5th percentile)
1988	UK	647	360	–	**288**	–	**390**	–	Hinson and Nicol (1992) (90th percentile)
1988	Germany	2291	–	–	**504**	192	**180**	–	Bär and Biermann (1992) (90th percentile)
1991	Denmark (all ages plus diabetics)	1233	280/400/480	–	**270**/576/1098	135/246/315	**300**/420/810	–	Renwick (1999) (90th/95th/97.5th percentiles)
1992	Netherlands	6218	160	–	**936**	147	**300**	–	Hulshof et al. (1995) (90th percentile)
1994	Australia	128	90	–	**1656**	354	**840**	–	NFA (1995) (90th percentile)
1997	France – diabetics aged 2–20 years	227	800	–	1404	–	390	–	Garnier-Sagne et al. (2001) (97.5th percentile)
1997–1998	Netherlands	National Food Survey	20	–	90	12	30	–	van Rooij-van den Bos et al. (2004) (95th percentile)
2001	UK – children aged 1.5–4.5 years	1110	740	–	2160	423	1140	–	Food Standards Agency UK (2001) (97.5th percentile)
2001–2002	USA – NHANES database	9701	–	–	**1872**/2394	–	–	–	Magnuson et al. (2007) (90th/95th percentiles)
Not stated	Canada – diabetic children	56	380	–	1404	0.0	–	540	Devitt et al. (2004) (90th percentile)
2002–2003	Australia and New Zealand – consumers	400 high consumers	184/278	–	**904**/1256	234/280	**384**/705	**792**/1386	Food Standards Australia New Zealand (2004) (90th/95th percentiles)

Values shown in bold font are those used to estimate the average sucrose replacement in general population adults.

ages and for diabetics, but the numbers in each group were not reported; food/beverage intake was assessed using a 7-day food diary; product-specific concentration data were used; only aspartame was assessed.

Hinson and Nicol (1992) – A total of 647 UK participants were studied, which included 60 children aged 1–5 years, 62 aged 6–9 years and 63 aged 10–14 years; food/beverage intake was assessed using a 7-day food diary; product-specific concentration data were used; the mean intakes were not reported for these subgroups.

Renwick (1999) – The Danish population studied included 28 children aged 1–5 years, 38 aged 6–9 years and 31 aged 10–14 years; food/beverage intakes were assessed using a 7-day food diary; product-specific concentration data were used for tabletop and beverages, and maximum permitted use levels for foodstuffs (which would have resulted in slight over-estimation of the total intakes).

Food Standards Agency UK (2001) – This UK study was reported with limited methodological data provided; a 7-day diary questionnaire sought information on beverages only; concentration data were provided by the product manufacturer; diaries were obtained for 1100 children aged 1.5–4.5 years; dilutable soft drinks were the main source of intake.

Leth et al. (2007) – The study was performed in Denmark and used data from a national dietary food survey combined with the concentrations of intense sweeteners measured in beverages. The food intake survey included data for 1261 children aged between 1 and 14 years. The study estimated intakes from beverages only, but the data for children from this study were retained because beverages are the single most important source of dietary exposure for children (Hinson and Nicol, 1992).

Magnuson et al. (2007) – The exposure assessment for different age groups was a theoretical analysis based on average intakes measured in the NHANES 2001–2002 survey of the food codes for which aspartame was approved multiplied by the maximum potential concentration. Thus, the resulting dietary exposures probably overestimate the true intakes, but the data are retained because of the size and reliability of the database used.

Analysis of the exposure data for children is complicated by the different age ranges investigated and reported in different studies. In order to provide conservative estimates for the predicted intake of rebaudioside A, the overall average and high exposure assessments for children are based on the age group within each study that showed the highest intake.

The dietary exposure data for non-diabetic children (Table 5) show an overall average intake expressed as sucrose equivalents of 425 mg/kg body weight (using values of 262, 200 and 184 for acesulfame-K, 369, 155, 684, 608 and 1019 for aspartame and 348 for saccharin). The intakes by high consumer non-diabetic children expressed as sucrose equivalents is 990 mg/kg body weight (using values of 666, 460, 1022 and 744 for acesulfame-K, 666, 1568, 504, 623, 1584 and 2162 for aspartame and 735 and 1149 for saccharin).

3.3.2. Daily intakes of approved sweeteners in adults with diabetes

The studies that provided data on exposure assessment for adults with diabetes were:

Butchko et al. (2002) – see Section 3.3.1 above.

