

# NUTRITION

## RESEARCH REVIEWS



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### **Expert consensus on low calorie sweeteners : facts, research gaps and suggested actions**

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# 1 Expert consensus on low calorie sweeteners: 2 facts, research gaps and suggested actions

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## 46 Abstract

47  
48 A consensus workshop on low calorie sweeteners (LCS) was held in November 2018 where  
49 seventeen experts (the panel) discussed three themes identified as key to the science and  
50 policy of LCS: (1) weight management and glucose control; (2) consumption, safety and  
51 perception; (3) nutrition policy. The aims were to identify the reliable facts on LCS, suggest  
52 research gaps and propose future actions. The panel agreed that the safety of LCS is  
53 demonstrated by a substantial body of evidence reviewed by regulatory experts and current  
54 levels of consumption, even for high users, are within agreed safety margins.. However,  
55 better risk communication is needed. More emphasis is required on the role of LCS in  
56 helping people reduce their sugar and energy intake, which is a public health priority. Based  
57 on reviews of clinical evidence to date, the panel concluded that LCS can be beneficial for  
58 weight management when they are used to replace sugar in products consumed in the diet  
59 (without calorie substitution). The available evidence suggests no grounds for concerns  
60 about adverse effects of LCS on sweet preference, appetite or glucose control ; indeed, LCS  
61 may improve diabetic control and dietary compliance. Regarding effects on the human gut  
62 microbiota, data are limited and do not provide adequate evidence that LCS affects gut  
63 health at doses relevant to human use. The panel identified research priorities, including  
64 collation of the totality of evidence on LCS and body weight control, monitoring and  
65 modelling of LCS intakes, impacts on sugar reduction and diet quality and developing  
66 effective communication strategies to foster informed choice. There is also a need to  
67 reconcile policy discrepancies between organisations and reduce regulatory hurdles that  
68 impede low energy product development and reformulation.  
69

## 70 Introduction and aim of the Consensus Report

71  
72 A number of reviews, some narrative and some systematic, have discussed the evidence for  
73 the safety of LCS and their effects on appetite, food intake, body weight, glucose control and  
74 other health outcomes [\(1\)](#) [\(2\)](#) [\(3\)](#) [\(4\)](#) [\(5\)](#) [\(6\)](#) [\(7\)](#) [\(8\)](#). Evidence has also been evaluated by authorities  
75 such as the European Food Safety Authority (EFSA), the (US) Dietary Guidelines Advisory  
76 Committee (DGAC), the French Agency for Food, Environmental and Occupational Health &  
77 Safety (ANSES) and Public Health England (PHE), who have issued statements or opinions  
78 on the use of low calorie sweeteners [\(9\)](#) [\(10\)](#) [\(11\)](#) [\(12\)](#) [\(13\)](#). Other groups of scientific experts  
79 have generated consensus statements, position papers, or other statements on LCS. These  
80 include the British Dietetic Association, Diabetes UK, the American Heart Association and  
81 American Diabetes Association (AHA/ADA) [\(14\)](#) [\(15\)](#) [\(16\)](#) [\(17\)](#) [\(18\)](#) [\(19\)](#) [\(20\)](#).

82  
83 This paper describes the results of a workshop in which seventeen experts convened to  
84 discuss and debate the science and policy relating to the use of LCS. The aims were to  
85 establish via consensus-forming techniques, clear and simple statements on LCS that all the  
86 panel agreed (facts), to highlight the areas where more research is required (gaps) and to  
87 propose how progress might be achieved (actions). It is hoped that the provision of these  
88 statements on safety and potential benefits of LCS will assist health practitioners and policy  
89 makers to promote consistent messages and develop strategies based on sound science.  
90 Identification of the gaps and actions will help promote better study designs, suggest  
91 priorities for research funding and thereby encourage more coherent public health policy.

## 92 Background to LCS and their regulatory approval process

93

94 All LCS have undergone an extensive safety evaluation process by international and  
95 national regulatory food safety bodies both before and after their approval for use in the  
96 market. The Food and Agriculture Organization (FAO)/World Health Organization (WHO)  
97 Joint Expert Committee on Food Additives (JECFA) (21), the US Food and Drug  
98 Administration (FDA) (22), and EFSA (9), have confirmed the safety of all approved LCS as  
99 food additives. Hence there is an extensive body of evidence from both animal models and  
100 human studies that support the safety of LCS. Each compound is considered individually as  
101 their characteristics, metabolism and metabolic fates are different (23). Furthermore, there is  
102 an ongoing review process to ensure that any new information on safety is evaluated, for  
103 example recent scientific opinions by EFSA on aspartame and sucralose (24) (25).

104  
105 As part of the LCS safety evaluations, the regulatory authorities establish the Acceptable  
106 Daily Intakes (ADI) for each sweetener (26). The ADI is defined as an estimate of the amount  
107 of a food additive, expressed per kg bodyweight, that can be ingested daily by individuals  
108 over a lifetime without appreciable risk to health. ‘Without appreciable risk’ means, based on  
109 the current knowledge, “certainty that no harm will result, even after a lifetime of exposure to  
110 the additive” (27). The current ADIs for LCS were established using the ‘No Observed  
111 Adverse Effect Level’ (NOAEL). This is the highest dietary level of an additive at which no  
112 adverse effects were observed in animal studies. The ADI is typically set at 1/100th of the  
113 NOAEL (10-fold reduction for inter-species variation and 10-fold reduction for intra-species  
114 variation) to give a large margin of safety for even the most sensitive consumer. The ADI  
115 refers to a lifelong exposure situation, not a single occasion, and thus infrequent  
116 consumption of levels higher than the ADI are not a health concern. Because of the large  
117 safety margin used in setting the ADI, it is likely that an ADI for a given additive would have  
118 to be exceeded by some considerable amount for an extended period of time for there to be  
119 any risk of harm to human health. However, if an intake estimate indicates that the ADI may  
120 be regularly exceeded by certain sectors of the population, the regulatory authority may  
121 advise a reduction of levels in foods, or to reduce the range of foods in which the additive is  
122 permitted for use (27). In some cases, the ADI may be “not specified” when the total  
123 potential intake from all possible sources does not represent a hazard to health, and hence  
124 no numerical ADI is needed. It should be noted that, in the future, the Benchmark Dose  
125 (BMD) will be the preferred approach for establishing a reference point (28). However,  
126 discussion of the expert considerations and data requirements for calculation of a BMD is  
127 beyond the scope of this paper.

128  
129 In relation to efficacy, EFSA has a system for evaluating dossiers of evidence submitted for  
130 the substantiation of health claims (29). In 2011, the EFSA Panel on Nutrition, Novel Foods  
131 and Food Allergens (NDA) concluded that there was sufficient scientific evidence to support  
132 the claims that intense sweeteners, like all sugar replacers, lead to a lower rise in blood  
133 sugar levels after meals if consumed instead of sugars, and maintain tooth mineralisation by  
134 decreasing tooth demineralisation; again if consumed instead of sugars. However at that  
135 time, EFSA’s experts found no clear cause and effect relationship to substantiate the claims  
136 that intense sweeteners when replacing sugars maintain normal blood sugar levels, or  
137 maintain/achieve a normal body weight (30).

