The intake of intense sweeteners – an update review

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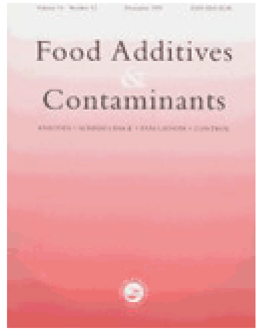

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Journal:	*Food Additives and Contaminants*
Manuscript ID:	TFAC-2005-266.R1
Manuscript Type:	Review
Date Submitted by the Author:	28-Oct-2005
Complete List of Authors:	Renwick, Andrew; University of Southampton, Clinical Pharmacology
Methods/Techniques:	Exposure
Additives/Contaminants:	Sweeteners
Food Types:	Beverages, Processed foods

The intake of intense sweeteners – an update review

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Short Title – Intake of Intense Sweeteners

Summary

Studies on the intakes of intense sweeteners in different countries published since the author's previous review in 1999 indicate that the average and 95th percentile intakes of acesulfame-K, aspartame, cyclamate and saccharin by adults are below the relevant ADI values. Fewer data are available for the newer sweeteners, sucralose and alitame, and because they are recent introductions to the market very low intakes were reported in those countries where they were available at the time of the intake study. Overall there has not been a significant change in the intakes of sweeteners in recent years. The only data indicating that the intake of an intense sweetener could exceed its ADI value were the 95th percentile intakes of cyclamate in children, particularly those with diabetes. This sub-group was identified as having high intakes of cyclamate in 1999, and recent studies have not generated reliable intake data to address this possibility.

Keywords:- Intense sweetener; intake; ADI; acesulfame-K; alitame; aspartame; cyclamate; saccharin; sucralose

Introduction

Intense sweeteners have been subject to scrutiny over the years, both in relation to their safety and the intakes that result from their dietary uses. All approved intense sweeteners have undergone extensive safety testing, and have acceptable daily intakes (ADIs) established by bodies such as the Scientific Committee on Food (SCF) for Europe and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for international trade. The ADI is an intake "that can be ingested daily over a lifetime without appreciable health risk" (WHO, 1987). Risk characterization requires comparison of human intakes with the output of hazard characterization (Renwick et al. 2003), which in the case of sweeteners is the relevant ADI. Intakes may vary over time, due to changing patterns of use and food intake, and therefore risk characterization needs to be undertaken at regular intervals, even though the basic safety data and hazard characterization may not have changed.

The intakes of intense sweeteners have been submitted to a previous systematic review, which evaluated all published data up to 1997 (Renwick 1999). At that time it was clear that the average intakes of all intense sweeteners were below the relevant ADI values. The intakes by the highest consumers of sweeteners other than cyclamate were also well below their ADI values. The highest estimated intakes of cyclamate by diabetics and children were close to or slightly above the ADI. The present paper considers more recent published intake data on intense sweeteners to determine whether the risk characterization of this group of approved food additives has altered. ADI values for the intense sweeteners have been defined by the Joint FAO/WHO Expert Committee on Food

(JECFA) and the Scientific Committee on Food of the European Union (SCF). The ADI values (in mg/kg body weight) for acesulfame-K are 0-15 (JECFA) and 0-9 (SCF), for alitame is 0-1 (JECFA), for aspartame is 0-40 (JECFA and SCF), for cyclamate are 0-11 (JECFA) and 0-7 (SCF), for saccharin is 0-5 (JECFA and SCF), and for sucralose is 0-15 (JECFA and SCF).

Methods used to estimate intakes, and their inherent assumptions

Estimation of the intake of an approved food additive is a potentially complex and costly procedure. Because many of the studies on intense sweeteners in recent years were not of optimal design, the different aspects that should be incorporated into an appropriately designed study are given below.

Study population

i. Should be sufficiently large to define the tail of the distribution of intakes, such as the 90^{th}, 95^{th} or 97.5^{th} percentile of those individuals who consume the additive or sweetener under study (high consumers).

ii. Should include any special groups who would be predicted to have higher than average intakes (such as diabetics for intense sweeteners).

iii. Should include any group that would generally be considered to be of concern irrespective of the subject of the survey, such as pregnant women and children.

Food intake estimation

i. Should include information on the intakes of those specific products that might contain the additive or sweetener under investigation. Less specific product classifications will result in greater predicted intakes and therefore greater overestimation, conservatism and unreliability in the data generated.

ii. Should give reliable measurements of the amounts of the specific food products consumed daily, which will require information on portion size and frequency of ingestion. Food intake estimates derived from a prospective food diary are more reliable than data derived from a retrospective questionnaire.

iii. Should differentiate between products in the same food classification group that contain the subject of the survey and those that do not. This is particularly important in the case of sweeteners, where different sweeteners can occur in different brands. For example, information on "cola" ingestion represents inadequate data because the product could be sweetened with sugar rather than an intense sweetener, with a single approved sweetener, with a blend of approved sweeteners or with a blend of sugar and sweeteners. Reliable data require analyses to be performed using brand-level intake data.

Product composition

i. Ideally the database should include brand-specific data on the concentrations of the additives under study in each product. This information could be obtained from the food producer or by direct measurement, and is particularly important for intense sweeteners since a single food product may contain a blend of different sweeteners.

ii. In the absence of product-specific data, it is common to assume that the concentration present is the maximum permitted under the relevant legislation. Because food additives are not always present at their maximum permitted concentrations, this represents another source of conservatism in the final intake estimation.

