The intake of intense sweeteners – an update review

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1 **The intake of intense sweeteners – an update review**

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15 Short Title – Intake of Intense Sweeteners

16 Summary

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

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

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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 90th, 95th or 97.5th 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

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- 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.

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

104 *Food additive intake calculation*

- 105 i. The amounts of each food product consumed and concentrations present are
106 multiplied, and the results for different products are summed and divided by
107 the body weight. The use of individual body weights is of critical importance
108 if the study group covers a wide range of body weights. For example, children
109 aged 1-4years vary widely in body weight but are often reported as a single
110 population group; dividing the highest intake in mg per individual per day by
111 the average body weight could result in a significant overestimation.
- 112 ii. There is an added complication in the case of cyclamate because the ADI was
113 calculated using toxicity data on its metabolite, cyclohexylamine, and an
114 assumption that a high % of the ingested cyclamate is converted to this active
115 metabolite (Renwick et al., 2004). However, only about 3-4% of the
116 population can metabolize cyclamate to the extent assumed in the ADI
117 calculation, and therefore individual data on the intake of cyclamate does not
118 directly relate to the exposure to cyclohexylamine.

119 *Data presentation*

- 120 i. Information should be provided on the percentage of the population that
121 consumed the additive, the average intake of the additive by those who

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122 consumed the relevant foods and beverages (consumers only) and the intake
123 by “high consumers”, such as the 95th or 97.5th percentile of the distribution
124 of intakes by consumers. Data for “consumers only” are normally reported
125 because the 95% intake of the additive for the total population would not be
126 representative of high intakes if only a small proportion of the total population
127 consumed foods containing the additive.

128 *Time-base for intake estimation*

- 129 i. It is widely recognized that the correct intake for comparison with the ADI as
130 part of risk characterization would be the average long-term intake by an
131 individual. Because the reliability of intake studies decreases with increasing
132 duration, reliable data can be obtained for only about 1-2 weeks of diary
133 collection.
- 134 ii. Intake data for a single day underestimates the % of a population who will be
135 consumers of an additive, but can grossly overestimate the average intake in
136 those individuals who do report intake of the additive on the day in question.

137
138 The intake studies on intense sweeteners conducted since the previous review (Renwick,
139 1999) are outlined below in chronological order of publication, with a description of the
140 findings and the strengths and weaknesses of the study design.

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142 **Recent intake studies on intense sweeteners.**

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3 144 Recent studies are listed in Table 1 in chronological order of publication. They have
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5 145 investigated different population groups in different countries and represent a significant
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7 146 body of new data.
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12 148 *Leclercq et al. (1999).*
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14 149 This was a specific study on the intakes of intense sweeteners in Italian teenagers using a
15
16 150 comprehensive 14-day food diary.
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18 151 *Study population* – 212 teenagers (aged 13-19 years) were recruited from a secondary
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20 152 school in Rome.
21
22 153 *Country* – Italy.
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24 154 *Time of intake data collection* – September 1996 to December 1996.
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26 155 *Nature of intake data* – Prospective 14-day food diary with brand information collected
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28 156 and the presence of sweeteners determined from product labels. The amounts of each
29
30 157 product consumed on each occasion were defined as small, medium or large. The data
31
32 158 were analyzed for acesulfame-K, aspartame, cyclamate and saccharin.
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34 159 *Product concentration data* – Data were obtained from the product manufacturer.
35
36 160 *Results* – The major sources for acesulfame-K, aspartame and cyclamate were beverages
37
38 161 and chewing gum, while for saccharin most of the intake was from table-top products.
39
40 162 The means and maximum intakes of all sweeteners were less than 1mg/kg body
41
42 163 weight/day and therefore below the corresponding ADI values.
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44 164 *Strengths* – The results represent a comprehensive assessment of sweetener intakes using
45
46 165 the best practical approach. Intakes were calculated using individual body weights and
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48 166 the results were 14-day averages.
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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.

190 *Time of intake data collection* – Not stated.