Heybach and Ross (1989) – see Section 3.3.1 above.

MAFF (1987) – This survey was performed by the UK Ministry of Agriculture, Fisheries and Food, and included 89 diabetic subjects; food/beverage intakes were assessed using a 7-day food diary; product-specific concentration data were used; the results were expressed as mg/day not mg/kg/day (a body weight of 65 kg has been used to convert the data to a body weight basis).

Table 5
Intakes of different intense sweeteners by average and high consumer children

Date	Country and group	Measure	Daily intake in consumers (mg/kg body weight)						References
			Acesulfame	Alitame	Aspartame	Cyclamate	Saccharin	Sucralose	
1984–1992	**USA**								Butchko et al. (2002)
	Children (2–5 years)	90th percentile	–	–	3.7	–	–	–	
	Children (2–5 years)	90th percentile as sucrose	–	–	***666***	–	–	–	
1987	**Canada**								Heybach and Ross (1989)
	Children (<2 years)	Mean	–	–	2.05	–	–	–	
	Children (<2 years)	Mean as sucrose	–	–	**369**	–	–	–	
	Children (<2 years)	90th percentile	–	–	7.57	–	–	–	
	Children (<2 years)	90th percentile as sucrose	–	–	1363	–	–	–	
	Children (2–5 years)	Mean	–	–	1.85	–	–	–	
	Children (2–5 years)	Mean as sucrose	–	–	333	–	–	–	
	Children (2–5 years)	90th percentile	–	–	8.71	–	–	–	
	Children (2–5 years)	90th percentile as sucrose	–	–	***1568***	–	–	–	
1988	**UK**								Hinson and Nicol (1992)
	Children (1–5 years)	90th percentile	3.33	–	2.8	–	2.45	–	
	Children (1–5 years)	90th percentile as sucrose	***666***	–	***504***	–	***735***	–	
	Children (6–9 years)	90th percentile	2.88	–	1.6	–	1.8	–	
	Children (6–9 years)	90th percentile as sucrose	576	–	288	–	540	–	
	Children (10–14 years)	90th percentile	0.9		2.4		0.75		
	Children (10–14 years)	90th percentile as sucrose	180		432		225	–	
1991	**Denmark**								Renwick (1999)
	Children (1–5 years)	Mean	1.31	–	0.86	2.86	0.13	–	
	Children (1–5 years)	Mean as sucrose	**262**	–	**155**	86	39	–	
	Children (1–5 years)	90th percentile	5.11	–	2.65	10.22	0.13	–	
	Children (1–5 years)	90th percentile as sucrose	***1022***	–	477	307	39	–	
	Children (6–9 years)	Mean	0.51	–	0.38	1.32	0.07	–	
	Children (6–9 years)	Mean as sucrose	102	–	68	40	21	–	
	Children (6–9 years)	90th percentile	1.10	–	0.77	2.35	0.19	–	
	Children (6–9 years)	90th percentile as sucrose	220	–	139	71	57	–	
	Children (10–14 years)	Mean	0.72	–	0.85	1.45	0.15	–	
	Children (10–14 years)	Mean as sucrose	144	–	153	44	45	–	
	Children (10–14 years)	90th percentile	1.71	–	3.46	3.42	0.78	–	
	Children (10–14 years)	90th percentile as sucrose	342	–	***623***	103	234	–	
1995	**Denmark**								Leth et al. (2007)
	Children (1–3 years)	Mean	1.0	–	3.7	1.8	0.2	–	
	Children (1–3 years)	Mean as sucrose	**200**	–	666	54	60	–	
	Children (1–3 years)	90th percentile	2.3	–	8.8	7.1	0.8	–	
	Children (1–3 years)	90th percentile as sucrose	***460***	–	***1584***	213	240	–	
	Children (4–6 years)	Mean	0.8	–	3.4	1.2	0.1	–	
	Children (4–6 years)	Mean as sucrose	160	–	612	36	30	–	
	Children (4–6 years)	90th percentile	1.7	–	7.3	5.8	0.7	–	
	Children (4–6 years)	90th percentile as sucrose	340	–	1314	174	210	–	
	Boys (7–10 years)	Mean	0.6	–	3.8	1.2	0.1	–	
	Boys (7–10 years)	Mean as sucrose	120	–	**684**	36	30	–	
	Boys (7–10 years)	90th percentile	1.6	–	7.3	5.8	0.6	–	
	Boys (7–10 years)	90th percentile as sucrose	320	–	1314	174	180	–	
	Girls (7–10 years)	Mean	0.6	–	3.4	1.0	0.1	–	
	Girls (7–10 years)	Mean as sucrose	120	–	612	30	30	–	
	Girls (7–10 years)	90th percentile	1.3	–	6.1	4.2	0.5	–	
	Girls (7–10 years)	90th percentile as sucrose	260	–	1098	126	150	–	
2001	**UK**								Food Standards
	Children (1.5–4.5 years)	Mean	0.92	–	3.38	4.46	1.16	–	Agency UK (2001)
	Children (1.5–4.5 years)	Mean as sucrose	**184**	–	**608**	134	**348**	–	
	Children (1.5–4.5 years)	97.5th percentile	3.72	–	12.01	14.07	3.83	–	
	Children (1.5–4.5 years)	97.5th percentile as sucrose	***744***	–	***2162***	422	***1149***	–	
2001/2002	**USA**								Magnuson et al. (2007)
	Children (1–2 years)	Mean	–	–	5.10	–	–	–	
	Children (1–2 years)	Mean as sucrose	–	–	918	–	–	–	
	Children (3–5 years)	Mean	–	–	5.66	–	–	–	
	Children (3–5 years)	Mean as sucrose	–	–	**1019**	–	–	–	
	Children (6–11 years)	Mean	–	–	5.51	–	–	–	
	Children (6–11 years)	Mean as sucrose	–	–	992	–	–	–	