138  
139 There are currently various jurisdiction-specific restrictions on the use of LCS in foods and  
140 beverages. For example, under European legislation, sweeteners are only permitted if used  
141 to replace sugars for the production of energy-reduced food (i.e. with 30% less energy), non-  
142 cariogenic food, or food with no added sugars (31). This limits the options available to  
143 manufacturers for more modest reformulation or stepwise reduction of sugar content in food  
144 and drink through the use of sweeteners.

145

## 146 Methods

147  
148 The consensus workshop was designed to follow a conference held by the International  
149 Sweeteners Association (ISA) in London on 6th November 2018 entitled 'The science behind  
150 low calorie sweeteners: where evidence meets policy'. The panel members were all  
151 speakers or chairs at that conference, chosen for their international expertise in LCS science  
152 and policy. The workshop was chaired and facilitated by two independent consultants in  
153 nutrition science, (MA and SG), who drafted the paper and coordinated responses from  
154 participants. The ISA provided funds for the venue and speakers' expenses. They were  
155 observers at the workshop but had no control over the paper.. Disclosures of interest for all  
156 authors are given.

157 The workshop leaders (MA and SG) identified 3 key Themes or topic areas for discussion at  
158 the workshop:

- 159  
160 1) Role of low calorie sweeteners in weight management and glucose control  
161 2) Consumption and safety of low calorie sweeteners and consumer perception  
162 3) Role of low calorie sweeteners in relation to nutrition policy

163 As the workshop was time-limited the choice of themes was based on the pertinence in  
164 terms of current debates on LCS, and the available expertise represented by the panel.

165  
166 Prior to the workshop, each panel member was asked to provide feedback on 3 questions  
167 with respect to their own area of expertise:

- 168  
169 a. Statements of fact: what do we know?  
170 b. Questions and type of evidence needed (gaps: what do we still need to know?)  
171 c. How this might translate to further research work or policy (actions: what should we  
172 do?).

173  
174  
175 Comments were minimally edited by MA and SG to produce the Working Document (WD)  
176 with provisional statements/questions/actions for each Theme.

177  
178 At the workshop all the participants discussed the WD in detail. A scoring system (1=strongly  
179 disagree to 10=strongly agree) was used to evaluate level of agreement on the 'facts'.  
180 Statements that achieved a high level of agreement were discussed further. Participants  
181 refined the wording of each statement to reach consensus. Having established agreement  
182 on the facts, participants identified the major gaps or research questions. Finally,  
183 participants identified the most important 'actions' suggested in the WD and these were then  
184 summarised. Participants agreed to the process for further review and publication, i.e. that  
185 the workshop leaders would circulate the draft consensus document for comments, integrate  
186 responses and write the discussion before presenting the final article to all participants for  
187 review and approval. Table 1 shows the Timeline of the project.

188  
189

## 190 Results

191

192 The results are given below in the form of the consensus statements for the three Themes  
193 and the three questions relating to each Theme. The panel agreed the most pertinent  
194 references to cite for each consensus statement.

195 **Theme 1: Role of low calorie sweeteners in weight management and  
196 glucose control: the scientific evidence**  
197

198 **1a Facts - What we know**

- 200 1. When substituted for sugars to reduce energy density of foods and drinks, LCS  
201 reduce net energy intake and assist weight management (3) (5) (12) (13).  
202
- 203 2. Intervention studies have shown that beverages containing LCS have at least a  
204 similar effect on appetite and energy intake to water (5) (32).  
205
- 206 3. The collective evidence supports the conclusion that LCS have no adverse effect on  
207 blood glucose and insulin regulation (HbA1c, fasting and post-prandial glucose and  
208 insulin levels) in people with, and without, diabetes (2) (33) (34)  
209
- 210 4. The potential value of LCS in dietary management of diabetes derives from their role  
211 as substitutes for sugars, and hence carbohydrates. (19).  
212
- 213 5. Confounding by adiposity, and reverse causality can explain the positive association  
214 between LCS and T2DM and other cardiometabolic diseases, reported in some  
215 observational studies. (35) (36) (37).  
216
- 217 6. Regarding effects involving the human gut microbiota, data are limited and do not  
218 provide adequate evidence that LCS influence gut health at doses relevant to human  
219 use. (38)

220 **1b Gaps: What we don't know**

- 222 1. What are the long-term effects of LCS on glucose tolerance, gut function,  
223 cardiometabolic effects, gut microbiota and weight management?  
224
- 225 2. How are these effects altered according to personal factors, such as age, sex,  
226 ethnicity, socio-economic status, health status, diet and lifestyle?  
227
- 228
- 229 3. How do these effects differ according to dietary context (ad lib vs. weight-control diet)  
230 and form of LCS (in liquids or solids), and type or blend of LCS?  
231
- 232 4. Does reducing exposure to sweetness have consequences for food choice and  
233 intake in the medium-to-long term?  
234
- 235
- 236 5. Can LCS help improve long term Type 2 diabetes (T2DM) management, when part of  
237 standard dietary and lifestyle approaches?  
238

239 **1c Actions - What should be done?**

- 241 1. There is a need for a portfolio of well-designed RCTs (with appropriate time frame of  
242 a year or more) with different comparators and different carriers of LCS (food and  
243 beverage matrices). The trials should be conducted by level of 'free sugar' intake in  
244 different populations; they should use multiple endpoints (diet quality, gut microbiota  
245 function and metabolomics, and wider health and quality of life measures). They

- 246 should be done in the context of weight-control diets, including for T2DM and also in  
247 non-restrictive diets.
- 248
- 249 2. There is a need for population cohort studies to model changes in weight/  
250 cardiometabolic risk in the context of changes in LCS consumption, not baseline LCS  
251 values. The studies should include substitution analysis (e.g. LCS beverages for  
252 caloric beverages, water, etc.) and adjustment for adiposity. Their data should be  
253 made available for further analysis.
- 254
- 255
- 256 3. There is a need for a collation of evidence to support future health claim submissions  
257 for LCS and body weight control, as data become available.
- 258

## 259 **Theme 2 - Consumption and safety of low calorie sweeteners and consumer 260 perception**

### 261 **2a Facts - What we know**

- 262
- 263 1. The safety of LCS is demonstrated by a substantial body of evidence as well as  
264 continued review by independent regulatory agencies/committees including  
265 JECFA/Codex, FDA and EFSA [\(21\)](#) [\(22\)](#) [\(9\)](#). These organisations have taken into  
266 account of the decades of both positive and negative human and animal studies to  
267 draw their conclusions. Continual monitoring and modelling of LCS exposures is  
268 undertaken and this demonstrates that intakes of LCS, even among high  
269 consumers, are within ADIs [\(39\)](#) [\(40\)](#) [\(41\)](#).
- 270
- 271 2. Currently, the major sources of LCS in the Western diet are beverages and table top  
272 sweeteners [\(39\)](#) [\(40\)](#) [\(42\)](#).
- 273
- 274 3. LCS can be used to reduce the sugar and energy content of beverages and some  
275 foods whilst maintaining a similar sensory profile. The potential for energy reduction  
276 is more limited in foods and depends on the options for reformulation and what  
277 replaces the bulk of sugar [\(43\)](#). LCS can be used synergistically in blends to achieve  
278 the desired sensory profile at lower levels of use.
- 279
- 280 4. The collective evidence supports the conclusion that there is no relationship  
281 between adiposity and liking/ preference for sweet taste in either adults or  
282 children [\(44\)](#).
- 283
- 284 5. Consumer perceptions vary with regard to LCS, with some people having concerns  
285 about their potential health effects [\(14\)](#) [\(20\)](#).

