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Andrew Gordon Renwick

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The intake of intense sweeteners – an update review

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Manuscripts

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4 1 **The intake of intense sweeteners – an update review**
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8 3 *Andrew G. Renwick*
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10 4
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12
13 5 School of Medicine,
14 6 University of Southampton,
15 7 Biomedical Sciences Building,
16 8 Bassett Crescent East,
17 9 Southampton, SO16 7PX
18 10 United Kingdom
19 11

20
21
22 12 Tel 023 80598510
23

24
25 13 Email agr@soton.ac.uk
26

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30 15 Short Title – Intake of Intense Sweeteners
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3 16 **Summary**
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5 17 Studies on the intakes of intense sweeteners in different countries published since the
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8 18 author's previous review in 1999 indicate that the average and 95th percentile intakes of
9
10 19 acesulfame-K, aspartame, cyclamate and saccharin by adults are below the relevant ADI
11
12 20 values. Fewer data are available for the newer sweeteners, sucralose and alitame, and
13
14 21 because they are recent introductions to the market very low intakes were reported in
15
16 22 those countries where they were available at the time of the intake study. Overall there
17
18 23 has not been a significant change in the intakes of sweeteners in recent years. The only
19
20 24 data indicating that the intake of an intense sweetener could exceed its ADI value were
21
22 25 the 95th percentile intakes of cyclamate in children, particularly those with diabetes. This
23
24 26 sub-group was identified as having high intakes of cyclamate in 1999, and recent studies
25
26 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

32 **Introduction**

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

45
46 The intakes of intense sweeteners have been submitted to a previous systematic review,
47 which evaluated all published data up to 1997 (Renwick 1999). At that time it was clear
48 that the average intakes of all intense sweeteners were below the relevant ADI values.
49 The intakes by the highest consumers of sweeteners other than cyclamate were also well
50 below their ADI values. The highest estimated intakes of cyclamate by diabetics and
51 children were close to or slightly above the ADI. The present paper considers more recent
52 published intake data on intense sweeteners to determine whether the risk
53 characterization of this group of approved food additives has altered. ADI values for the
54 intense sweeteners have been defined by the Joint FAO/WHO Expert Committee on Food

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3 55 (JECFA) and the Scientific Committee on Food of the European Union (SCF). The ADI
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5 56 values (in mg/kg body weight) for acesulfame-K are 0-15 (JECFA) and 0-9 (SCF), for
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7
8 57 alitame is 0-1 (JECFA), for aspartame is 0-40 (JECFA and SCF), for cyclamate are 0-11
9
10 58 (JECFA) and 0-7 (SCF), for saccharin is 0-5 (JECFA and SCF), and for sucralose is 0-15
11
12 59 (JECFA and SCF).
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19 20 61 **Methods used to estimate intakes, and their inherent assumptions**

21 62 Estimation of the intake of an approved food additive is a potentially complex and costly
22
23 63 procedure. Because many of the studies on intense sweeteners in recent years were not of
24
25 64 optimal design, the different aspects that should be incorporated into an appropriately
26
27 65 designed study are given below.
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33 34 67 *Study population*

- 35 68 i. Should be sufficiently large to define the tail of the distribution of intakes,
36
37 69 such as the 90th, 95th or 97.5th percentile of those individuals who consume the
38
39 70 additive or sweetener under study (high consumers).
40
41 71 ii. Should include any special groups who would be predicted to have higher
42
43 72 than average intakes (such as diabetics for intense sweeteners).
44
45 73 iii. Should include any group that would generally be considered to be of concern
46
47 74 irrespective of the subject of the survey, such as pregnant women and
48
49 75 children.
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53 76 *Food intake estimation*

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3 77 i. Should include information on the intakes of those specific products that
4
5 78 might contain the additive or sweetener under investigation. Less specific
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8 79 product classifications will result in greater predicted intakes and therefore
9
10 80 greater overestimation, conservatism and unreliability in the data generated.
11
12 81 ii. Should give reliable measurements of the amounts of the specific food
13
14 82 products consumed daily, which will require information on portion size and
15
16 83 frequency of ingestion. Food intake estimates derived from a prospective food
17
18 84 diary are more reliable than data derived from a retrospective questionnaire.
19
20 85 iii. Should differentiate between products in the same food classification group
21
22 86 that contain the subject of the survey and those that do not. This is particularly
23
24 87 important in the case of sweeteners, where different sweeteners can occur in
25
26 88 different brands. For example, information on “cola” ingestion represents
27
28 89 inadequate data because the product could be sweetened with sugar rather than
29
30 90 an intense sweetener, with a single approved sweetener, with a blend of
31
32 91 approved sweeteners or with a blend of sugar and sweeteners. Reliable data
33
34 92 require analyses to be performed using brand-level intake data.
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41 93 *Product composition*
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- 43 94 i. Ideally the database should include brand-specific data on the concentrations
44
45 95 of the additives under study in each product. This information could be
46
47 96 obtained from the food producer or by direct measurement, and is particularly
48
49 97 important for intense sweeteners since a single food product may contain a
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51 98 blend of different sweeteners.
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3 99 ii. In the absence of product-specific data, it is common to assume that the
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6 100 concentration present is the maximum permitted under the relevant legislation.
7
8 101 Because food additives are not always present at their maximum permitted
9
10 102 concentrations, this represents another source of conservatism in the final
11
12 103 intake estimation.