Food additive intake calculation

i. The amounts of each food product consumed and concentrations present are multiplied, and the results for different products are summed and divided by the body weight. The use of individual body weights is of critical importance if the study group covers a wide range of body weights. For example, children aged 1-4years vary widely in body weight but are often reported as a single population group; dividing the highest intake in mg per individual per day by the average body weight could result in a significant overestimation.

ii. There is an added complication in the case of cyclamate because the ADI was calculated using toxicity data on its metabolite, cyclohexylamine, and an assumption that a high % of the ingested cyclamate is converted to this active metabolite (Renwick et al., 2004). However, only about 3-4% of the population can metabolize cyclamate to the extent assumed in the ADI calculation, and therefore individual data on the intake of cyclamate does not directly relate to the exposure to cyclohexylamine.

Data presentation

i. Information should be provided on the percentage of the population that consumed the additive, the average intake of the additive by those who consumed the relevant foods and beverages (consumers only) and the intake by "high consumers", such as the 95th or 97.5th percentile of the distribution of intakes by consumers. Data for "consumers only" are normally reported because the 95% intake of the additive for the total population would not be representative of high intakes if only a small proportion of the total population consumed foods containing the additive.

Time-base for intake estimation

i. It is widely recognized that the correct intake for comparison with the ADI as part of risk characterization would be the average long-term intake by an individual. Because the reliability of intake studies decreases with increasingn duration, reliable data can be obtained for only about 1-2 weeks of diary collection.

ii. Intake data for a single day underestimates the % of a population who will be consumers of an additive, but can grossly overestimate the average intake in those individuals who do report intake of the additive on the day in question.

The intake studies on intense sweeteners conducted since the previous review (Renwick, 1999) are outlined below in chronological order of publication, with a description of the findings and the strengths and weaknesses of the study design.

Recent intake studies on intense sweeteners.

Recent studies are listed in Table 1 in chronological order of publication. They have investigated different population groups in different countries and represent a significant body of new data.

Leclercq et al. (1999).

This was a specific study on the intakes of intense sweeteners in Italian teenagers using a comprehensive 14-day food diary.

Study population – 212 teenagers (aged 13-19 years) were recruited from a secondary school in Rome.

Country – Italy.

Time of intake data collection – September 1996 to December 1996.

Nature of intake data – Prospective 14-day food diary with brand information collected and the presence of sweeteners determined from product labels. The amounts of each product consumed on each occasion were defined as small, medium or large. The data were analyzed for acesulfame-K, aspartame, cyclamate and saccharin.

Product concentration data – Data were obtained from the product manufacturer.

Results – The major sources for acesulfame-K, aspartame and cyclamate were beverages and chewing gum, while for saccharin most of the intake was from table-top products. The means and maximum intakes of all sweeteners were less than 1mg/kg body weight/day and therefore below the corresponding ADI values.

Strengths – The results represent a comprehensive assessment of sweetener intakes using the best practical approach. Intakes were calculated using individual body weights and the results were 14-day averages.

Weaknesses – The sample was from a single school of "medium social class", and therefore not representative of teenagers in general. Other age groups and high potential consumers such as diabetics were not included.

Conclusions – The patterns of sweetener intake were similar to previous publications and the intakes were well below the ADI values. The authors used the dietary pattern for the whole group to predict that intakes of cyclamate or saccharin could approach the ADI but only if subjects had high intakes of both soft drinks and table-top products and only if sugar was substituted in these items with either cyclamate or saccharin; this conclusion is consistent with the more theoretical calculations made by other studies.

Wilson et al. (1999).

This study used 24 hour urinary excretions of acesulfame-K and saccharin as biomarkers of intake. The method would only be applicable to these two sweeteners, because they are almost completely absorbed from the intestine and excreted unchanged in urine. The method was validated by giving known amounts of acesulfame-K and saccharin to different volunteers and measuring their urinary excretion over the following 24 hours. The use of the urinary biomarker was then compared with intake estimates derived from a dietary questionnaire specifically on sweetener intake for the same 2-day period, and it is this part of the study which is presented below.

Study population – 188 volunteers aged 3-74 years who were family and friends of the laboratory staff. There were 78 adult males, 85 adult females, 19 boys and 6 girls.

Country – UK.

Time of intake data collection – Not stated.

Nature of intake data – Sweetener intake was measured using a 48 hour intake diary, with information provided on the amounts and brands consumed. The urinary biomarker data were collected only on the second day of the food diary record. The urinary data were accepted only if there was evidence of a complete 24 hour collection based on the urinary recovery of the marker substance p-aminobenzoic acid which was given as three doses with meals.

Product concentration data – Data were supplied by the food product manufacturers.

Results – The mean intakes of acesulfame-K and saccharin determined by the questionnaire were 45mg/day and 33mg/day respectively, and these values were slightly higher than the values derived from the urinary biomarker (35mg/day and 23mg/day respectively). The correlation between the two measurements of intake was analysed in 138 subjects submitting complete urine collections, as judged by PABA recovery, was described by the authors as showing generally good agreement ($R^2 = 0.6$ to 0.7). The highest intakes determined by urinary excretion and questionnaire were 101 and 111mg/day respectively for saccharin and 110 and 168mg/day respectively for acesulfame-K.

Strengths – The intake diaries were comprehensive and could be related to the urinary biomarker data. The questionnaire and concentration data were analyzed down to brand-level detail.

Weaknesses – The study used a small number of subjects for an intake survey, because it was primarily an exercise for the development and validation of biomarkers. The data refer to a 48 hour period only and do not represent long-term average intakes. Detailed results from the intake questionnaire were not given in the publication. The intakes were reported in mg/day.