### 286 **2b Gaps – What we don't know**

- 287
- 288 1. Which factors (including knowledge, attitudes and behaviours) influence consumer  
289 perception of risks and benefits of LCS consumption? Are these the same for health  
290 professionals?
- 291
- 292 2. There is a need for in-depth data relating to current patterns of LCS consumption at  
293 multiple levels, and across countries and regions, to strengthen the evidence base.
- 294
- 295 3. There is a need for more reliable measures of LCS exposure, such as biomarkers.  
296 Further development of these and better linkage of food composition and dietary  
297 databases is needed to help monitor changing use and consumption of LCS.

298 **2c Actions - What should be done?**

299

- 300 1. There is a need to research and develop evidence-based strategies to communicate  
301 all of the above to consumers, health professionals and policy makers. The extensive  
302 body of scientific evidence that backs regulatory approval and the on-going safety  
303 assessment of LCS can then encourage better informed public health decisions. The  
304 media or other organisations could be provided, for example, with simple  
305 explanations of the ADI.
- 306
- 307 2. There is a need to develop communications to foster more informed public attitudes  
308 towards LCS, for example by emphasizing the potential health gains associated with  
309 sugar (and energy) intake reduction and the role of LCS in achieving this. It is  
310 important to explain that the overall impact of LCS will depend on the amount of  
311 sugars replaced in the diet and the overall reduction in calorie (energy) intake that  
312 ensues. Use of LCS alone cannot be expected to act as a 'silver bullet' for weight  
313 loss.
- 314
- 315
- 316 3. Research into biomarkers for individual LCS is needed to complement the exposure  
317 assessment based on consumption records. There is a need to improve linkage of  
318 databases and to model intakes in future scenarios.

320 **Theme 3 - Role of low calorie sweeteners in relation to nutrition policy**

321

322 **3a Facts - What we know**

323

- 324 1. Reduction in the intake of 'free sugars' and 'added sugars' is being recommended  
325 around the world to reduce the risk and prevalence of obesity, which is a major public  
326 health concern ([10](#)) ([45](#)) ([46](#)). LCS is one of the strategies to consider.
- 327
- 328 2. LCS can be useful in dietary approaches to both prevent and manage diabetes and  
329 obesity. Benefit will depend on how foods and beverages containing LCS are  
330 substituted, as well as on the overall quality of the diet and the overall energy  
331 provision ([16](#)).
- 332
- 333 3. Despite repeated and consistent reassurances from food safety authorities, there is  
334 still some distrust of LCS among health professionals and policy makers. ([47](#))
- 335
- 336 4. Some policies acknowledge LCS consumption as a useful strategy to reduce sugars  
337 intake ([12](#)). However, there are discrepancies with other national and international  
338 policies ([10](#); [11](#)) and regarding use in children.

339 **3b Gaps - What we don't know**

340

- 341 1. Can LCS help individuals meet the population level dietary recommendations for  
342 reduction of sugars intake (e.g. to 5% (average) ([48](#)) or 10% (for individuals) ([10](#); [45](#))?  
343 If so, how can this be achieved?
- 344
- 345 2. How does a dietary approach that includes LCS-sweetened foods and drinks affect  
346 dietary quality compared to low-sugar diets?

349        3. What are the best strategies to communicate LCS safety and efficacy to interested  
350        parties such as health professionals and the general public?  
351

352 **3c Actions - What should be done?**

- 353
- 354        1. There is a need to model the potential for LCS to reduce sugar content and sugar  
355        intakes whilst ensuring that other dietary recommendations can also be met in the  
356        overall diet.
- 357
- 358        2. Trends in dietary intake of LCS need to be monitored, linked with food and beverage  
359        reformulation and ultimately with health outcomes.
- 360
- 361        3. Policies relating to LCS from different countries should be reviewed to compare their  
362        remit, priorities, evidence base and interpretation.
- 363
- 364        4. To help reconcile policy discrepancies, policy makers, scientists and regulatory  
365        affairs experts should agree on their understanding of the role of LCS in the diet.
- 366
- 367        5. In the context of sugar reduction and obesity, it would be helpful to review the  
368        regulatory and public health policy hurdles that prevent wider use of LCS in food  
369        products for those sweeteners where dietary intake is very low compared to the ADI.
- 370

371 **DISCUSSION**

372 **Strengths and limitations of approach**

373

374        The methodology followed a planned and transparent process. All 17 experts were  
375        requested ahead of the workshop to generate a summary of their topic in the form of  
376        answers to the three questions. These were then collated under three Themes by the  
377        workshop leaders and combined for the working document, which was circulated prior to the  
378        workshop. At the start of the group discussion, scoring was used as a consensus-forming  
379        technique to allow participants to indicate the strength of their agreement with each  
380        statement. Alternative forms of wording suggested by participants were considered in order  
381        to improve clarity of each statement. The resulting statements were circulated after the  
382        workshop, with supporting references, to allow for further reflection and improvement. A  
383        strength of the process was the expertise represented on the panel in many aspects of LCS  
384        (including toxicology, regulation, food science, medicine, microbiology, psychology,  
385        epidemiology, public health nutrition and dietetics). Finally, holding the workshop  
386        immediately after a scientific conference on the topic ensured that all experts were fully  
387        prepared and engaged to discuss the issues and formulate consensus.

388

389        The workshop was wide in scope but was not intended to be exhaustive; the themes were  
390        selected as being pertinent to current debate on LCS and within scope of the expertise of the  
391        panel. Consensus was based on expert opinion and key references including systematic  
392        reviews; the group did not review all the primary literature on these themes. Other possible  
393        limitations of the methodology were that all our participants were scientists or public health  
394        experts, unlike the broader stakeholder panel used by Bright et al. (49). The workshop was  
395        instigated and funded by ISA; however, ISA had no control over the choice of Themes, and  
396        no role in the discussion or this paper. Participants all acted completely independently to  
397        express their views in open debate and to contribute to the resulting paper.

398

399 **Comparison with other consensus papers relating to LCS**

400 **Goals and methodology**

401 To our knowledge, there have been three previous papers published in English that contain  
402 consensus statements about LCS (14) (15) (49). In addition, there have been a number of  
403 position papers and evidence reviews whose methodology and scope differ from that of the  
404 present report and these are discussed later.

405 The goal of the consensus report by Gibson et al. (14) was to summarise the role and  
406 potential benefits of LCS on appetite, energy intake, body weight, diabetes and dental health  
407 to give clarity to health professionals and educators on use of LCS. The goal of the Ibero–  
408 American Consensus on LCS (15) was “to develop a consensus on the use of low- and no-  
409 calorie sweeteners as substitutes for sugars and other caloric sweeteners in line with current  
410 international public health recommendations, in the context of the prevention and treatment  
411 of obesity and related diseases in Latin American countries”. The report (15) also provides a  
412 comprehensive overview of the position of international and national regulatory bodies on  
413 LCS safety and efficacy studies on individual LCS. Both these consensus reports (14) (15)  
414 were compiled by panels limited to international scientists and public health experts.