Values used to calculate the average and high consumer intakes by children are shown in bold font and bold italic font, respectively.

Hinson and Nicol (1992) – This UK study included 35 diabetics; food/beverage intakes were assessed using a 4-day diary; product-specific concentration data were used.

Bär and Biermann (1992) – The study was performed in Germany and included 58 subjects consuming a diabetic diet; food/beverage intakes were assessed using a 24 h food diary (which would tend

Table 6
Intakes of different intense sweeteners by average and high consumer diabetic subjects (adults and children)

Date	Country	Measure	Daily intake in consumers (mg/kg body weight)						References
			Acesulfame	Alitame	Aspartame	Cyclamate	Saccharin	Sucralose	
1984–1992	**USA**								Butchko et al. (2002)
	Diabetic adults	90th percentile	–	–	2.83	–	–	–	
	Diabetic adults	90th percentile as sucrose	–	–	***509***	–	–	–	
1987	**Canada**								Heybach and Ross (1989)
	Diabetic adults	Mean	–	–	2.37	–	–	–	
	Diabetic adults	Mean as sucrose	–	–	**427**	–	–	–	
	Diabetic adults	90th percentile	–	–	8.25	–	–	–	
	Diabetic adults	90th percentile as sucrose	–	–	***1485***	–	–	–	
1987	**UK**								MAFF (1987)
	Diabetic adults	Median	0.41	–	1.97	–	0.86	–	
	Diabetic adults	Median as sucrose	82	–	**354**	–	**258**	–	
	Diabetic adults	97.5th percentile	–	–	9.2	–	7.0	–	
	Diabetic adults	97.5th percentile as sucrose	–	–	***1656***	–	***2100***	–	
1988	**UK**								Hinson and Nicol (1992)
	Diabetic adults	90th percentile	1.0	–	2.4	–	1.75	–	
	Diabetic adults	90th percentile as sucrose	200	–	***432***	–	***525***	–	
1988	**Germany**								Bär and Biermann (1992)
	Diabetic adults	Mean	–	–	0.13	2.53	0.3	–	
	Diabetic adults	Mean as sucrose	–	–	23	76	90	–	
	Diabetic adults	90th percentile	–	–	0.0	6.38	0.75	–	
	Diabetic adults	90th percentile as sucrose	–	–	0	191	225	–	
1991	**Denmark**								Renwick (1999)
	Diabetic adults	Mean	0.64	–	1.20	2.43	0.44	–	
	Diabetic adults	Mean as sucrose	128	–	**216**	73	**132**	–	
	Diabetic adults	90th percentile	1.66	–	4.40	4.10	1.33	–	
	Diabetic adults	90th percentile as sucrose	332	–	***792***	123	***399***	–	
1997	**France**								Garnier-Sagne et al. (2001)
	Diabetic children (2–20 years)	Mean	1.1	–	2.4	–	0.4	–	
	Diabetic children (2–20 years)	Mean as sucrose	220	–	432	–	120	–	
	Diabetic children (2–20 years)	97.5th percentile	4.0	–	7.8	–	1.3	–	
	Diabetic children (2–20 years)	97.5th percentile as sucrose	***800***	–	***1404***	–	***390***	–	
	Diabetic children (2–6 years)	Mean	2.75	–	5.95	–	1.1	–	
	Diabetic children (2–6 years)	Mean as sucrose	**550**	–	**1071**	–	**330**	–	
	Diabetic children (7–10 years)	Mean	1.0	–	2.35	–	0.35	–	
	Diabetic children (7–10 years)	Mean as sucrose	200	–	423	–	105	–	
	Diabetic children (11–14 years)	Mean	1.0	–	2.25	–	0.35	–	
	Diabetic children (11–14 years)	Mean as sucrose	200	–	405	–	105	–	
Not stated	**Canada**								Devitt et al. (2004)
	Diabetic children (2–6 years)	Mean	0.6	–	4.1	0.0	–	0.2	
	Diabetic children (2–6 years)	Mean as sucrose	120	–	**738**	0	–	120	
	Diabetic children (2–6 years)	90th percentile	1.9	–	7.8	0	–	0.9	
	Diabetic children (2–6 years)	90th percentile as sucrose	380	–	***1404***	0	–	***540***	
2002–2003	**Australia and New Zealand**								Food Standards Australia New Zealand (2004)
	Diabetic adults	Mean	0.55	–	2.31	3.26	0.53	0.46	
	Diabetic adults	Mean as sucrose	110	–	**416**	98	**159**	**276**	
	Diabetic adults	90th percentile	1.03	–	5.32	8.76	1.29	1.04	
	Diabetic adults	90th percentile as sucrose	206	–	***958***	263	***387***	***624***	
	Diabetic adults	95th percentile	1.95	–	7.47	11.62	1.89	1.89	
	Diabetic adults	95th percentile as sucrose	390	–	1345	349	567	1134	