Conclusions – These data provide an interesting approach for the future, rather than giving comprehensive intake data that can be compared with previous studies. The mean intakes of acesulfame-K and saccharin were reported to be below their ADI values. Assuming an average body weight of 60kg for an adult, the maximum intakes of acesulfame-K and saccharin corresponded to less than 1.5mg/kg body weight/day.

Garnier-Sagne et al. (2001).

This study focused on diabetic children, and used a worst-case analysis to determine the potential for the ADI to be exceeded in this group.

Study population – 400 subjects aged 2-20 years, who were recruited from the French Aid for Young Diabetics Association, were sent a food intake questionnaire; 227 completed forms were returned.

Country – France.

Time of intake data collection – June to October 1997.

Nature of intake data – The questionnaire included a 5-day prospective food diary which paid particular attention to the types and amounts of sweetened foods that were consumed. The forms were completed by the individual or a parent.

Product concentration data – A sweetener concentration database was constructed in which it was assumed that all sugar-free products had been sweetened with the same sweetener and that the concentrations of acesulfame K, aspartame and saccharin used were the maximum permitted under European legislation. Such a highly conservative method was used in order to give theoretically maximum daily intakes or TMDIs.

Results – The mean TMDIs of acesulfame K, aspartame and saccharin by consumers were 1.1, 2.4 and 0.4mg/kg body weight respectively, and the 97.5th percentile TMDIs were 4.0, 7.8 and 1.3mg/kg body weight respectively, indicating that intakes by high consumers did not exceed the ADI values.

Strengths – The study calculated the maximum potential intakes based on 5-day averages.

Weaknesses – The assumptions about the distribution of sweeteners in food products and the concentrations used are too conservative to allow the data to be taken as realistic estimates, but they do provide an upper bound on the possible intakes of each individual sweetener in the population group predicted to have the highest intake on a body weight basis. Cyclamate intake was not among the sweeteners measured.

Conclusions – The data appear to be a worst-case analysis of intake in a group of the population with high potential intakes. The study supports the findings of other studies that the intakes of acesulfame K, aspartame and saccharin would not exceed their ADI values, even in the highest consumers.

Food Standards Agency UK (2003).

This study focused on intakes by children, because previous survey data had indicated that this group was likely to have sweetener intakes above the ADI values due to their high intakes of sweetened soft drinks, when expressed per kg of body weight.

Study population – 1110 children aged 1.5 to 4.5 years across 12 areas of the UK.

Country – UK.

Time of intake data collection – January to September 2001.

Nature of intake data – The intakes of acesulfame-K, aspartame, cyclamate and saccharin from beverage consumption were measured using a 7-day diary. The volumes of different types or categories of beverage consumed (carbonated, dilutable and powdered drinks, tea/coffee and natural still drinks) were recorded. The report does not state clearly whether the drinks recorded were separated into those sweetened with sugar and low-calorie sweeteners or whether brand information was obtained, but it is unclear how the product concentration data could have been used without such detailed information.

Product concentration data – Data obtained from the food product manufacturer.

Results – The average daily intakes of acesulfame K, aspartame, cyclamate and saccharin by consumers were 0.92, 3.38, 4.46 and 1.16 mg/kg body weight respectively, and the 97.5th percentile intakes were 3.72, 12.01, 14.07 and 3.83 mg/kg body weight respectively, indicating that the intakes of cyclamate by high consumers would exceed the ADI values set by the JECFA and the SCF.

Strengths – The study focused on a very large group of children with high potential intakes of soft drinks expressed per kg body weight. The results are 7-day averages.

Weaknesses – The survey was restricted to beverages only, but this is the main source in the age group studied. In some cases, assumptions had to be made about body weight, which can vary widely across the age range 1.5 to 4 years. It is not clear if the data for high consumers related to recorded body weights or to assumptions. It is not clear to what extent brand level information was used because the beverages appear to have been reported as groups rather than brands (the word "brand" does not appear in the report)

Conclusions – The data appear to be a worst-case analysis of intake in a group of the population with high potential intakes. The results support the findings of other studies that it is only cyclamate where the ADI might be exceeded by the highest intakes in young children.

Ilback et al. (2003).

This study investigated the intakes of acesulfame-K, aspartame, cyclamate and saccharin in diabetic children and adults.

Study population – Subjects were recruited randomly from members of the Association of Diabetics in Stockholm. Data were collected for 243 children (aged 0-15 years), 236 adult males (aged 16-90 years) and 311 adult females (aged 16-90 years).

Country – Sweden.

Time of intake data collection – January 1999.

Nature of intake data – Intakes were estimated from a food-frequency questionnaire (retrospective but of undefined duration) concerning the amounts and frequency of intakes of diet soda, cider, fruit syrup, tabletop sweeteners, light ice cream, chewing gums, sweets, yoghurt, vitamin C supplements, throat lozenges and fluid and dried table sweeteners. The individual intake estimates were based on the consumption on a single occasion. Although not stated clearly in the original publication, it appears that the "worst-case" estimates were made by addition of the maximum intake for each product recorded in a single day. This would be highly conservative because the main sources of sweetener intake were fruit syrups, diet sodas and cider and a high consumption of one source on a single day would not coincide with high intake of the other two sources on the same day.

Product concentration data – The maximum permitted concentrations for each product category were used and it was assumed that the total intake of that product contained a single sweetener.