415 The report by Bright et al. (49), focused on future research needs, and involved a wider  
416 stakeholder panel who participated in interactive webinars, surveys and interviews with the  
417 research team and generated a list of 18 questions across 5 broad research areas, ranking  
418 them in order of priority. The stakeholder panel was recruited according to the “7 P’s” of  
419 stakeholder engagement i.e. patients, providers, researchers, policymakers, product  
420 makers, payers, and purchasers (50). It therefore included policymakers, lay audience  
421 members, health providers, a research funder, individuals with food industry experience, and  
422 researchers of several different specialties.

423 **Content and conclusions**

424 The consensus statements agreed by our expert panel were produced independently but  
425 have been compared with previous consensus statements in Table 2. Further details can be  
426 found in supplementary Tables S1 and S2. Some topics were not covered in other reports:  
427 for example, the statements in this paper have included association between sweetness  
428 preference and obesity, effects of LCS on gut bacteria and sources of LCS, which were not  
429 covered by Gibson et al. (14) or Serra-Majem et al. (15); conversely, this panel did not  
430 consider the effects of LCS on dental health.

431 Table 2 shows there was broad agreement between the sentiments expressed in our  
432 statements and these two reports.

433 The gaps identified by our panel have been compared with the research priorities from Bright  
434 et al. (49) (Table S3). Most of the important future research questions identified by their  
435 stakeholder panel were also selected by our panel as areas in need of study. In the case of  
436 effects of LCS beverages on appetite and energy intake (Bright et al. (49) Q2), our panel  
437 considered the evidence to be sufficiently strong for ‘no effect or at least similar effect’  
438 compared to water to be classed as fact, and for a reduction in energy intake compared to  
439 sugar also to be classed as fact. Research gaps identified by our panel and not identified by  
440 Bright et al. (49) included research on biomarkers of LCS consumption to aid intake  
441 assessments, research on communication with consumers and other stakeholders about  
442 LCS and more research on issues related to policy. Conversely Bright’s (49) questions on the

444 sensing of LCS by the brain and the impact of LCS on the fetus, did not feature directly in  
445 our workshop discussion.

#### 446 Comparison with other reviews and position statements

447  
448 In 2011 EFSA was of the opinion that a cause and effect relationship had not been  
449 established between the use of intense sweeteners and maintenance of normal body weight  
450 or blood glucose, but several high quality studies and reviews have since been published  
451 ([51](#)) ([52](#)) ([53](#); [54](#)) and others are currently underway: the SWITCH project ([55](#)) and the SWEET  
452 project; (available at <https://sweetproject.eu>). A number of reviews and position statements  
453 have addressed the evidence for and against health benefits of LCS. Our panel observed  
454 that differences between the positions and policies of different organisations with regard to  
455 LCS are a cause of confusion. Reasons for discrepancies may include different remits and  
456 approaches. The goal of systematic review and meta-analysis is frequently hampered by  
457 differing study designs that make comparison difficult and meta-analysis unreliable; hence  
458 the need for cautious wording, which may be interpreted as a negative statement.. It is  
459 important to clearly establish that LCS are food additives and, as such cannot provide health  
460 benefits, except in relation to the reduction of sugar within an adequate diet and lifestyle. Our  
461 panel concluded that, when used to replace dietary sugar, the use of LCS facilitates  
462 reduction in energy intake and weight loss. This was based on evidence from RCTs of 6m to  
463 2 years in length and recent systematic reviews that pay careful attention to appropriate  
464 comparators. The panel also stated the need for studies of longer-term effects. By contrast,  
465 a recent wide-ranging review on health effects of non-sugar sweeteners (which in practice  
466 were LCS as polyols were excluded.) concluded that "there were no significant or clinically  
467 important effects on most outcomes" ([8](#)). However due to very strict inclusion and exclusion  
468 criteria, their analyses omitted some notable studies on body weight ([51](#); [52](#)), ([53](#)) ([54](#)) and  
469 combined studies with different comparators, potentially diluting the effect size ([56](#)). Another  
470 recent review ([57](#)) has been criticised on the same grounds ([37](#)). Toews et al. ([8](#)) also stated  
471 that "potential harms from the consumption of non-sugar sweeteners could not be excluded",  
472 a statement which relates to lack of evidence, not evidence of harm. Our panel took a harm-  
473 reduction approach, where LCS are a desirable substitute for sugar and one route to helping  
474 achieve sugar and energy reduction whilst still maintaining dietary diversity and pleasure.  
475

476 Other position statements, particularly those published before 2014, have offered cautious  
477 conclusions on potential benefits of LCS. For example, the 2012 joint scientific statement  
478 from the American Heart Association and the American Diabetes Association (AHA/ADA)  
479 concluded that "at present there are insufficient data to determine conclusively that non-  
480 nutritive sweeteners (NNS) benefit appetite, energy intake or body weight" ([20](#)). However, the  
481 AHA/ADA document also stated that "when used judiciously, NNS could facilitate reductions  
482 in added sugars intake, thereby resulting in decreased total energy and weight loss/weight  
483 control and promoting beneficial effects on related metabolic parameters".  
484

485 The latest AHA advisory statement ([19](#)) (which focussed on LCS beverages and  
486 cardiometabolic outcomes) concluded that the use of LCS beverages may be an effective  
487 strategy to help control energy intake and promote weight loss. Nonetheless due to the lack  
488 of long-term trials in children, the AHA thought it prudent to advise against prolonged  
489 consumption of LCS beverages by children, preferring water, other unsweetened beverages  
490 or milk as the primary drink. Policy statements from professional bodies of dietitians and  
491 nutritionists have generally been pragmatic, seeing LCS as a helpful tool in helping people  
492 reduce their sugar intake and manage their weight in the context of a healthy balanced diet  
493 that meets other dietary recommendations ([16](#)) ([17](#); [18](#)).

#### 494 Extension of our consensus statements to actions and policies

495 The main strategy of our consensus workshop was to stimulate forward thinking as well as to  
496 restate principles. The consensus statements on actions put the focus firmly on what is

497 required to deliver. For example, the panel made recommendations for further long-term  
498 randomised controlled trials of LCS with different comparators and multiple endpoints, for  
499 prospective studies that control for adiposity and other confounders, and for better estimates  
500 of LCS exposure. Such recommendations may help research funding bodies select priorities.  
501 Clarity and consistency of policy would be improved by a comprehensive evaluation of all the  
502 evidence on effects of LCS. Others have also called for larger and longer clinical trials with  
503 careful selection of comparators (7) (37) (44) (58). The review by Toews et al. (8) was also  
504 critical of the size, short duration, and methodological and reporting quality of studies. It also  
505 called for more data on benefits and risks of non-sugar sweeteners in doses and patterns  
506 more akin to real life consumption (8). Our expert panel considered the safety data to be  
507 robust but agreed that there is a continued need for ongoing exposure assessment to  
508 account for changing LCS use, and also consideration of any new evidence that might  
509 emerge. Novel recommendations made by the panel included better strategies and methods  
510 to improve communications about the safety and efficacy of LCS, modelling of the effect of  
511 LCS on sugar reduction and diet quality, relaxing regulation to increase the potential for  
512 reformulation using LCS, and review and reconciliation of policy differences on the use of  
513 LCS.