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

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

198 *Results* – The mean intakes of acesulfame-K and saccharin determined by the
199 questionnaire were 45mg/day and 33mg/day respectively, and these values were slightly
200 higher than the values derived from the urinary biomarker (35mg/day and 23mg/day
201 respectively). The correlation between the two measurements of intake was analysed in
202 138 subjects submitting complete urine collections, as judged by PABA recovery, was
203 described by the authors as showing generally good agreement ($R^2 = 0.6$ to 0.7). The
204 highest intakes determined by urinary excretion and questionnaire were 101 and
205 111mg/day respectively for saccharin and 110 and 168mg/day respectively for
206 acesulfame-K.

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

210 *Weaknesses* – The study used a small number of subjects for an intake survey, because it
211 was primarily an exercise for the development and validation of biomarkers. The data
212 refer to a 48 hour period only and do not represent long-term average intakes. Detailed

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213 results from the intake questionnaire were not given in the publication. The intakes were
214 reported in mg/day.

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

220
221 *Garnier-Sagne et al. (2001).*
222 This study focused on diabetic children, and used a worst-case analysis to determine the
223 potential for the ADI to be exceeded in this group.

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

227 *Country* – France.

228 *Time of intake data collection* – June to October 1997.

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

232 *Product concentration data* – A sweetener concentration database was constructed in
233 which it was assumed that all sugar-free products had been sweetened with the same
234 sweetener and that the concentrations of acesulfame K, aspartame and saccharin used

235 were the maximum permitted under European legislation. Such a highly conservative
236 method was used in order to give theoretically maximum daily intakes or TMDIs.

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

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

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

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

251

252 *Food Standards Agency UK (2003).*

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

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

257 *Country* – UK.

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258 *Time of intake data collection* – January to September 2001.

259 *Nature of intake data* – The intakes of acesulfame-K, aspartame, cyclamate and saccharin

260 from beverage consumption were measured using a 7-day diary. The volumes of different

261 types or categories of beverage consumed (carbonated, dilutable and powdered drinks,

262 tea/coffee and natural still drinks) were recorded. The report does not state clearly

263 whether the drinks recorded were separated into those sweetened with sugar and low-

264 calorie sweeteners or whether brand information was obtained, but it is unclear how the

265 product concentration data could have been used without such detailed information.

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

267 *Results* – The average daily intakes of acesulfame K, aspartame, cyclamate and saccharin

268 by consumers were 0.92, 3.38, 4.46 and 1.16 mg/kg body weight respectively, and the

269 97.5th percentile intakes were 3.72, 12.01, 14.07 and 3.83 mg/kg body weight

270 respectively, indicating that the intakes of cyclamate by high consumers would exceed

271 the ADI values set by the JECFA and the SCF.

272 *Strengths* – The study focused on a very large group of children with high potential

273 intakes of soft drinks expressed per kg body weight. The results are 7-day averages.

274 *Weaknesses* – The survey was restricted to beverages only, but this is the main source in

275 the age group studied. In some cases, assumptions had to be made about body weight,

276 which can vary widely across the age range 1.5 to 4 years. It is not clear if the data for

277 high consumers related to recorded body weights or to assumptions. It is not clear to what

278 extent brand level information was used because the beverages appear to have been

279 reported as groups rather than brands (the word “brand” does not appear in the report)

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

284

285 *Ilback et al. (2003).*

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

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

291 *Country* – Sweden.

292 *Time of intake data collection* – January 1999.

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

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302 source on a single day would not coincide with high intake of the other two sources on
303 the same day.

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

307 *Results* – The main sources of intake were tabletop sweeteners and beverages, especially
308 fruit syrups in children . Although it is unclear from the data presentation, it appears that
309 the average intakes for each of the sweeteners in all groups, using these highly
310 conservative assumptions were below the respective ADI values. Estimates of the intakes
311 by high consumers were based on the data for the 10 or 20 individuals in each population
312 subgroup with the highest intakes from all sources. The intakes of aspartame (46mg/kg
313 body weight per day) and saccharin (about 6.3mg/kg body weight per day) slightly
314 exceeded the relevant ADI values for the top 10 children. The intakes for the top 10
315 adults were below the ADI values. The intakes of cyclamate for the 10 children with the
316 highest intakes (about 35mg/kg body weight per day) were about 3 times the JECFA ADI
317 (0-11mg/kg body weight per day) and 5 times the more recent SCF ADI (7mg/kg body
318 weight per day) for cyclamate. The intake for the highest 10 adults slightly exceeded the
319 JEFCA ADI.