Results – The main sources of intake were tabletop sweeteners and beverages, especially fruit syrups in children . Although it is unclear from the data presentation, it appears that the average intakes for each of the sweeteners in all groups, using these highly conservative assumptions were below the respective ADI values. Estimates of the intakes by high consumers were based on the data for the 10 or 20 individuals in each population subgroup with the highest intakes from all sources. The intakes of aspartame (46mg/kg body weight per day) and saccharin (about 6.3mg/kg body weight per day) slightly exceeded the relevant ADI values for the top 10 children. The intakes for the top 10 adults were below the ADI values. The intakes of cyclamate for the 10 children with the highest intakes (about 35mg/kg body weight per day) were about 3 times the JECFA ADI (0-11mg/kg body weight per day) and 5 times the more recent SCF ADI (7mg/kg body weight per day) for cyclamate. The intake for the highest 10 adults slightly exceeded the JEFCA ADI.

Strengths – The study focused on diabetics because this was the group expected to have the highest potential intakes. Individual body weights were used.

Weaknesses – The authors described the findings as a “worst-case” analysis based on maximum permitted concentrations and maximum intake on a single day. The inclusion of conservative assumptions at each point in the intake calculation results in an unrealistic intake estimate.

Conclusions – The data show that only cyclamate could have an intake significantly above its ADI, and this would only be in a proportion of children. Extrapolation of this observation to non-diabetic children is difficult because the children studied had a high intake of table-top sweeteners, an observation not made for non-diabetic children in other intake studies. The use of highly conservative worst-case assumptions means that this study should be used to identify a possible problem, and should not be interpreted as proving the existence of a real problem. It is unclear why a study which has the power only for hypothesis generation should be performed in 1999, at a time when it was clear that diabetic children consuming cyclamate would represent a group where the ADI for a sweetener might be exceeded.

Serra-Majem et al. (2003).

This was an epidemiological study to investigate the possibility of a relationship between male fertility in humans and the intakes of cyclamate and its metabolism to cyclohexylamine. Cyclohexylamine produces testicular atrophy in experimental animals and this effect was used as the basis for calculation of the ADI of cyclamate.

Study population – 405 adult males (30-50 years) with clinically defined infertility and 379 adult male controls (30-50 years).

Country – Spain.

Time of intake data collection – February 1994 – December 1996.

Nature of intake data – A specially designed retrospective food-frequency questionnaire was used but no details were given.

Product concentration data – Information from the cyclamate manufacturer in Spain was used.

Results – 32% of cases and 29% of controls consumed cyclamate, with 3% and 2% having intakes greater than 5mg/kg body weight/day.

Strengths – The study employed large group sizes, but this was essential because the majority of individuals do not metabolize cyclamate to cyclohexylamine (Renwick et al., 2004). This was the only recent study that has tried to relate cyclamate intake to the excretion of its metabolite cyclohexylamine in urine.

Weaknesses – The population investigated was adult males only, and intake was based on a food frequency questionnaire.

Conclusions – The intake data support the findings of previous studies in a population that probably has higher than average cyclamate intakes because of the widespread use of cyclamate in Spain and the use of this sweetener in the popular drink "gaseosa" - a combination of carbonated water containing saccharin and cyclamate taken with wine.

Arcella et al. (2004).

This was a follow up study to that of Leclercq et al. (1999) in a larger study group which included increased numbers of individuals who reported high intakes.

Study population – A randomly selected sample of 3982 teenagers in Rome completed a food frequency questionnaire designed to identify adolescents who were high consumers of sugar-free soft drinks or tabletop sweeteners. From the results, intakes in a group of

362 individuals aged 14-17 years were measured using a food diary as described below. The food diary was completed by 125 males and 108 females selected at random and by 139 females who were high consumers of either diet soft drinks or table-top products or both.

Country – Italy

Time of intake data collection – October 2000 to May 2001 (three 4-day food diaries)

Nature of intake data – The randomly selected group and the identified female high consumers from the food frequency questionnaire completed a 4-day food diary on three separate occasions, with different subjects in each group covering all days of the week. Brand information was collected and presence of sweeteners determined from the product label. The amounts of each product consumed on each occasion were defined as small, medium or large. Data were analyzed for saccharin, aspartame, acesulfame-K and cyclamate.

Product concentration data – Data were obtained from the product manufacturer.

Results – The mean and 95th percentile intakes of all sweeteners in all individuals who completed the 4-day food diary were well below the corresponding ADI values. The 95th percentile of cyclamate intake in the selected group of female high consumers of sugar-free soft drinks was 0.55mg/kg body weight/day (5% of the JECFA ADI), while the corresponding intakes for acesulfame-K, aspartame and saccharin were 0.25, 0.30 and 0.0mg/kg body weight/day (less than 2% of the ADI values).

Strengths – This study provides a comprehensive assessment of the intake using the best practical approach. Intakes were calculated using individual body weights. Results were averages of three 4-day diaries collected in different months for all subjects and therefore are best estimates of long term average intakes.

Weaknesses – The study did not include other groups with high predicted intake, i.e. children or diabetics

Conclusions – The intakes were well below the ADI values. The results of this study are similar to the study of Leclercq et al. (1999) in Italian teenagers.

Devitt et al. (2004).

This study focused on a small number of children treated for Type 1 diabetes mellitus.

Study population – A group of 56 children aged 2-6 years were recruited from a total of 116 eligible subjects at the Diabetic Clinic at the Hospital for Sick Children in Toronto.

Country – Canada.

Time of intake data collection – Data were collected over a period of 7 months (dates not given).