514

## 515 Conclusion

516

517 The panel considered that the substantial body of evidence concerning LCS safety should  
518 be communicated in a consistent manner. More emphasis is required on the role of LCS in  
519 helping people reduce their sugar and energy intake, which is a public health priority.

520

521 Research priorities should include

- 522 a. a dossier of the totality of evidence on LCS and body weight control,
- 523 b. studies to monitor and model LCS intakes and their impact on sugar reduction and  
524 diet quality,
- 525 c. effective communication strategies to inform consumers, non-governmental  
526 organisations (NGOs), health professionals, research funding bodies and the food  
527 and beverage industry

528

529 Efforts should be made to understand and, where possible, reconcile policy discrepancies  
530 between organisations and reduce regulatory hurdles that impede product development and  
531 reformulation designed to reduce sugars and/or calories.

532

533 It is hoped that these consensus statements and recommendations arising from the expert  
534 workshop will assist policy makers, and other stakeholders including NGOs, health  
535 professionals, research funding bodies and the food and beverage industry.

536

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540 All authors completed ICMJE Forms. Independent consultants, MA and SG, received a fee  
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542

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544 All authors report personal or institutional honoraria and/or expenses from International  
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546

547  
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550  
551 M. Ashwell: Sugar Nutrition UK, Global Stevia Institute.  
552 S. Gibson: Sugar Nutrition UK, PepsiCo International.  
553 F. Bellisle: International Sweeteners Association.  
554 J. Buttriss: British Nutrition Foundation  
555 A. Drewnowski: food, beverage, and ingredient companies and other commercial and  
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558 M. Fantino: International Sweeteners Association, The Coca Cola Company.  
559 A. Gallagher: International Sweeteners Association.  
560 K.de Graaf: Top Institute of Food and Nutrition and TKI Agri-Food (Netherlands), Dutch  
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568 D. Mellor: International Sweeteners Association,  
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570 Sweeteners Association,  
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572 W. Russell: International Sweeteners Association.  
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575 C. La Vecchia: International Sweeteners Association

576  
577  
578

## 579 **References**

- 580  
581 1. Mortensen A (2006) Sweeteners permitted in the European Union, Safety aspects. . .  
582 *Scandinavian Journal of Food and Nutrition* **50**, 104-116.  
583 2. Wiebe N, Padwal R, Field C *et al.* (2011) A systematic review on the effect of sweeteners  
584 on glycemic response and clinically relevant outcomes. *BMC Med* **9**, 123.  
585 3. Miller PE, Perez V (2014) Low-calorie sweeteners and body weight and composition: a  
586 meta-analysis of randomized controlled trials and prospective cohort studies. *Am J Clin Nutr*  
587 **100**, 765-777.  
588 4. Bellisle F (2015) Intense Sweeteners, Appetite for the Sweet Taste, and Relationship to  
589 Weight Management. *Curr Obes Rep* **4**, 106-110.  
590 5. Rogers PJ, Hogenkamp PS, de Graaf C *et al.* (2016) Does low-energy sweetener  
591 consumption affect energy intake and body weight? A systematic review, including meta-  
592 analyses, of the evidence from human and animal studies. *Int J Obes (Lond)* **40**, 381-394.  
593 6. Lohner S, Toews I, Meerpohl JJ (2017) Health outcomes of non-nutritive sweeteners:  
594 analysis of the research landscape. *Nutr J* **16**, 55.  
595 7. Mosdol A, Vist GE, Svendsen C *et al.* (2018) Hypotheses and evidence related to intense  
596 sweeteners and effects on appetite and body weight changes: A scoping review of reviews.  
597 *PLoS One* **13**, e0199558.

- 598 8. Toews I, Lohner S, Kullenberg de Gaudry D *et al.* (2019) Association between intake of  
599 non-sugar sweeteners and health outcomes: systematic review and meta-analyses of  
600 randomised and non-randomised controlled trials and observational studies. *BMJ* **364**, k4718.  
601 9. European Food Safety Authority Topics: Sweeteners.  
602 <https://www.efsa.europa.eu/en/topics/topic/sweeteners> (accessed 30 August 2019)  
603 10. US Department of Agriculture (2015) Scientific report of the 2015 Dietary Guidelines  
604 Advisory Committee.  
605 <https://health.gov/dietaryguidelines/2015-scientific-report/> (accessed August 2019)  
606 11. ANSES (French Agency for Food Environmental and Occupational Health & Safety)  
607 (2015) OPINION of the French Agency for Food Environmental and Occupational Health &  
608 Safety on the assessment of the nutritional benefits and risks related to intense sweeteners.  
609 revised on 9 January 2015. <https://www.anses.fr/en/content/opinion-french-agency-food-environmental-and-occupational-health-safety-19-november-2014> (accessed August 2019)  
610 12. Public Health England (2015) Sugar Reduction: The evidence for action. *PHE publications gateway number 2015391*. <https://www.gov.uk/government/publications/sugar-reduction-from-evidence-into-action>  
611 (accessed August 2019)  
612 13. Public Health England (2015) Sugar Reduction: The evidence for action. Annex 5: Food  
613 supply. *PHE publications gateway number 2015391*.  
614 <https://www.gov.uk/government/publications/sugar-reduction-from-evidence-into-action>  
615 (accessed August 2019)  
616 14. Gibson S, Drewnowski A, Hill J *et al.* (2014) Consensus statement on benefits of low-  
617 calorie sweeteners. *Nutrition Bulletin* **39**, 386-389.  
618 15. Serra-Majem L, Raposo A, Aranceta-Bartrina J *et al.* (2018) Ibero-American Consensus  
619 on Low- and No-Calorie Sweeteners: Safety, Nutritional Aspects and Benefits in Food and  
620 Beverages. *Nutrients* **10**, 818.  
621 16. British Dietetic Association (2016) Policy Statement : the use of Artificial Sweeteners.  
622 17. Diabetes UK (2018) The use of low and no calorie sweeteners: position statement  
623 <https://www.diabetes.org.uk/professionals/position-statements-reports/food-nutrition-lifestyle/use-of-low-or-no-calorie-sweetners> (accessed February 12, 2019)  
624 18. Dyson PA, Twenefour D, Breen C *et al.* (2018) Diabetes UK evidence-based nutrition  
625 guidelines for the prevention and management of diabetes. *Diabet Med* **35**, 541-547.  
626 19. Johnson RK, Lichtenstein AH, Anderson CAM *et al.* (2018) Low-Calorie Sweetened  
627 Beverages and Cardiometabolic Health: A Science Advisory From the American Heart  
628 Association. *Circulation* **138**, e126-e140.  
629 20. Gardner C, Wylie-Rosett J, Gidding SS *et al.* (2012) Nonnutritive sweeteners: current use  
630 and health perspectives: a scientific statement from the American Heart Association and the  
631 American Diabetes Association. *Circulation* **126**, 509-519.  
632 21. Food and Agriculture Organisation of the United Nations Chemical risks and JECFA.  
633 <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/> (accessed 30 August  
634 2019)  
635 22. US Food and Drug Administration Additional Information about High-Intensity  
636 Sweeteners Permitted for Use in Food in the United States. <https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states> (accessed 30th August 2019)  
637 23. Magnuson BA, Carakostas MC, Moore NH *et al.* (2016) Biological fate of low-calorie  
638 sweeteners. *Nutr Rev* **74**, 670-689.  
639 24. European Food Safety Authority (2013) Scientific Opinion on the re-evaluation of  
640 aspartame (E 951) as a food additive. *EFSA Journal* **2013**; . Available online:  
641 [www.efsa.europa.eu/efsajournal](http://www.efsa.europa.eu/efsajournal) (accessed August 2019)  
642