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

322 *Weaknesses* – The authors described the findings as a “worst-case” analysis based on
323 maximum permitted concentrations and maximum intake on a single day. The inclusion

324 of conservative assumptions at each point in the intake calculation results in an unrealistic
325 intake estimate.

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

336

337 *Serra-Majem et al. (2003).*

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

342 *Study population* – 405 adult males (30-50 years) with clinically defined infertility and
343 379 adult male controls (30-50 years).

344 *Country* – Spain.

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

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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

369 362 individuals aged 14-17 years were measured using a food diary as described below.

370 The food diary was completed by 125 males and 108 females selected at random and by
371 139 females who were high consumers of either diet soft drinks or table-top products or
372 both.

373 *Country* – Italy

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

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

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

383 *Results* – The mean and 95th percentile intakes of all sweeteners in all individuals who
384 completed the 4-day food diary were well below the corresponding ADI values. The 95th
385 percentile of cyclamate intake in the selected group of female high consumers of sugar-
386 free soft drinks was 0.55mg/kg body weight/day (5% of the JECFA ADI), while the
387 corresponding intakes for acesulfame-K, aspartame and saccharin were 0.25, 0.30 and
388 0.0mg/kg body weight/day (less than 2% of the ADI values).

389 *Strengths* – This study provides a comprehensive assessment of the intake using the best
390 practical approach. Intakes were calculated using individual body weights. Results were
391 averages of three 4-day diaries collected in different months for all subjects and therefore

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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 90th percentile intakes of cyclamate and sucralose were below 1mg/kg body weight/day, indicating little market penetration by these sweeteners. The mean and 90th

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

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437 recruited from other sources giving a total of 298 subjects with diabetes or impaired
438 glucose tolerance.
439 *Country* – Australia and New Zealand.
440 *Time of intake data collection* – The initial screen was performed between September
441 2002 to February 2003. A diary agreement letter was sent to participants in February
442 2003, but the exact time span of diary completions was not given in the report.
443 *Nature of intake data* – The intakes in the potential high consumers used a prospective 7-
444 day food diary that focused on key products, including details of brands that would
445 contain intense sweeteners.
446 *Product concentration data* – Data were supplied in confidence by product
447 manufacturers. The diary study analyzed for acesulfame-K, alitame, aspartame,
448 cyclamate, saccharin and sucralose
449 *Results* – The initial screen showed that the consumption patterns were similar in the two
450 countries, and that diabetics consumed more products containing intense sweeteners.
451 Overall there were significant increases in the average daily intakes of certain products
452 containing intense sweeteners, particularly carbonated soft drinks amongst Australian
453 consumers aged 12-39 years, compared with the data for 1994 (the changes are discussed
454 in the 2004 report). The 7-day food diary in the selected sub-group showed that the
455 intakes of acesulfame-K were increased compared with the 1994 data. The mean intakes
456 of all sweeteners were below their respective ADI values, with means in the group of 400
457 high consumers of intense sweeteners (see above) of 0.4, <0.1, 2.4, 2.1, 0.3 and 0.2
458 mg/kg body weight/day for acesulfame-K, alitame, aspartame, cyclamate, saccharin and
459 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 95th 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 95th 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 95th 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.

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483 *Country* – The Netherlands.

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

485 *Nature of intake data* – Data were collected using a two-day diary. Food consumed at

486 home was recorded in the diaries by the person who usually prepared the meal for the

487 household. Each participant recorded foods consumed out of the house. All products in a

488 single food coding in the food composition database that could contain an intense

489 sweetener were assumed to contain the same sweetener. If the food product could not be

490 related to an existing food coding the intake was assumed to be that of the closest non-

491 sweetened coding with correction for the market share of sweetened products in that food

492 coding. For worst-case calculations, the highest consumptions (95th percentiles) of soft

493 drink, lemonade syrup, yogurt drink and chocolate milk were calculated assuming that all

494 of the products in each category consumed were sweetened with a single sweetener using

495 the average measured concentration.