Nature of intake data – Intake estimates were based on a single interactive 24-hour dietary recall by the parents. Products containing acesulfame-K, aspartame, cyclamate and sucralose were identified by showing product labels to the parents. Saccharin was not used as a food additive in Canada at this time.

Product concentration data – Data were obtained from the label or the product manufacturer.

Results – The proportion of the group who consumed products containing acesulfame-K, aspartame, cyclamate and sucralose were 25%, 43%, 12% and 2% respectively. The mean and 90^{th} percentile intakes of cyclamate and sucralose were below 1mg/kg body weight/day, indicating little market penetration by these sweeteners. The mean and 90^{th}

percentile intakes of acesulfame-K were 0.6 and 1.9mg/kg body weight/day respectively. The mean and 90th percentile intakes of aspartame were 4.1 and 7.8mg/kg body weight/day respectively.

Strengths – The study focused in diabetic children. The absence of saccharin in food products and the low use of cyclamate mean that the intake data for aspartame represent a worst-case scenario.

Weaknesses – The intake data were based on a single recall assessment and would over-estimate average intakes but under-estimate the % consumers.

Conclusions – The intakes for all sweeteners were below their ADI values.

Food Standards Australia and New Zealand (2004).

This study was a follow up to the 1994 Australian study which showed that high consumers of saccharin and cyclamate could have intakes that approached or exceeded the ADI. The survey comprised 3 phases; an initial national telephone screen to determine patterns of food intake, a diary survey of potential high consumers of products containing intense sweeteners identified in the screen and a supplementary survey of individuals with diabetes or impaired glucose tolerance.

Study population – The initial screen, which was in 3529 individuals aged over 12 years and selected to be representative of the general population, was used to identify 400 respondents with high potential intakes of intense sweeteners. The supplementary study in diabetics comprised 111 subjects identified within the group of 400 high consumers of products containing intense sweeteners and these were supplemented by 187 diabetics recruited from other sources giving a total of 298 subjects with diabetes or impaired glucose tolerance.

Country – Australia and New Zealand.

Time of intake data collection – The initial screen was performed betweeen September 2002 to February 2003. A diary agreement letter was sent to participants in February 2003, but the exact time span of diary completions was not given in the report.

Nature of intake data – The intakes in the potential high consumers used a prospective 7-day food diary that focused on key products, including details of brands that would contain intense sweeteners.

Product concentration data – Data were supplied in confidence by product manufacturers. The diary study analyzed for acesulfame-K, alitame, aspartame, cyclamate, saccharin and sucralose

Results – The initial screen showed that the consumption patterns were similar in the two countries, and that diabetics consumed more products containing intense sweeteners. Overall there were significant increases in the average daily intakes of certain products containing intense sweeteners, particularly carbonated soft drinks amongst Australian consumers aged 12-39 years, compared with the data for 1994 (the changes are discussed in the 2004 report). The 7-day food diary in the selected sub-group showed that the intakes of acesulfame-K were increased compared with the 1994 data. The mean intakes of all sweeteners were below their respective ADI values, with means in the group of 400 high consumers of intense sweeteners (see above) of 0.4, <0.1, 2.4, 2.1, 0.3 and 0.2 mg/kg body weight/day for acesulfame-K, alitame, aspartame, cyclamate, saccharin and sucralose respectively. The corresponding 95th percentile intakes were 1.4, <0.1, 7.0, 9.3, 2.4 and 2.3 mg/kg body weight/day respectively. The mean intakes in the 298 diabetics were 0.6, <0.1, 2.3, 3.3, 0.5 and 0.5 mg/kg body weight/day for acesulfame-K, alitame, aspartame, cyclamate, saccharin and sucralose respectively and the 95^{th} percentile intakes were 2.0, <0.1, 7.5, 11.6, 1.9 and 1.9 mg/kg body weight/day respectively.

Strengths – A major strength of this study is the size of the cohort from which the high consumers and diabetics were selected. It was a recent study in a population where 6 different intense sweeteners were available. The study appears to have been conducted in February which corresponds to a potentially high summer intake of beverages containing intense sweeteners.

Weaknesses – The participants were not given an individual interview, and the absence of a personal explanation of the protocol may have reduced understanding and compliance with diary completion.

Conclusions – The means and 95^{th} percentile intakes were below the ADI values of the different sweeteners in the selected high consumers and diabetics, with the exception of cyclamate in diabetics, where the 95^{th} percentile slightly exceeded the JECFA ADI value.

Van Rooij-Van Den Bos et al. (2004)

This study combined data on the concentrations of intense sweeteners in retail food available in 2003 with data from the third Dutch National Food Consumption Survey 1997/1998 in order to provide updated intake estimates.

Study population – Data from the National Food Consumption Survey were used, which was based on 6250 persons in 2774 households with all household members asked to participate.

Country – The Netherlands.

Time of intake data collection – April 1997 to March 1998.

Nature of intake data – Data were collected using a two-day diary. Food consumed at home was recorded in the diaries by the person who usually prepared the meal for the household. Each participant recorded foods consumed out of the house. All products in a single food coding in the food composition database that could contain an intense sweetener were assumed to contain the same sweetener. If the food product could not be related to an existing food coding the intake was assumed to be that of the closest non-sweetened coding with correction for the market share of sweetened products in that food coding. For worst-case calculations, the highest consumptions (95^{th} percentiles) of soft drink, lemonade syrup, yogurt drink and chocolate milk were calculated assuming that all of the products in each category consumed were sweetened with a single sweetener using the average measured concentration.