- 647 25. European Food Safety Authority (2017) Statement on the validity of the conclusions of a  
648 mouse carcinogenicity study on sucralose (E 955) performed by the Ramazzini Institute.  
649 *EFSA Journal* 2017; **15**.
- 650 26. Benford D (2000) The Acceptable Daily Intake: A Tool for Ensuring Food Safety. *ILSI*  
651 *Europe Concise Monograph*. <http://ilsi.org/publication/the-acceptable-daily-intake-a-tool-for-ensuring-food-safety/>  
652 (accessed August 2019)
- 653 27. European Food Information Council (EUFIC) (2013) Acceptable Daily Intakes (ADIs)  
654 <https://www.eufic.org/en/understanding-science/article/qas-on-acceptable-daily-intakes-adis>  
655 (accessed August 2019)
- 656 28. Haber LT, Dourson ML, Allen BC *et al.* (2018) Benchmark dose (BMD) modeling:  
657 current practice, issues, and challenges. *Critical Reviews in Toxicology* **48**, 387-415.
- 658 29. Buttriss JL (2015) Nutrition and Health Claims in Practice. *Proc Nutr Soc* **40**, 211- 222.
- 659 30. European Food Safety Authority (2011) Scientific Opinion on the substantiation of health  
660 claims related to intense sweeteners and contribution to the maintenance or achievement of a  
661 normal body weight (ID 1136, 1444, 4299), reduction of post-prandial glycaemic responses  
662 (ID 4298), maintenance of normal blood glucose concentrations (ID1221, 4298), and  
663 maintenance of tooth mineralisation by decreasing tooth demineralisation (ID 1134, 1167,  
664 1283) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal*; **9**(6):2229  
665 [26pp] *Online* [www.efsa.europa.eu/efsajournal](http://www.efsa.europa.eu/efsajournal) (accessed August 2019)
- 666 31. EUR-Lex (2008) Regulation (EC) No 1333/2008 of the European Parliament and of the  
667 Council of 16 December 2008 on food additives. *Official Journal of the European Union*,  
668 <http://data.europa.eu/eli/reg/2008/1333/oj> (accessed August 2019)
- 669 32. Fantino M, Fantino A, Matray M *et al.* (2018) Beverages containing low energy  
670 sweeteners do not differ from water in their effects on appetite, energy intake and food  
671 choices in healthy, non-obese French adults. *Appetite* **125**, 557-565.
- 672 33. Tucker RM, Tan SY (2017) Do non-nutritive sweeteners influence acute glucose  
673 homeostasis in humans? A systematic review. *Physiol Behav* **182**, 17-26.
- 674 34. Nichol AD, Holle MJ, An R (2018) Glycemic impact of non-nutritive sweeteners: a  
675 systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr* **72**, 796-  
676 804.
- 677 35. Imamura F, O'Connor L, Ye Z *et al.* (2015) Consumption of sugar sweetened beverages,  
678 artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic  
679 review, meta-analysis, and estimation of population attributable fraction. *BMJ* **351**, h3576.
- 680 36. Romo-Romo A, Aguilar-Salinas CA, Brito-Cordova GX *et al.* (2016) Effects of the Non-  
681 Nutritive Sweeteners on Glucose Metabolism and Appetite Regulating Hormones: Systematic  
682 Review of Observational Prospective Studies and Clinical Trials. *PLoS One* **11**, e0161264.
- 683 37. Sievenpiper JL, Khan TA, Ha V *et al.* (2017) The importance of study design in the  
684 assessment of nonnutritive sweeteners and cardiometabolic health. *CMAJ* **189**, E1424-E1425.
- 685 38. Lobach AR, Roberts A, Rowland IR (2018) Assessing the in vivo data on low/no-calorie  
686 sweeteners and the gut microbiota. *Food Chem Toxicol*.
- 687 39. Le Donne C, Mistura L, Goscinnny S *et al.* (2017) Assessment of dietary intake of 10  
688 intense sweeteners by the Italian population. *Food and Chemical Toxicology* **102**, 186-197.
- 689 40. Buffini M, Goscinnny S, Van Loco J *et al.* (2018) Dietary intakes of six intense sweeteners  
690 by Irish adults. *Food Additives & Contaminants: Part A* **35**, 425-438.
- 691 41. Martyn D, Darch M, Roberts A *et al.* (2018) Low-/No-Calorie Sweeteners: A Review of  
692 Global Intakes. *Nutrients* **10**, 357.
- 693 42. Malek AM, Hunt KJ, DellaValle DM *et al.* (2018) Reported Consumption of Low-  
694 Calorie Sweetener in Foods, Beverages, and Food and Beverage Additions by US Adults:  
695 NHANES 2007-2012. *Curr Dev Nutr* **2**, doi: 10.1093/cdn/nzy1054.
- 696