14
15 104 *Food additive intake calculation*

16
17 105 i. The amounts of each food product consumed and concentrations present are
18
19 106 multiplied, and the results for different products are summed and divided by
20
21 107 the body weight. The use of individual body weights is of critical importance
22
23 108 if the study group covers a wide range of body weights. For example, children
24
25 109 aged 1-4years vary widely in body weight but are often reported as a single
26
27 110 population group; dividing the highest intake in mg per individual per day by
28
29 111 the average body weight could result in a significant overestimation.
30
31
32 112 ii. There is an added complication in the case of cyclamate because the ADI was
33
34 113 calculated using toxicity data on its metabolite, cyclohexylamine, and an
35
36 114 assumption that a high % of the ingested cyclamate is converted to this active
37
38 115 metabolite (Renwick et al., 2004). However, only about 3-4% of the
39
40 116 population can metabolize cyclamate to the extent assumed in the ADI
41
42 117 calculation, and therefore individual data on the intake of cyclamate does not
43
44 118 directly relate to the exposure to cyclohexylamine.

45
46 119 *Data presentation*

47
48 120 i. Information should be provided on the percentage of the population that
49
50 121 consumed the additive, the average intake of the additive by those who
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3 122 consumed the relevant foods and beverages (consumers only) and the intake
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5 123 by “high consumers”, such as the 95th or 97.5th percentile of the distribution
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7
8 124 of intakes by consumers. Data for “consumers only” are normally reported
9
10 125 because the 95% intake of the additive for the total population would not be
11
12 126 representative of high intakes if only a small proportion of the total population
13
14
15 127 consumed foods containing the additive.
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17
18 128 *Time-base for intake estimation*

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20 129 i. It is widely recognized that the correct intake for comparison with the ADI as
21
22 130 part of risk characterization would be the average long-term intake by an
23
24 131 individual. Because the reliability of intake studies decreases with increasing
25
26
27 132 duration, reliable data can be obtained for only about 1-2 weeks of diary
28
29 133 collection.
30
31 134 ii. Intake data for a single day underestimates the % of a population who will be
32
33 135 consumers of an additive, but can grossly overestimate the average intake in
34
35 136 those individuals who do report intake of the additive on the day in question.
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41 138 The intake studies on intense sweeteners conducted since the previous review (Renwick,
42
43 139 1999) are outlined below in chronological order of publication, with a description of the
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46 140 findings and the strengths and weaknesses of the study design.
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51 142 **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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8 146 body of new data.
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13 148 *Leclercq et al. (1999).*

14
15 149 This was a specific study on the intakes of intense sweeteners in Italian teenagers using a
16
17 150 comprehensive 14-day food diary.

18
19
20 151 *Study population* – 212 teenagers (aged 13-19 years) were recruited from a secondary
21
22 152 school in Rome.

23
24 153 *Country* – Italy.

25
26
27 154 *Time of intake data collection* – September 1996 to December 1996.

28
29 155 *Nature of intake data* – Prospective 14-day food diary with brand information collected
30
31 156 and the presence of sweeteners determined from product labels. The amounts of each
32
33 157 product consumed on each occasion were defined as small, medium or large. The data
34
35 158 were analyzed for acesulfame-K, aspartame, cyclamate and saccharin.

36
37 159 *Product concentration data* – Data were obtained from the product manufacturer.

38
39 160 *Results* – The major sources for acesulfame-K, aspartame and cyclamate were beverages
40
41 161 and chewing gum, while for saccharin most of the intake was from table-top products.

42
43 162 The means and maximum intakes of all sweeteners were less than 1mg/kg body
44
45 163 weight/day and therefore below the corresponding ADI values.

46
47 164 *Strengths* – The results represent a comprehensive assessment of sweetener intakes using
48
49 165 the best practical approach. Intakes were calculated using individual body weights and
50
51 166 the results were 14-day averages.
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3 167 *Weaknesses* – The sample was from a single school of “medium social class”, and
4
5 168 therefore not representative of teenagers in general. Other age groups and high potential
6
7 169 consumers such as diabetics were not included.
8
9
10 170 *Conclusions* – The patterns of sweetener intake were similar to previous publications and
11
12 171 the intakes were well below the ADI values. The authors used the dietary pattern for the
13
14 172 whole group to predict that intakes of cyclamate or saccharin could approach the ADI but
15
16 173 only if subjects had high intakes of both soft drinks and table-top products and only if
17
18 174 sugar was substituted in these items with either cyclamate or saccharin; this conclusion is
19
20 175 consistent with the more theoretical calculations made by other studies.
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23 176
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26 177 *Wilson et al. (1999).*
27
28 178 This study used 24 hour urinary excretions of acesulfame-K and saccharin as biomarkers
29
30 179 of intake. The method would only be applicable to these two sweeteners, because they are
31
32 180 almost completely absorbed from the intestine and excreted unchanged in urine. The
33
34 181 method was validated by giving known amounts of acesulfame-K and saccharin to
35
36 182 different volunteers and measuring their urinary excretion over the following 24 hours.
37
38 183 The use of the urinary biomarker was then compared with intake estimates derived from a
39
40 184 dietary questionnaire specifically on sweetener intake for the same 2-day period, and it is
41
42 185 this part of the study which is presented below.
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48 187 *Study population* – 188 volunteers aged 3-74 years who were family and friends of the
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50 188 laboratory staff. There were 78 adult males, 85 adult females, 19 boys and 6 girls.
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53 189 *Country* – UK.
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3 190 *Time of intake data collection* – Not stated.
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5 191 *Nature of intake data* – Sweetener intake was measured using a 48 hour intake diary, with
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7
8 192 information provided on the amounts and brands consumed. The urinary biomarker data
9
10 193 were collected only on the second day of the food diary record. The urinary data were
11
12 194 accepted only if there was evidence of a complete 24 hour collection based on the urinary
13
14 195 recovery of the marker substance p-aminobenzoic acid which was given as three doses
15
16 196 with meals.
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18