Product concentration data – Concentrations were measured in food products that were purchased in 2003 and which was likely to contain an intense sweetener based on the label.

Results – The estimated average and 95^{th} percentile intakes of acesulfame-K, aspartame, cyclamate and saccharin were all 1mg/kg body weight or less. The highest calculated 95^{th} percentile intakes were in the 1-4 years age range and the highest value in this age group was for cyclamate (1.1mg/kg body weight/day). The results from the worst-case calculations indicated that for the whole population (1-97years old) the 95^{th} percentile consumers of soft drinks had intakes of 2, 2, 4 and 0.5mg/kg body weight/day of acesulfame-K, aspartame, cyclamate and saccharin respectively. The corresponding daily intakes for the 1-4 years age range were 6, 8, 14 and 2mg/kg body weight respectively.

Strengths – The concentrations of sweeteners were measured directly.

Weaknesses – The intakes of foods categories are based on national estimates and therefore major assumptions had to be made. Intake and concentration data do not relate to the same time period or to the same products.

Conclusions – Despite the conservative assumptions made the mean and 95th percentile intakes were below the ADI values. The worst-case calculations of the intakes of sweeteners indicated that the only sweetener with the potential to exceed the relevant ADI was cyclamate in 1-4 year olds.

In addition to the studies outlined above, limited information has been published in summary form for Korea and Japan in which the bases for the intake estimates were not clearly explained and the results were not corrected for body weight. The estimated intakes of acesulfame-K and saccharin in Koreans were 1.3 and 4.1mg/person/day and the theoretical maximum daily intakes were 31 and 106mg/person/day, values that are well below the corresponding ADI values (Kim et al. 2004). The average daily intakes of acesulfame-K, aspartame, saccharin and sucralose in Japan were reported as 0.8, 7.3, 0.7 and 0.4 mg/person (Yomota et al. 2002).

Estimates of sweetener intakes in the European Union are given in the European Commission Report on Dietary Food Additive Intake. Estimates were made using the "Tier 2" approach, in which the theoretical intake was calculated by combining the mean

528 national food consumption data of the population with the maximum permitted use levels
529 of the sweetener, and the "Tier 3" approach, in which the theoretical intake was
530 calculated by combining the mean national food consumption data of the whole
531 population with the actual use levels of the sweetener. The results were expressed as the
532 % of the corresponding SCF ADI values (using the old SCF ADI for cyclamate of 0-
533 11mg/kg body weight per day). The ranges of intakes in adults were 2-37% for
534 acesulfame-K (Tier 2 data for Denmark, France, Italy, The Netherlands, UK and Norway)
535 and 0-11% for cyclamate (Tier 2 data for Denmark, France, Italy, The Netherlands, UK
536 and Norway). The ranges of intakes in children were 3-107% for acesulfame-K (Tier 3
537 data for France, The Netherlands and UK), 1-40% for aspartame (Tier 2 data for The
538 Netherlands and UK), 1-74% for cyclamate (Tier 2 data for France, The Netherlands and
539 UK) and 2-51% for saccharin (Tier 2 data for France, The Netherlands and UK).

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542 **Discussion**

543 The recently published studies can be divided into 4 types.

544 i. Those that were of comprehensive design and capable of producing realistic
545 intake estimates (Leclercq et al. 1999, Arcella et al. 2004 and Food Standards
546 Australia New Zealand 2004).

547 ii. Those where the data presentation make it difficult to judge the extent of
548 conservatism in the reported intake estimates (Food Standards Agency UK
549 2001).

550 *iii.* Those that included significant weaknesses or conservative assumptions, such
551 that the data obtained can be regarded as "worst-case" estimates only, or

which combined national dietary survey data with approved use levels and do not really provide reliable new information (Garnier-Sagne et al. 2001, Ilback et al. 2003, Devitt et al. 2004 and van Rooij-van den Bos et al. 2004).

iv. Those that were designed primarily for other purposes or to address specific issues, such as assessing exposure from urinary excretion data for the sweetener and/or its metabolites (Wilson et al.1999 and Serra-Majem et al. 2003).

Comparisons of the data from these studies with the findings reviewed previously (Renwick, 1999) show that the intakes of intense sweeteners have not increased substantially in the past 10 years. The recent studies consistently show that the average and 95th percentile intakes of all sweeteners by adults are below the corresponding ADI values. One of the most comprehensive and reliable of the recent studies was that of Leclercq et al. (1999) which focused on a potential high intake group, used a 14-day prospective diary and obtained brand-related concentration data. This study found that the mean and maximum intakes of the sweeteners investigated (aspartame, acesulfame-K, cyclamate and saccharin) were below 1mg/kg body weight/day. The follow-up study of Arcella et al. (2004) reached similar conclusions while focusing on individuals identified as high consumers. The large and comprehensive study by Food Standards Australia New Zealand (2004) showed that, with the exception of the 95th percentile intake of cyclamate in diabetics, the means and 95th percentile intakes of intense sweeteners were below the corresponding ADI values.

Recent studies have focused on children (Food Standards Agency UK 2001, Garnier-Sagne et al. 2001, Ilback et al. 2003 and Devitt et al. 2004) because of their higher intakes of foods and beverages on a body weight basis, and on diabetics (Garnier-Sagne et al. 2001, Ilback et al. 2003, Devitt et al. 2004 and Food Standards Australia New Zealand 2004) because of their higher potential intakes of intense sweeteners. The studies reported have used a variety of conservative assumptions, and therefore do not provide definitive data, but simply confirm that these groups may have higher than average intakes.