Values used to calculate the average and high consumer intakes by diabetics are shown in bold and bold italic font, respectively. The mean intake for sucralose in diabetic children expressed as sucrose in the study by Devitt et al. (2004) was not used in the overall average because it was lower than the values reported for non-diabetic children (Table 5).

to over-predict average intakes by consumers but under-predict the % consumers); brand-specific concentration data were used.

Renwick (1999) – The Danish population study included 76 subjects with diabetes; food/beverage intakes were assessed using

a 7-day food diary; product-specific concentration data were used for tabletop and beverages and maximum permitted use levels for foodstuffs (which would have resulted in slight over-estimation of the total intakes).

Food Standards Australia New Zealand (2004) – The study involved an initial screen of 3529 subjects aged over 12 years and a supplementary study in diabetics which comprised 111 subjects identified in the screen, supplemented by 187 diabetics recruited from other sources, giving a total of 298 subjects with diabetes or impaired glucose tolerance; food/beverage intakes were assessed using a 7-day food diary; product-specific concentration data were used.

The dietary exposure data for aspartame, saccharin and sucralose in Table 6 were used to calculate the overall average and high consumer intakes in diabetic subjects (after excluding the data from Bär and Biermann (1992) because the values reported were abnormally low).

The overall average daily intake for adult diabetic subjects expressed as sucrose equivalents is 280 mg/kg body weight (using values of 427, 354, 216 and 416 for aspartame, 258, 132 and 159 for saccharin and 276 for sucralose), and the overall high consumer daily intake is 897 mg/kg body weight (using values of 509, 1485, 1656, 432, 792 and 958 for aspartame, 2100, 525, 399 and 387 for saccharin and 624 for sucralose).

3.3.3. Daily intakes of approved sweeteners in children with diabetes

The studies that provided data on exposure assessment for children with diabetes were:

Garnier-Sagne et al. (2001) – The study was performed in France on 227 diabetic children aged 2–20 years, which included nine children aged 2–6 years, 38 aged 7–10 years and 133 aged 11–14 years; food/beverage intakes were assessed using a 5-day food diary; product-specific concentration data were used for tabletop, while for foods and beverages, the concentrations were the maximum permitted in the EU; all sugar free products were assumed to be sweetened by the same sweetener (which would result in a significant over-estimation of the actual intakes).

Devitt et al. (2004) – The study was performed in Canada on 56 diabetic children (aged 2–6 years); food/beverage intakes were assessed using an interactive 24 h dietary recall (which would tend to over-predict the long-term average intakes by consumers but under-predict the % consumers); brand-specific concentration data were used.