19 197 *Product concentration data* – Data were supplied by the food product manufacturers.
20

21 198 *Results* – The mean intakes of acesulfame-K and saccharin determined by the
22
23 199 questionnaire were 45mg/day and 33mg/day respectively, and these values were slightly
24
25 200 higher than the values derived from the urinary biomarker (35mg/day and 23mg/day
26
27 201 respectively). The correlation between the two measurements of intake was analysed in
28
29 202 138 subjects submitting complete urine collections, as judged by PABA recovery, was
30
31 203 described by the authors as showing generally good agreement ($R^2 = 0.6$ to 0.7). The
32
33 204 highest intakes determined by urinary excretion and questionnaire were 101 and
34
35 205 111mg/day respectively for saccharin and 110 and 168mg/day respectively for
36
37 206 acesulfame-K.
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43 207 *Strengths* – The intake diaries were comprehensive and could be related to the urinary
44
45 208 biomarker data. The questionnaire and concentration data were analyzed down to brand-
46
47 209 level detail.
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49 210 *Weaknesses* – The study used a small number of subjects for an intake survey, because it
50
51 211 was primarily an exercise for the development and validation of biomarkers. The data
52
53 212 refer to a 48 hour period only and do not represent long-term average intakes. Detailed
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3 213 results from the intake questionnaire were not given in the publication. The intakes were
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5 214 reported in mg/day.

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7
8 215 *Conclusions* – These data provide an interesting approach for the future, rather than
9
10 216 giving comprehensive intake data that can be compared with previous studies. The mean
11
12 217 intakes of acesulfame-K and saccharin were reported to be below their ADI values.
13
14 218 Assuming an average body weight of 60kg for an adult, the maximum intakes of
15
16 219 acesulfame-K and saccharin corresponded to less than 1.5mg/kg body weight/day.
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22 221 *Garnier-Sagne et al. (2001).*

23
24 222 This study focused on diabetic children, and used a worst-case analysis to determine the
25
26 223 potential for the ADI to be exceeded in this group.

27
28 224 *Study population* – 400 subjects aged 2-20 years, who were recruited from the French Aid
29
30 225 for Young Diabetics Association, were sent a food intake questionnaire; 227 completed
31
32 226 forms were returned.

33
34 227 *Country* – France.

35
36 228 *Time of intake data collection* – June to October 1997.

37
38 229 *Nature of intake data* – The questionnaire included a 5-day prospective food diary which
39
40 230 paid particular attention to the types and amounts of sweetened foods that were
41
42 231 consumed. The forms were completed by the individual or a parent.

43
44 232 *Product concentration data* – A sweetener concentration database was constructed in
45
46 233 which it was assumed that all sugar-free products had been sweetened with the same
47
48 234 sweetener and that the concentrations of acesulfame K, aspartame and saccharin used
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3 235 were the maximum permitted under European legislation. Such a highly conservative
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5 236 method was used in order to give theoretically maximum daily intakes or TMDIs.
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8 237 *Results* – The mean TMDIs of acesulfame K, aspartame and saccharin by consumers
9
10 238 were 1.1, 2.4 and 0.4mg/kg body weight respectively, and the 97.5th percentile TMDIs
11
12 239 were 4.0, 7.8 and 1.3mg/kg body weight respectively, indicating that intakes by high
13
14 240 consumers did not exceed the ADI values.
15
16

17 241 *Strengths* – The study calculated the maximum potential intakes based on 5-day averages.
18
19

20 242 *Weaknesses* – The assumptions about the distribution of sweeteners in food products and
21
22 243 the concentrations used are too conservative to allow the data to be taken as realistic
23
24 244 estimates, but they do provide an upper bound on the possible intakes of each individual
25
26 245 sweetener in the population group predicted to have the highest intake on a body weight
27
28 246 basis. Cyclamate intake was not among the sweeteners measured.
29
30

31 247 *Conclusions* – The data appear to be a worst-case analysis of intake in a group of the
32
33 248 population with high potential intakes. The study supports the findings of other studies
34
35 249 that the intakes of acesulfame K, aspartame and saccharin would not exceed their ADI
36
37 250 values, even in the highest consumers.
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43 252 *Food Standards Agency UK (2003).*
44
45