The only sub-group analyses that have indicated that the 95th percentile intake of a sweetener may exceed the ADI are for cyclamate in children, particularly those with diabetes. Such a conclusion was apparent from calculations available at the time of the earlier review (Renwick 1999), and recent publications do not include a specifically designed study producing reliable data for this group, but simply confirm the possibility by further theoretical worst-case calculations. Resolution of this theoretical possibility will require a specifically-designed study using a quantitative prospective 5-day or 7-day diary combined with brand-specific data on intakes and concentrations, in which any dilution of beverages for children is recorded accurately. The recent reduction in the ADI of cyclamate from 0-11mg/kg body weight/day to 0-7 mg/kg body weight/day by the EU-SCF (SCF, 2000) has resulted in changes to the uses of cyclamate. Any specifically-designed study should be undertaken after these changes have taken effect and the new pattern of uses has stabilized. Interpretation of the intake data on cyclamate is also complex because the ADI is based on the effects of its metabolite cyclohexylamine, and

598 only a small percentage of humans, about 3-4% of the population, are able to form significant amounts of this metabolite (Renwick et al. 2004). Theoretically, the best study design for estimating exposure to cyclohexylamine following cyclamate ingestion would be based on that of Serra-Majem et al. (2003), and combine an optimized food-diary, as outlined above, with measurements of the daily urinary excretion of cyclamate and cyclohexylamine. However such a design would not be practicable for studying a group of diabetic children that was large enough to include individuals with high cyclamate metabolizing ability.

REFERENCES

Arcella D, Le Donne C, Piccinelli R, Leclercq C. 2004. Dietary estimated intake of intense sweeteners by Italian teenagers. Present levels and projections derived from the INRAN-RM-2001 food survey. Food and Chemical Toxicology 42: 677-685.

Devitt L, Daneman D, Buccino J. 2004. Assessment of intakes of artificial sweeteners in children with type 1 diabetes mellitus. Canadian Journal of Diabetes 28: 142-146.

European Commission Report on Dietary Food Additive Intake in the European Union. http://europa.eu.int/comm/food/fs/sfp/addit_flavor/flav15_en.pdf

Food Standards Agency UK. 2003. Diary survey of the intake of intense sweeteners by young children from soft drinks. No. 36/03 Month 2003. Available at e-mail: fsalibrary&info@foodstandards.gsi.gov.uk

Food Standards Australia New Zealand. 2004. Consumption of intense sweeteners in Australia and New Zealand: Benchmark Survey 2003. Evaluation Report Series No8. ISBN 0 642 34598 8

Garnier-Sagne I, Leblanc JC, Verger P. 2001. Calculation of the intake of three intense sweeteners in young insulin-dependent diabetics. Food and Chemical Toxicology 39: 745-749.

Ilback N-G, Alzin M, Jahrl S, Enghardt-Barbieri H, Busk L. 2003. Estimated intake of the artificial sweeteners acesulfame-K, aspartame, cyclamate and saccharin in a group of Swedish diabetics. Food Additives and Contaminants 20: 99-114.

Kim HY, Yoon HJ, Hong KH, Choi DJ, Park SK, Park HO, Jin MS, Choi WJ, Park SY, Lee KJ, Lee CW. 2004. Estimated dietary intake of sodium saccharin and acesulfame potassium in Koreans. Korean Journal of Food Science and Technology 36: S804-S811.

Leclercq C, Berardi D, Sorbillo MR, Lambe J. 1999. Intake of saccharin, aspartame, acesulfame-K and cyclamate in Italian teenagers: present levels and projections. Food Additives and Contaminants 16: 99-109.

Renwick AG. 1999. Intake of intense sweeteners, *In:* Corti, A., *ed. Low-Calorie Sweeteners: Present and Future, World Review of Nutrition and Dietetics,* Basel, Karger, pp 178-200.

Renwick AG, Barlow SM, Hertz-Picciotto I, Boobis AR, Dybing E, Edler L, Eisenbrand G, Greig JB, Kleiner J, Lambe J, Müller DJG, Smith MR, Tritscher A, Tuijtelaars S, van den Brandt PA, Walker R, Kroes R. 2003. Risk characterization of chemicals in food and diet. Food and Chemical Toxicology 41: 1211-1271.

Renwick AG, Thompson JP, O'Shaughnessy M, Walter EJ. 2004. The metabolism of cyclamate to cyclohexylamine in humans during long-term administration. Toxicology and Applied Pharmacology 196: 367-380.

SCF, 2000. Scientific Committee on Food of the European Commission. Opinion on cyclamic acid and its sodium and calcium salts (expressed on 9th March 2000). (http://europa.eu.int/comm/food/fs/sc/scf/outcome_en.html)

Serra-Majem L, Bassas L, Garcia-Glosas R, Ribas L, Ingles C, Casals I, Saavedra P, Renwick AG. 2003. Cyclamate intake and cyclohexylamine excretion are not related to male fertility in humans. Food Additives and Contaminants 20: 1097-1104.

van Rooij-van den Bos L, Konings EJM, Heida P, van Hamersveld ICM, van der Wielen J, Kooijman M. 2004. Onderzoek naar de kunstmatige zoetstoffen Sacharine, Aspartaam, Acesulfaam-K en Cyclamaat in levensmiddelen. (Investigation on the artificial sweeteners saccharin, aspartame, acesulfame-K and cyclamate in food products). Projectnummer: ZD 03 K120. Dutch Food Safety Authority.