Only limited data are available for intakes by diabetic children (Table 6). These show an overall average intake expressed as sucrose equivalents of 672 mg/kg body weight (using values of 550 for acesulfame-K, 1071 and 738 for aspartame and 330 for saccharin), and intakes for high consumer diabetic children of 908 mg/kg body weight (using values of 800 for acesulfame-K, 1404 and 1404 for aspartame, 390 for saccharin and 540 for sucralose).

3.4. Conversion of the overall sucrose substitution data into the predicted intake of rebaudioside A

The overall intakes by average and high consumers in the different groups (expressed as sucrose equivalents in mg/kg body weight/day) are summarized in Table 7. These data have been used to provide exposure assessments for average and high consumers of rebaudioside A by assuming a relative sweetness for rebaudioside A which is 200 times that of sucrose.

The predicted dietary exposures for average and high consumers of rebaudioside A for the general population are 1.3 mg/kg body weight per day and 3.4 mg/kg body weight per day, respectively. As expected, the predicted average dietary exposure estimates for children are about 1.5-fold higher than those in adults at 2.1 and 5.0 mg/kg body weight per day for average and high consumer children, respectively.

Table 7
The predicted dietary exposures of rebaudioside A based on sweetener substitution

Population group	Intakes of intense sweeteners expressed as sucrose equivalents in mg/kg body weight per day		Predicted intakes of rebaudioside A in mg/kg body weight per day	
	Average consumer	High consumer	Average consumer	High consumer
Non-diabetic adults	255	675	1.3	3.4
Diabetic adults	280	897	1.4	4.5
Non-diabetic children	425	990	2.1	5.0
Diabetic children	672	908	3.4	4.5

The average and high consumer dietary exposures for diabetic adults are 1.4 and 4.5 mg/kg body weight per day, respectively, which are higher than predicted for the general population. Average predicted intakes by average and high consumer diabetic children are 3.4 and 4.5 mg/kg body weight per day, respectively.

4. Discussion

Given the wealth of survey data on the intake of intense sweeteners, the use of highly conservative budget calculations for a novel sweetener is unjustified and unscientific. The substitution method has the major advantage that it is based on actual intakes of intense sweeteners, but is still considered to be conservative because

i. it is assumed that the novel compound achieves the same market penetration as currently available intense sweeteners,
ii. the analysis focuses on those studies and sweeteners that show the highest sucrose replacement, and studies giving low intakes were not used to calculate the values in Table 7,
iii. the analysis of the dietary exposures of children in Table 7 used data for the age group with the highest intakes,
iv. the analysis provides data for high consumers for whom the intake would reflect brand loyalty,
v. data are available for groups with higher than average intakes, i.e. diabetics and children and
vi. data for Australia and New Zealand, which contribute significantly to the values in Table 6, are for subjects selected from a preliminary screen as likely to have higher than average intakes.

As expected, the highest predicted dietary exposures are in diabetics and children. All predicted dietary exposures are less than 6 mg/kg body weight per day, which would be equivalent to about 300–400 mg per adult.

The molecular weight of rebaudioside A (967) is about three times of that of steviol (318), and therefore, the overall intakes by average and high consumers given in Table 7 are equivalent to approximately 0.4 and 1.1 mg/kg body weight, respectively, when expressed as steviol. The highest predicted dietary exposure, which is in high consumer children, would be equivalent to about 1.7 mg steviol/kg body weight per day. These intakes are all below the temporary ADI defined by the JECFA for steviol glycosides (JECFA, 2005) of 0–2 mg/kg body weight expressed as steviol. In consequence, this analysis shows that the intake of rebaudioside A by average or high consumers would not exceed the JECFA temporary ADI set for steviol glycosides.

Indeed, the calculations made in this paper probably overestimate the potential intake of rebaudioside A because of the assumptions made in many of the studies, such as the use of food groups rather than individual food items and brands, and the use of maximum permitted use levels. In addition, in the future the intense sweetener market is unlikely to be dominated by a single sweetener, as was the case in some of the studies used in this analysis; the presence of multiple sweeteners is likely to reduce the intakes of individual compounds compared with the data given in this paper.

Conflict of interest statement

A.G. Renwick acted as a paid scientific consultant to Cantox in the design of the studies, interpretation and analysis of data and preparation of some of the papers on rebaudioside A published in this issue.

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