- 697 43. Gibson S, Ashwell M, Arthur J *et al.* (2017) What can the food and drink industry do to  
698 help achieve the 5% free sugars goal? *Perspect Public Health* **137**, 237-247.
- 699 44. Wittekind A, Higgins K, McGale L *et al.* (2018) A workshop on 'Dietary sweetness-Is it  
700 an issue?'. *Int J Obes (Lond)* **42**, 934-938.
- 701 45. World Health Organisation (2015) Guideline: Sugars intake for children and adults: WHO,  
702 Geneva. [https://www.who.int/nutrition/publications/guidelines/sugars\\_intake/en/](https://www.who.int/nutrition/publications/guidelines/sugars_intake/en/).
- 703 46. Scientific Advisory Committee on Nutrition (2015) *Carbohydrates and Health*. Public  
704 Health England. available online <https://www.gov.uk/government/publications/sacn-carbohydrates-and-health-report>.
- 705 47. Harricharan M, Wills J, Metzger N *et al.* (2015) Dietitian perceptions of low-calorie  
706 sweeteners. *Eur J Public Health* **25**, 472-476.
- 707 48. Public Health England (2015) Why 5%? An explanation of the Scientific Advisory  
708 Committee on Nutrition's recommendations about sugars and health, in the context of current  
709 intakes of free sugars, other dietary recommendations and the changes in dietary habits  
710 needed to reduce consumption of free sugars to 5% of dietary energy. *PHE publications*  
711 *gateway number 2015193*. <https://www.gov.uk/government/publications/sacns-sugars-and-health-recommendations-why-5> (accessed August 2019)
- 712 49. Bright OM, Wang DD, Shams-White M *et al.* (2017) Research Priorities for Studies  
713 Linking Intake of Low-Calorie Sweeteners and Potentially Related Health Outcomes:  
714 Research Methodology and Study Design. *Curr Dev Nutr* **1**, e000547.
- 715 50. Concannon TW, Meissner P, Grunbaum JA *et al.* (2012) A new taxonomy for stakeholder  
716 engagement in patient-centered outcomes research. *J Gen Intern Med* **27**, 985-991.
- 717 51. de Ruyter JC, Olthof MR, Seidell JC *et al.* (2012) A trial of sugar-free or sugar-sweetened  
718 beverages and body weight in children. *The New England journal of medicine* **367**, 1397-  
719 1406.
- 720 52. Tate DF, Turner-McGrievy G, Lyons E *et al.* (2012) Replacing caloric beverages with  
721 water or diet beverages for weight loss in adults: main results of the Choose Healthy Options  
722 Consciously Everyday (CHOICE) randomized clinical trial. *The American journal of clinical*  
723 *nutrition* **95**, 555-563.
- 724 53. Peters JC, Wyatt HR, Foster GD *et al.* (2014) The effects of water and non-nutritive  
725 sweetened beverages on weight loss during a 12 week weight loss treatment program. *Obesity*  
726 **22**, 1415-1421.
- 727 54. Peters JC, Beck J, Cardel M *et al.* (2016) The effects of water and non-nutritive  
728 sweetened beverages on weight loss and weight maintenance: A randomized clinical trial.  
729 *Obesity (Silver Spring)* **24**, 297-304.
- 730 55. Masic U, Harrold JA, Christiansen P *et al.* (2017) EffectS of non-nutritive sWeetened  
731 beverages on appetITe during aCTive weigHt loss (SWITCH): Protocol for a randomized,  
732 controlled trial assessing the effects of non-nutritive sweetened beverages compared to water  
733 during a 12-week weight loss period and a follow up weight maintenance period. *Contemp*  
734 *Clin Trials* **53**, 80-88.
- 735 56. Malik VS (2019) Non-sugar sweeteners and health. *BMJ* **364**, k5005.
- 736 57. Azad MB, Abou-Setta AM, Chauhan BF *et al.* (2017) Nonnutritive sweeteners and  
737 cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials  
738 and prospective cohort studies. *CMAJ* **189**, E929-E939.
- 739 58. Sylvetsky AC, Rother KI (2018) Nonnutritive Sweeteners in Weight Management and  
740 Chronic Disease: A Review. *Obesity (Silver Spring)* **26**, 635-640.
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744 **Table 1: Timeline of the project**

745

January 2018	Identification of ISA conference speakers and chairs
April 2018	Workshop leaders (MA & SG) appointed
	Conference speakers and chairs invited to workshop
May 2018	Three key workshop Themes identified by workshop leaders
May 2018	Workshop leaders agree questions for experts based on the 3 Themes for workshop
July 2018	Experts asked to provide provisional answers to questions
September 2018	Workshop leaders collate expert comments into working document
November 6 <sup>th</sup> , 2018	ISA Conference
November 7 <sup>th</sup> , 2018	Expert workshop
November 2018	Draft consensus statements agreed at workshop, circulated to experts
December 2018	Comments received from experts
December 2018- January 2019	Draft paper written by workshop leaders
January 2019	Draft paper circulated to experts for approval
February 2019	Paper finalised and submitted to journal
July and August 2019	Revisions to paper agreed by panel

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752**Table 2: Comparison of our consensus statements on LCS with those of others.**753  
754  
755

(+ = broad correspondence with our Consensus statements; blank = not (or not fully) addressed)

<b>Theme 1:</b> <b>Role of low calorie sweeteners in weight management and glucose control: the scientific evidence</b>	Gibson et al (2014) (14)	Serra-Majem et al (2018) (15)
1. When substituted for sugars to reduce energy density of foods and drinks, LCS can reduce net energy intake and assist weight management.	+	+
2. Intervention studies have shown that LCS beverages have at least a similar effect on appetite and energy intake to water	+	
3. The collective evidence supports the conclusion that LCS have no adverse effect on blood glucose and insulin regulation (HbA1c, fasting and post-prandial glucose and insulin levels) in people with, and without, diabetes	+	+
4. The potential value of LCS in dietary management of diabetes derives from their role as substitutes for sugars. and hence carbohydrates.	+	+
5. Confounding by adiposity, and reverse causality can explain the positive association between LCS and T2DM and other cardiometabolic diseases, reported in some observational studies.		+
6. Regarding effects involving the human gut microbiota, current evidence is limited and does not provide adequate evidence that LCS influence gut health at doses relevant to human use.		
<b>Theme 2:</b> <b>Consumption and safety of low calorie sweeteners and consumer perception</b>		
1. The safety of LCS is demonstrated by a substantial body of evidence as well as continued review by independent regulatory agencies/committees including JECFA/Codex, FDA and EFSA. These organisations have taken into account of the decades of both positive and negative human and animal studies to draw their conclusions. Continual monitoring and modelling of LCS exposures is undertaken and this demonstrates that intakes of LCS, even among high consumers, are within ADIs		+
2. Currently, the major sources of LCS in the Western diet are beverages and table top sweeteners		
3. LCS can be used to reduce the sugar and energy content of beverages (and some foods) whilst maintaining a similar sensory profile. The potential for energy reduction is more limited in foods and depends on the options for reformulation and what replaces the bulk of sugar. LCS can be used synergistically in blends to achieve the desired sensory profile at lower levels of use	+	+
4. The collective evidence supports the conclusion that there is no		

relationship between adiposity and liking/ preference for sweet taste in either adults or children		
5. Consumer perceptions vary with regard to LCS, with some people having concerns about their potential health effects	+	+
<b>Theme 3:</b> <b>Role of low calorie sweeteners in relation to nutrition policy</b>		
1. Reduction in the intake of 'free sugars' and 'added sugars' is being recommended around the world to reduce the risk of obesity, which is a major public health concern. LCS should be one of the strategies to consider.	+	+
2. LCS can be useful in dietary approaches to both prevent and manage diabetes and obesity. Benefit will depend on how foods and beverages containing LCS are substituted, as well as on the overall quality of the diet and the overall energy provision.	+	+
3. Despite repeated and consistent reassurances from food safety authorities, there is still some distrust of LCS among health professionals and policy makers	+	+
4. Some policies acknowledge LCS consumption as a useful strategy to reduce sugars intake. However, there are discrepancies with other national and international policies and regarding use in children.		+

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759 **Supplementary information**

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761 **Comparison of Consensus statements from others with the Consensus**  
 762 **statements in this paper**

763 **Table S1: Conclusions from Gibson et al. (2014)**

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	Relevant to our consensus statement Blank = not addressed
(1) LCS do not increase appetite and have no discernible effect on satiety	1a2
(2).LCS help to reduce energy when used in place of higher energy ingredients	1a1
(3).LCS can enhance weight loss under real-life conditions when used as part of a behavioural weight loss programme	1a1
(4).LCS may have a beneficial effect on post-prandial glucose and insulin in healthy individuals and in people with diabetes	1a3 1a4
(5).LCS have dental benefits when used in food, beverages, toothpaste and medications, provided other constituents are also non-cariogenic and non-erosive	

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767 **Table S2: Conclusions from Serra-Majem et al ( 2018)**