WHO. 1987. Principles for the Safety Assessment of Food Additives and Contaminants in Food. Environmental Health Criteria 70, 174pp. World Health Organization, Geneva.

Wilson LA, Wilkinson K, Crews HM, Davies AM, Dick CS, Dumsday VL. 1999. Urinary monitoring of saccharin and acesulfame-K as biomarkers of exposure to these additives. Food Additives and Contaminants 16: 227-238.

Yomota C, Onishi-abe Y, Tanamoto K, Aizawa H, Osawa T, Miyazaki T, Mouri T, Yamato Y, Tamanaha K. 2002. A study on intake of eight kinds of sweeteners by market basket method in fiscal year 2002. Paper presented at the Japanese Society of Food Chemistry's 9th General Assembly and Academic Convention.

Date of study	Subjects studied	Design	Average intake by consumers (% ADI)	Intake by high consumers[1] (% ADI)	Ref.
1996	212 teenagers (aged 13-19 years) in Italy	Prospective 14-day food diary with brand information	0.1% (Ace), 0.1% (Asp), 2.2% (Cyc) and 4.2% (Sac)	1.5% (Ace), 1.0% (Asp), 5.6% (Cyc) and 10.6% (Sac)[2]	Leclercq et al. 1999
Not stated	188 subjects (aged 3-74 years) in UK	Designed to validate the use of urinary excretion of acesulfame-K and of saccharin as biomarkers of intake.	9% (Ace) and 14% (Sac)	Not reported	Wilson et al. 1999
1997	227 insulin-dependent diabetics (aged 2-20 years) in France	A 5-day prospective food diary, with the assumption that all sugar-free products contained the same sweetener	7% (Ace), 6% (Asp), 8% (Sac)	27% (Ace), 20% (Asp), 26% (Sac)	Garnier-Sagne et al. 2001
2001	1110 children (aged 1.5-4.5 years) in UK	A 7-day diary of beverage consumption, but brand information was not obtained	6% (Ace), 8% (Asp), 41% (Cyc) and 23% (Sac)	25% (Ace), 30% (Asp), 128% (Cyc) and 77% (Sac)	Food Standards Agency UK 2003
1999	243diabetic children aged (0-15 years) and 547 adult diabetics (aged 16-90 years) in Sweden	A retrospective food-frequency questionnaire; maximum permitted concentration for each product category and assumed	Intakes were <ADI values for Ace, Asp, Cyc and Sac, but the published data are difficult to interpret	45% (Asp), 114% (Cyc) and 46% (Sac) in adults and 115% (Asp), 317% (Cyc) and 126% (Sac) in children[3]	Ilback et al. 2003

1994-1996	784 men (aged 30-50 years) in Spain	A retrospective food-frequency questionnaire designed to focus on cyclamate intake in relation to its metabolism	6% (Cyc)[4]	Not reported	Serra-Majem et al. 2003
2000-2001	362 teenagers (aged 14-17 years) (including 139 female high consumers of sugar-free soft drinks) in Italy	Three prospective 4-day food diaries with brand information	0.3% (Ace), 0.2% (Asp), 4.5% (Cyc), 0.7% (Sac) in the female high consumers	0.7% (Ace), 0.4% (Asp), 4.5% (Cyc), 0.7% (Sac) in the female high consumers	Arcella et al. 2004
Not stated	56 diabetic children (aged 2-6 years) in Canada	An interactive 24-hour dietary recall by the parents with food items identified from product labels	4% (Ace), 10% (Asp), 0% (Cyc) and 1% (Suc)	13% (Ace), 20% (Asp), 0% (Cyc) and 6% (Suc)	Devitt et al. 2004
2002-2003	298 diabetics and 299 non-diabetic subjects with high intakes of sugar-free products (aged 12-60+ years) in Australia and New Zealand	A prospective 7-day food diary that included brand information	3% (Ace), 6% (Asp), 27% (Cyc), 9% (Sac) and 3% (Suc)	9% (Ace), 19% (Asp), 85% (Cyc), 47% (Sac) and 15% (Suc)	Food Standards Australia New Zealand 2004
1997-1998	National Food Survey on 6250 subjects (aged 1-97 years) in The	A prospective 2-day food diary	<0.5% (Ace), <0.3% (Asp), 0.9% (Cyc) and 0.4% (Sac)	0.7% (Ace), 1.3% (Asp), 3.6% (Cyc) and 0.4% (Sac)	van Rooij-van den Bos et al. 2004

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Table 1 – Summary of recent studies on the intakes of intense sweeteners (in chronological order of publication).

[1] – 95th percentile intakes used for high consumer data except for Garnier-Sagne et al. 2001(97.5th percentile of the theoretical maximum daily intake), FSA, 2003 (97.5th percentile) and Devitt et al., 2004 (90th percentile)

[2] – maximum reported intake

[3] – intakes by the 10 children and 10 adults with the highest intakes (values read from published histograms)

[4] – the arithmetic mean of the median intakes reported for cases and controls which include non-consumers; the maximum intake was reported to be less than the ADI

Ace – Acesulfame-K; Ali – Alitame; Asp – Aspartame; Cyc – Cyclamate; Sac – Saccharin: Suc – Sucralose.

The % ADI values are calculated using the ADIs established by the WHO/FAO Joint Expert Committee on Food Additives of 0-15 (Ace), 0-1 (Ali), 0-40 (Asp), 0-11 (Cyc), 0-5 (Sac) and 0-15 (Suc) mg/kg body weight per day.