46 253 This study focused on intakes by children, because previous survey data had indicated
47
48 254 that this group was likely to have sweetener intakes above the ADI values due to their
49
50 255 high intakes of sweetened soft drinks, when expressed per kg of body weight.
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53 256 *Study population* – 1110 children aged 1.5 to 4.5 years across 12 areas of the UK.
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56 257 *Country* – UK.
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3 258 *Time of intake data collection* – January to September 2001.
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5 259 *Nature of intake data* – The intakes of acesulfame-K, aspartame, cyclamate and saccharin
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8 260 from beverage consumption were measured using a 7-day diary. The volumes of different
9
10 261 types or categories of beverage consumed (carbonated, dilutable and powdered drinks,
11
12 262 tea/coffee and natural still drinks) were recorded. The report does not state clearly
13
14 263 whether the drinks recorded were separated into those sweetened with sugar and low-
15
16 264 calorie sweeteners or whether brand information was obtained, but it is unclear how the
17
18 265 product concentration data could have been used without such detailed information.
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21
22 266 *Product concentration data* – Data obtained from the food product manufacturer.
23

24 267 *Results* – The average daily intakes of acesulfame K, aspartame, cyclamate and saccharin
25
26 268 by consumers were 0.92, 3.38, 4.46 and 1.16 mg/kg body weight respectively, and the
27
28 269 97.5th percentile intakes were 3.72, 12.01, 14.07 and 3.83 mg/kg body weight
29
30 270 respectively, indicating that the intakes of cyclamate by high consumers would exceed
31
32 271 the ADI values set by the JECFA and the SCF.
33

34 272 *Strengths* – The study focused on a very large group of children with high potential
35
36 273 intakes of soft drinks expressed per kg body weight. The results are 7-day averages.
37
38

39 274 *Weaknesses* – The survey was restricted to beverages only, but this is the main source in
40
41 275 the age group studied. In some cases, assumptions had to be made about body weight,
42
43 276 which can vary widely across the age range 1.5 to 4 years. It is not clear if the data for
44
45 277 high consumers related to recorded body weights or to assumptions. It is not clear to what
46
47 278 extent brand level information was used because the beverages appear to have been
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49 279 reported as groups rather than brands (the word “brand” does not appear in the report)
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3 280 *Conclusions* – The data appear to be a worst-case analysis of intake in a group of the
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5 281 population with high potential intakes. The results support the findings of other studies
6
7 282 that it is only cyclamate where the ADI might be exceeded by the highest intakes in
8
9 283 young children.
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15 285 *Illback et al. (2003).*
16

17 286 This study investigated the intakes of acesulfame-K, aspartame, cyclamate and saccharin
18
19 287 in diabetic children and adults.
20
21

22 288 *Study population* – Subjects were recruited randomly from members of the Association of
23
24 289 Diabetics in Stockholm. Data were collected for 243 children (aged 0-15 years), 236 adult
25
26 290 males (aged 16-90 years) and 311 adult females (aged 16-90 years).
27
28

29 291 *Country* – Sweden.
30
31

32 292 *Time of intake data collection* – January 1999.
33

34 293 *Nature of intake data* – Intakes were estimated from a food-frequency questionnaire
35
36 294 (retrospective but of undefined duration) concerning the amounts and frequency of
37
38 295 intakes of diet soda, cider, fruit syrup, tabletop sweeteners, light ice cream, chewing
39
40 296 gums, sweets, yoghurt, vitamin C supplements, throat lozenges and fluid and dried table
41
42 297 sweeteners. The individual intake estimates were based on the consumption on a single
43
44 298 occasion. Although not stated clearly in the original publication, it appears that the
45
46 299 “worst-case” estimates were made by addition of the maximum intake for each product
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48 300 recorded in a single day. This would be highly conservative because the main sources of
49
50 301 sweetener intake were fruit syrups, diet sodas and cider and a high consumption of one
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3 302 source on a single day would not coincide with high intake of the other two sources on
4
5 303 the same day.
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8 304 *Product concentration data* – The maximum permitted concentrations for each product
9
10 305 category were used and it was assumed that the total intake of that product contained a
11
12 306 single sweetener.
13

14
15 307 *Results* – The main sources of intake were tabletop sweeteners and beverages, especially
16
17 308 fruit syrups in children . Although it is unclear from the data presentation, it appears that
18
19 309 the average intakes for each of the sweeteners in all groups, using these highly
20
21 310 conservative assumptions were below the respective ADI values. Estimates of the intakes
22
23 311 by high consumers were based on the data for the 10 or 20 individuals in each population
24
25 312 subgroup with the highest intakes from all sources. The intakes of aspartame (46mg/kg
26
27 313 body weight per day) and saccharin (about 6.3mg/kg body weight per day) slightly
28
29 314 exceeded the relevant ADI values for the top 10 children. The intakes for the top 10
30
31 315 adults were below the ADI values. The intakes of cyclamate for the 10 children with the
32
33 316 highest intakes (about 35mg/kg body weight per day) were about 3 times the JECFA ADI
34
35 317 (0-11mg/kg body weight per day) and 5 times the more recent SCF ADI (7mg/kg body
36
37 318 weight per day) for cyclamate. The intake for the highest 10 adults slightly exceeded the
38
39 319 JEFCA ADI.
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45 320 *Strengths* – The study focused on diabetics because this was the group expected to have
46
47 321 the highest potential intakes. Individual body weights were used.
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50 322 *Weaknesses* – The authors described the findings as a “worst-case” analysis based on
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52 323 maximum permitted concentrations and maximum intake on a single day. The inclusion
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3 324 of conservative assumptions at each point in the intake calculation results in an unrealistic
4
5 325 intake estimate.