496 *Product concentration data* – Concentrations were measured in food products that were

497 purchased in 2003 and which was likely to contain an intense sweetener based on the

498 label.

499 *Results* – The estimated average and 95th percentile intakes of acesulfame-K, aspartame,

500 cyclamate and saccharin were all 1mg/kg body weight or less. The highest calculated 95th

501 percentile intakes were in the 1-4 years age range and the highest value in this age group

502 was for cyclamate (1.1mg/kg body weight/day). The results from the worst-case

503 calculations indicated that for the whole population (1-97years old) the 95th percentile

504 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

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3 528 national food consumption data of the population with the maximum permitted use levels
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5 529 of the sweetener, and the “Tier 3” approach, in which the theoretical intake was
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8 530 calculated by combining the mean national food consumption data of the whole
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10 531 population with the actual use levels of the sweetener. The results were expressed as the
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12 532 % of the corresponding SCF ADI values (using the old SCF ADI for cyclamate of 0-
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14 533 11mg/kg body weight per day). The ranges of intakes in adults were 2-37% for
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16 534 acesulfame-K (Tier 2 data for Denmark, France, Italy, The Netherlands, UK and Norway)
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18 535 and 0-11% for cyclamate (Tier 2 data for Denmark, France, Italy, The Netherlands, UK
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20 536 and Norway). The ranges of intakes in children were 3-107% for acesulfame-K (Tier 3
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22 537 data for France, The Netherlands and UK), 1-40% for aspartame (Tier 2 data for The
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24 538 Netherlands and UK), 1-74% for cyclamate (Tier 2 data for France, The Netherlands and
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26 539 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

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3 552 which combined national dietary survey data with approved use levels and do
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5 553 not really provide reliable new information (Garnier-Sagne et al. 2001, Ilback
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8 554 et al. 2003, Devitt et al. 2004 and van Rooij-van den Bos et al. 2004).
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10 555 iv. Those that were designed primarily for other purposes or to address specific
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12 556 issues, such as assessing exposure from urinary excretion data for the
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14 557 sweetener and/or its metabolites (Wilson et al. 1999 and Serra-Majem et al.
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17 558 2003).
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22 560 Comparisons of the data from these studies with the findings reviewed previously
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24 561 (Renwick, 1999) show that the intakes of intense sweeteners have not increased
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27 562 substantially in the past 10 years. The recent studies consistently show that the average
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29 563 and 95th percentile intakes of all sweeteners by adults are below the corresponding ADI
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32 564 values. One of the most comprehensive and reliable of the recent studies was that of
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34 565 Leclercq et al. (1999) which focused on a potential high intake group, used a 14-day
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36 566 prospective diary and obtained brand-related concentration data. This study found that the
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39 567 mean and maximum intakes of the sweeteners investigated (aspartame, acesulfame-K,
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41 568 cyclamate and saccharin) were below 1mg/kg body weight/day. The follow-up study of
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44 569 Arcella et al. (2004) reached similar conclusions while focusing on individuals identified
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46 570 as high consumers. The large and comprehensive study by Food Standards Australia New
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48 571 Zealand (2004) showed that, with the exception of the 95th percentile intake of cyclamate
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50 572 in diabetics, the means and 95th percentile intakes of intense sweeteners were below the
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53 573 corresponding ADI values.
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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 0-11 mg/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

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3 598 only a small percentage of humans, about 3-4% of the population, are able to form
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6 599 significant amounts of this metabolite (Renwick et al. 2004). Theoretically, the best study
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8 600 design for estimating exposure to cyclohexylamine following cyclamate ingestion would
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10 601 be based on that of Serra-Majem et al. (2003), and combine an optimized food-diary, as
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12 602 outlined above, with measurements of the daily urinary excretion of cyclamate and
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14 603 cyclohexylamine. However such a design would not be practicable for studying a group
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16 604 of diabetic children that was large enough to include individuals with high cyclamate
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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	243 diabetic 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.