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8 326 *Conclusions* – The data show that only cyclamate could have an intake significantly
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10 327 above its ADI, and this would only be in a proportion of children. Extrapolation of this
11
12 328 observation to non-diabetic children is difficult because the children studied had a high
13
14 329 intake of table-top sweeteners, an observation not made for non-diabetic children in other
15
16 330 intake studies. The use of highly conservative worst-case assumptions means that this
17
18 331 study should be used to identify a possible problem, and should not be interpreted as
19
20 332 proving the existence of a real problem. It is unclear why a study which has the power
21
22 333 only for hypothesis generation should be performed in 1999, at a time when it was clear
23
24 334 that diabetic children consuming cyclamate would represent a group where the ADI for a
25
26 335 sweetener might be exceeded.

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33
34 337 *Serra-Majem et al. (2003).*

35
36 338 This was an epidemiological study to investigate the possibility of a relationship between
37
38 339 male fertility in humans and the intakes of cyclamate and its metabolism to
39
40 340 cyclohexylamine. Cyclohexylamine produces testicular atrophy in experimental animals
41
42 341 and this effect was used as the basis for calculation of the ADI of cyclamate.

43
44 342 *Study population* – 405 adult males (30-50 years) with clinically defined infertility and
45
46 343 379 adult male controls (30-50 years).

47
48 344 *Country* – Spain.

49
50 345 *Time of intake data collection* – February 1994 – December 1996.
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3 346 *Nature of intake data* – A specially designed retrospective food-frequency questionnaire
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5
6 347 was used but no details were given.

7
8 348 *Product concentration data* – Information from the cyclamate manufacturer in Spain was
9
10 349 used.

11
12 350 *Results* – 32% of cases and 29% of controls consumed cyclamate, with 3% and 2%
13
14
15 351 having intakes greater than 5mg/kg body weight/day.

16
17 352 *Strengths* – The study employed large group sizes, but this was essential because the
18
19
20 353 majority of individuals do not metabolize cyclamate to cyclohexylamine (Renwick et al.,
21
22 354 2004). This was the only recent study that has tried to relate cyclamate intake to the
23
24
25 355 excretion of its metabolite cyclohexylamine in urine.

26
27 356 *Weaknesses* – The population investigated was adult males only, and intake was based on
28
29
30 357 a food frequency questionnaire.

31
32 358 *Conclusions* – The intake data support the findings of previous studies in a population
33
34 359 that probably has higher than average cyclamate intakes because of the widespread use of
35
36 360 cyclamate in Spain and the use of this sweetener in the popular drink “gaseosa” - a
37
38
39 361 combination of carbonated water containing saccharin and cyclamate taken with wine.

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42
43 363 *Arcella et al. (2004).*

44
45
46 364 This was a follow up study to that of Leclercq et al. (1999) in a larger study group which
47
48 365 included increased numbers of individuals who reported high intakes.

49
50 366 *Study population* – A randomly selected sample of 3982 teenagers in Rome completed a
51
52
53 367 food frequency questionnaire designed to identify adolescents who were high consumers
54
55
56 368 of sugar-free soft drinks or tabletop sweeteners. From the results, intakes in a group of
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3 369 362 individuals aged 14-17 years were measured using a food diary as described below.

4
5
6 370 The food diary was completed by 125 males and 108 females selected at random and by
7
8 371 139 females who were high consumers of either diet soft drinks or table-top products or
9
10 372 both.

11
12 373 *Country* – Italy

13
14
15 374 *Time of intake data collection* – October 2000 to May 2001 (three 4-day food diaries)

16
17 375 *Nature of intake data* – The randomly selected group and the identified female high

18
19
20 376 consumers from the food frequency questionnaire completed a 4-day food diary on three

21
22 377 separate occasions, with different subjects in each group covering all days of the week.

23
24
25 378 Brand information was collected and presence of sweeteners determined from the product

26
27 379 label. The amounts of each product consumed on each occasion were defined as small,

28
29 380 medium or large. Data were analyzed for saccharin, aspartame, acesulfame-K and

30
31 381 cyclamate.

32
33
34 382 *Product concentration data* – Data were obtained from the product manufacturer.

35
36 383 *Results* – The mean and 95th percentile intakes of all sweeteners in all individuals who

37
38 384 completed the 4-day food diary were well below the corresponding ADI values. The 95th

39
40 385 percentile of cyclamate intake in the selected group of female high consumers of sugar-

41
42 386 free soft drinks was 0.55mg/kg body weight/day (5% of the JECFA ADI), while the

43
44 387 corresponding intakes for acesulfame-K, aspartame and saccharin were 0.25, 0.30 and

45
46 388 0.0mg/kg body weight/day (less than 2% of the ADI values).

47
48 389 *Strengths* – This study provides a comprehensive assessment of the intake using the best

49
50
51 390 practical approach. Intakes were calculated using individual body weights. Results were

52
53 391 averages of three 4-day diaries collected in different months for all subjects and therefore

1
2
3 392 are best estimates of long term average intakes.
4

5 393 *Weaknesses* – The study did not include other groups with high predicted intake, i.e.
6
7
8 394 children or diabetics
9

10 395 *Conclusions* – The intakes were well below the ADI values. The results of this study are
11
12 396 similar to the study of Leclercq et al. (1999) in Italian teenagers.
13

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16
17 398 *Devitt et al. (2004).*
18

19
20 399 This study focused on a small number of children treated for Type 1 diabetes mellitus.
21

22 400 *Study population* – A group of 56 children aged 2-6 years were recruited from a total of
23
24 401 116 eligible subjects at the Diabetic Clinic at the Hospital for Sick Children in Toronto.
25

26
27 402 *Country* – Canada.
28

29 403 *Time of intake data collection* – Data were collected over a period of 7 months (dates not
30
31 404 given).
32

33
34 405 *Nature of intake data* – Intake estimates were based on a single interactive 24-hour
35
36 406 dietary recall by the parents. Products containing acesulfame-K, aspartame, cyclamate
37
38 407 and sucralose were identified by showing product labels to the parents. Saccharin was not
39
40 408 used as a food additive in Canada at this time.
41
42

43 409 *Product concentration data* – Data were obtained from the label or the product
44
45 410 manufacturer.
46
47

48 411 *Results* – The proportion of the group who consumed products containing acesulfame-K,
49
50 412 aspartame, cyclamate and sucralose were 25%, 43%, 12% and 2% respectively. The
51
52 413 mean and 90th percentile intakes of cyclamate and sucralose were below 1mg/kg body
53
54 414 weight/day, indicating little market penetration by these sweeteners. The mean and 90th
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3 415 percentile intakes of acesulfame-K were 0.6 and 1.9mg/kg body weight/day respectively.

4
5 416 The mean and 90th percentile intakes of aspartame were 4.1 and 7.8mg/kg body

6
7
8 417 weight/day respectively.

9
10 418 *Strengths* – The study focused in diabetic children. The absence of saccharin in food

11
12 419 products and the low use of cyclamate mean that the intake data for aspartame represent a

13
14 420 worst-case scenario.

15
16
17 421 *Weaknesses* – The intake data were based on a single recall assessment and would over-

18
19 422 estimate average intakes but under-estimate the % consumers.

20
21 423 *Conclusions* – The intakes for all sweeteners were below their ADI values.

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24 424

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26
27 425 *Food Standards Australia and New Zealand (2004).*

28
29 426 This study was a follow up to the 1994 Australian study which showed that high

30
31 427 consumers of saccharin and cyclamate could have intakes that approached or exceeded

32
33 428 the ADI. The survey comprised 3 phases; an initial national telephone screen to

34
35 429 determine patterns of food intake, a diary survey of potential high consumers of products

36
37 430 containing intense sweeteners identified in the screen and a supplementary survey of

38
39 431 individuals with diabetes or impaired glucose tolerance.

40
41 432 *Study population* – The initial screen, which was in 3529 individuals aged over 12 years

42
43 433 and selected to be representative of the general population, was used to identify 400

44
45 434 respondents with high potential intakes of intense sweeteners. The supplementary study

46
47 435 in diabetics comprised 111 subjects identified within the group of 400 high consumers of

48
49 436 products containing intense sweeteners and these were supplemented by 187 diabetics

1
2
3 437 recruited from other sources giving a total of 298 subjects with diabetes or impaired
4
5 438 glucose tolerance.
6
7
8 439 *Country* – Australia and New Zealand.
9
10 440 *Time of intake data collection* – The initial screen was performed between September
11
12 441 2002 to February 2003. A diary agreement letter was sent to participants in February
13
14 442 2003, but the exact time span of diary completions was not given in the report.
15
16
17 443 *Nature of intake data* – The intakes in the potential high consumers used a prospective 7-
18
19 444 day food diary that focused on key products, including details of brands that would
20
21 445 contain intense sweeteners.
22
23
24 446 *Product concentration data* – Data were supplied in confidence by product
25
26 447 manufacturers. The diary study analyzed for acesulfame-K, alitame, aspartame,
27
28 448 cyclamate, saccharin and sucralose
29
30
31 449 *Results* – The initial screen showed that the consumption patterns were similar in the two
32
33 450 countries, and that diabetics consumed more products containing intense sweeteners.
34
35 451 Overall there were significant increases in the average daily intakes of certain products
36
37 452 containing intense sweeteners, particularly carbonated soft drinks amongst Australian
38
39 453 consumers aged 12-39 years, compared with the data for 1994 (the changes are discussed
40
41 454 in the 2004 report). The 7-day food diary in the selected sub-group showed that the
42
43 455 intakes of acesulfame-K were increased compared with the 1994 data. The mean intakes
44
45 456 of all sweeteners were below their respective ADI values, with means in the group of 400
46
47 457 high consumers of intense sweeteners (see above) of 0.4, <0.1, 2.4, 2.1, 0.3 and 0.2
48
49 458 mg/kg body weight/day for acesulfame-K, alitame, aspartame, cyclamate, saccharin and
50
51 459 sucralose respectively. The corresponding 95th percentile intakes were 1.4, <0.1, 7.0, 9.3,
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3 460 2.4 and 2.3 mg/kg body weight/day respectively. The mean intakes in the 298 diabetics
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5
6 461 were 0.6, <0.1, 2.3, 3.3, 0.5 and 0.5 mg/kg body weight/day for acesulfame-K, alitame,
7
8 462 aspartame, cyclamate, saccharin and sucralose respectively and the 95th percentile intakes
9
10 463 were 2.0, <0.1, 7.5, 11.6, 1.9 and 1.9 mg/kg body weight/day respectively.

11
12 464 *Strengths* – A major strength of this study is the size of the cohort from which the high
13
14 465 consumers and diabetics were selected. It was a recent study in a population where 6
15
16 466 different intense sweeteners were available. The study appears to have been conducted in
17
18 467 February which corresponds to a potentially high summer intake of beverages containing
19
20 468 intense sweeteners.

21
22 469 *Weaknesses* – The participants were not given an individual interview, and the absence of
23
24 470 a personal explanation of the protocol may have reduced understanding and compliance
25
26 471 with diary completion.

27
28 472 *Conclusions* – The means and 95th percentile intakes were below the ADI values of the
29
30 473 different sweeteners in the selected high consumers and diabetics, with the exception of
31
32 474 cyclamate in diabetics, where the 95th percentile slightly exceeded the JECFA ADI value.

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34 475
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36 476 *Van Rooij-Van Den Bos et al. (2004)*

37
38 477 This study combined data on the concentrations of intense sweeteners in retail food
39
40 478 available in 2003 with data from the third Dutch National Food Consumption Survey
41
42 479 1997/1998 in order to provide updated intake estimates.

43
44 480 *Study population* – Data from the National Food Consumption Survey were used, which
45
46 481 was based on 6250 persons in 2774 households with all household members asked to
47
48 482 participate.

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2
3 483 *Country* – The Netherlands.
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5 484 *Time of intake data collection* – April 1997 to March 1998.
6

7
8 485 *Nature of intake data* – Data were collected using a two-day diary. Food consumed at
9
10 486 home was recorded in the diaries by the person who usually prepared the meal for the
11
12 487 household. Each participant recorded foods consumed out of the house. All products in a
13
14 488 single food coding in the food composition database that could contain an intense
15
16 489 sweetener were assumed to contain the same sweetener. If the food product could not be
17
18 490 related to an existing food coding the intake was assumed to be that of the closest non-
19
20 491 sweetened coding with correction for the market share of sweetened products in that food
21
22 492 coding. For worst-case calculations, the highest consumptions (95th percentiles) of soft
23
24 493 drink, lemonade syrup, yogurt drink and chocolate milk were calculated assuming that all
25
26 494 of the products in each category consumed were sweetened with a single sweetener using
27
28 495 the average measured concentration.
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34 496 *Product concentration data* – Concentrations were measured in food products that were
35
36 497 purchased in 2003 and which was likely to contain an intense sweetener based on the
37
38 498 label.
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40
41 499 *Results* – The estimated average and 95th percentile intakes of acesulfame-K, aspartame,
42
43 500 cyclamate and saccharin were all 1mg/kg body weight or less. The highest calculated 95th
44
45 501 percentile intakes were in the 1-4 years age range and the highest value in this age group
46
47 502 was for cyclamate (1.1mg/kg body weight/day). The results from the worst-case
48
49 503 calculations indicated that for the whole population (1-97years old) the 95th percentile
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51 504 consumers of soft drinks had intakes of 2, 2, 4 and 0.5mg/kg body weight/day of
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3 505 acesulfame-K, aspartame, cyclamate and saccharin respectively. The corresponding daily
4
5 506 intakes for the 1-4 years age range were 6, 8, 14 and 2mg/kg body weight respectively.
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8 507 *Strengths* – The concentrations of sweeteners were measured directly.
9

10 508 *Weaknesses* – The intakes of foods categories are based on national estimates and
11
12 509 therefore major assumptions had to be made. Intake and concentration data do not relate
13
14 510 to the same time period or to the same products.
15
16

17 511 *Conclusions* – Despite the conservative assumptions made the mean and 95th percentile
18
19 512 intakes were below the ADI values. The worst-case calculations of the intakes of
20
21 513 sweeteners indicated that the only sweetener with the potential to exceed the relevant
22
23 514 ADI was cyclamate in 1-4 year olds.
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29 516 In addition to the studies outlined above, limited information has been published in
30
31 517 summary form for Korea and Japan in which the bases for the intake estimates were not
32
33 518 clearly explained and the results were not corrected for body weight. The estimated
34
35 519 intakes of acesulfame-K and saccharin in Koreans were 1.3 and 4.1mg/person/day and
36
37 520 the theoretical maximum daily intakes were 31 and 106mg/person/day, values that are
38
39 521 well below the corresponding ADI values (Kim et al. 2004). The average daily intakes of
40
41 522 acesulfame-K, aspartame, saccharin and sucralose in Japan were reported as 0.8, 7.3, 0.7
42
43 523 and 0.4 mg/person (Yomota et al. 2002).
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48 524
49
50 525 Estimates of sweetener intakes in the European Union are given in the European
51
52 526 Commission Report on Dietary Food Additive Intake. Estimates were made using the
53
54 527 “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
4
5 529 of the sweetener, and the “Tier 3” approach, in which the theoretical intake was
6
7
8 530 calculated by combining the mean national food consumption data of the whole
9
10 531 population with the actual use levels of the sweetener. The results were expressed as the
11
12 532 % of the corresponding SCF ADI values (using the old SCF ADI for cyclamate of 0-
13
14 533 11mg/kg body weight per day). The ranges of intakes in adults were 2-37% for
15
16
17 534 acesulfame-K (Tier 2 data for Denmark, France, Italy, The Netherlands, UK and Norway)
18
19
20 535 and 0-11% for cyclamate (Tier 2 data for Denmark, France, Italy, The Netherlands, UK
21
22 536 and Norway). The ranges of intakes in children were 3-107% for acesulfame-K (Tier 3
23
24 537 data for France, The Netherlands and UK), 1-40% for aspartame (Tier 2 data for The
25
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27 538 Netherlands and UK), 1-74% for cyclamate (Tier 2 data for France, The Netherlands and
28
29 539 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
4
5 553 not really provide reliable new information (Garnier-Sagne et al. 2001, Ilback
6
7
8 554 et al. 2003, Devitt et al. 2004 and van Rooij-van den Bos et al. 2004).

9
10 555 iv. Those that were designed primarily for other purposes or to address specific
11
12 556 issues, such as assessing exposure from urinary excretion data for the
13
14 557 sweetener and/or its metabolites (Wilson et al. 1999 and Serra-Majem et al.
15
16
17 558 2003).

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20 559
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22 560 Comparisons of the data from these studies with the findings reviewed previously
23
24 561 (Renwick, 1999) show that the intakes of intense sweeteners have not increased
25
26
27 562 substantially in the past 10 years. The recent studies consistently show that the average
28
29 563 and 95th percentile intakes of all sweeteners by adults are below the corresponding ADI
30
31 564 values. One of the most comprehensive and reliable of the recent studies was that of
32
33
34 565 Leclercq et al. (1999) which focused on a potential high intake group, used a 14-day
35
36 566 prospective diary and obtained brand-related concentration data. This study found that the
37
38
39 567 mean and maximum intakes of the sweeteners investigated (aspartame, acesulfame-K,
40
41 568 cyclamate and saccharin) were below 1mg/kg body weight/day. The follow-up study of
42
43
44 569 Arcella et al. (2004) reached similar conclusions while focusing on individuals identified
45
46 570 as high consumers. The large and comprehensive study by Food Standards Australia New
47
48 571 Zealand (2004) showed that, with the exception of the 95th percentile intake of cyclamate
49
50 572 in diabetics, the means and 95th percentile intakes of intense sweeteners were below the
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52
53 573 corresponding ADI values.

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3 575 Recent studies have focused on children (Food Standards Agency UK 2001, Garnier-
4
5 576 Sagne et al. 2001, Ilback et al. 2003 and Devitt et al. 2004) because of their higher intakes
6
7 577 of foods and beverages on a body weight basis, and on diabetics (Garnier-Sagne et al.
8
9 578 2001, Ilback et al. 2003, Devitt et al. 2004 and Food Standards Australia New Zealand
10
11 579 2004) because of their higher potential intakes of intense sweeteners. The studies
12
13 580 reported have used a variety of conservative assumptions, and therefore do not provide
14
15 581 definitive data, but simply confirm that these groups may have higher than average
16
17 582 intakes.
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23
24 584 The only sub-group analyses that have indicated that the 95th percentile intake of a
25
26 585 sweetener may exceed the ADI are for cyclamate in children, particularly those with
27
28 586 diabetes. Such a conclusion was apparent from calculations available at the time of the
29
30 587 earlier review (Renwick 1999), and recent publications do not include a specifically
31
32 588 designed study producing reliable data for this group, but simply confirm the possibility
33
34 589 by further theoretical worst-case calculations. Resolution of this theoretical possibility
35
36 590 will require a specifically-designed study using a quantitative prospective 5-day or 7-day
37
38 591 diary combined with brand-specific data on intakes and concentrations, in which any
39
40 592 dilution of beverages for children is recorded accurately. The recent reduction in the ADI
41
42 593 of cyclamate from 0-11 mg/kg body weight/day to 0-7 mg/kg body weight/day by the EU-
43
44 594 SCF (SCF, 2000) has resulted in changes to the uses of cyclamate. Any specifically-
45
46 595 designed study should be undertaken after these changes have taken effect and the new
47
48 596 pattern of uses has stabilized. Interpretation of the intake data on cyclamate is also
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51 597 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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5
6 599 significant amounts of this metabolite (Renwick et al. 2004). Theoretically, the best study
7
8 600 design for estimating exposure to cyclohexylamine following cyclamate ingestion would
9
10 601 be based on that of Serra-Majem et al. (2003), and combine an optimized food-diary, as
11
12 602 outlined above, with measurements of the daily urinary excretion of cyclamate and
13
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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20 605 metabolizing ability.
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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.