	Relevant to our consensus statement Blank = not addressed
1) LNCS are some of the most extensively evaluated dietary constituents, and their safety has been reviewed and confirmed by regulatory bodies globally including the World Health Organisation, the US Food and Drug Administration and the European Food Safety Authority;	2a1
2) Consumer education, which is based on the most robust scientific evidence and regulatory processes, on the use of products containing LNCS should be strengthened in a comprehensive and objective way;	2b1 2a5
3) The use of LNCS in weight reduction programmes that involve replacing caloric sweeteners with LNCS in the context of structured diet plans may favour sustainable weight reduction.  Furthermore, their use in diabetes management programmes may contribute to a better glycaemic control in patients, albeit with modest results.	1a1 1a3 1a4

LNCS also provide dental health benefits when used in place of free sugars	
4) It is proposed that foods and beverages with LNCS could be included in dietary guidelines as alternative options to products sweetened with free sugars;	2a3 3c1 3a4
5) Continued education of health professionals is required, since they are a key source of information on issues related to food and health for both the general population and patients. With this in mind, the publication of position statements and consensus documents in the academic literature are extremely desirable.	3a3 3c4

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**Table S3: Conclusions from Bright (2018) on Future Research Needs**

Blank = not addressed

	Relevant to our consensus statement
Q1. Do LCSs aid weight loss and/or weight maintenance?	1a1 1b1
Q2. Does LCS consumption modify appetite (hunger, fullness, desire to eat /prospective consumption) and/or total energy intake and, if so, how?	1a1, 1a2
Q3. Does the use of LCSs affect insulin secretion, carbohydrate metabolism, or the gut microbiota and its function? If so, where is this happening (cognition, sweet receptors on tongue, receptors in gastrointestinal tract, etc.) and does it have any physiologic consequences on health?	1b1
Q4. Are there potential long-term health risks (obesity, diabetes, cancer, CVD, etc.) of LCS consumption in humans? Are certain population groups (diabetics, children, pregnant women, those with genetic disease) more susceptible to the potential health risk(s)?	1b1, 1b2
Q5. Is LCS sweetness perceived by the brain as energy in the same way as other sweeteners? Do those who are overweight or obese sense LCSs differently than normal-weight people?	
Q6. Are there impacts of LCS consumption during pregnancy on the fetus?	
Q7. Do LCSs differentially affect long-term food intake, eating frequency, and portion sizes in children, adolescents, and adults? Is there an impact on dietary quality and adherence to recommended dietary patterns?	1b4? 3b1 3b2
Q8. In individuals with diabetes and prediabetes, does chronic consumption of LCSs have an impact on glycemic control, alter glucose transport, or invoke a cephalic phase response?	1b5
Q9. Does LCS consumption affect consumption of other sweeteners or sugars or total carbohydrate intake? Is the effect different than that from consumption of nutritive sweeteners?	1b4 2b3
Q10. Do LCSs affect energy metabolism and fat storage?	1b1
Q11. Should study findings be evaluated for each LCS individually or collectively? To which health outcome(s) are the findings from individual	1b3

LCSs generalizable to the class of ingredients?	
Q12. Is LCS intake accurately estimated in current dietary assessment tools?	2b3
Q13. Are there interactions between the combination of fat substitutes and sweetener substitutes on appetite (hunger, fullness, desire to eat or prospective consumption) and/or total energy intake?	related to 1b2
Q14. Is there any variation in how LCSs affect those of different ages, races, and ethnicities?	1b2
Q15. Do individuals with different dietary patterns (high protein vs. high carbohydrate, etc.) affect the metabolism of LCSs differently and, if so, how?	1b2
Q16. How do we design a system or methodology to address the differences in existing LCS compounds vs. compounds that will be emerging down the road?	2a1? 2b2 2b3
Q17. Do the effects of LCS consumption on body weight differ by sex? If so, what are the sex-specific mechanisms of the impact of LCS consumption on body weight?	1b2
Q18. Has there been a gradual increase in the overall sweetness in our diet?	related to 1b4

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## 1 Expert consensus on low calorie sweeteners: 2 facts, research gaps and suggested actions

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## 46 Abstract

47 A consensus workshop on low calorie sweeteners (LCS) was held in November 2018 where  
48 seventeen experts (the panel) discussed three themes identified as key to the science and  
49 policy of LCS: (1) weight management and glucose control; (2) consumption, safety and  
50 perception; (3) nutrition policy. The aims were to identify the reliable facts on LCS, suggest  
51 research gaps and propose future actions. The panel agreed that the safety of LCS is  
52 demonstrated by a substantial body of evidence reviewed by regulatory experts and current  
53 levels of consumption, even for high users, are within agreed safety margins. even highest  
54 consumption estimates are not a concern. However, better risk communication is needed.  
55 More emphasis is required on the role of LCS in helping people reduce their sugar and  
56 energy intake, which is a public health priority. Based on reviews of clinical evidence to  
57 date, the panel concluded that LCS can be beneficial for weight management when they are  
58 used to replace sugar in products consumed in the diet (without calorie substitution). The  
59 available evidence suggests no grounds for concerns about adverse effects of LCS on sweet  
60 preference, appetite or glucose control. Concerns about adverse effects of LCS on sweet  
61 preference, appetite or glucose control are not supported by the evidence currently  
62 available; indeed, LCS may improve diabetic control and dietary compliance. Regarding  
63 effects on the human gut microbiota, Limited data are limited and do not provide  
64 adequate evidence that LCS affects gut health at doses relevant to human use. The effects  
65 of LCS on gut health at doses relevant to human use is currently based on limited evidence.  
66 The panel identified research priorities, including collation of the totality of evidence on LCS  
67 and body weight control, monitoring and modelling of LCS intakes, impacts on sugar  
68 reduction and diet quality and developing effective communication strategies to foster  
69 informed choice. There is also a need to reconcile policy discrepancies between  
70 organisations and reduce regulatory hurdles that impede low energy product development  
71 and reformulation.

## 73 Introduction and aim of the Consensus Report

74 A number of reviews, some narrative and some systematic, have discussed the evidence for  
75 the safety of LCS and their effects on appetite, food intake, body weight, glucose control and  
76 other health outcomes (1) (2) (3) (4) (5) (6) (7) (8). Evidence has also been evaluated by authorities  
77 such as the European Food Safety Authority (EFSA), the (US) Dietary Guidelines Advisory  
78 Committee (DGAC), the French Agency for Food, Environmental and Occupational Health &  
79 Safety (ANSES) and Public Health England (PHE), who have issued statements or opinions  
80 on the use of low calorie sweeteners (9) (10) (11) (12) (13). Other groups of scientific experts  
81 have generated consensus statements, position papers, or other statements on LCS. These  
82 include-including the British Dietetic Association, Diabetes UK, the American Heart  
83 Association and American Diabetes Association (AHA/ADA) (14) (15) (16) (17) (18) (19) (20).

84 This paper describes the results of a workshop in which seventeen experts convened to  
85 discuss and debate the science and policy relating to the use of low-calorie sweeteners  
86 (LCS). The aims were to establish via consensus-forming techniques, clear and simple  
87 statements on LCS that all the panel agreed (facts), to highlight the areas where more  
88 research is required (gaps) and to propose how progress might be achieved (actions). It is  
89 hoped that the provision of these statements on safety and potential benefits of LCS will  
90 assist health practitioners and policy makers to promote consistent messages and develop  
91 strategies based on sound science. Identification of the gaps and actions will help promote  
92 better study designs, suggest priorities for research funding and thereby encourage more  
93 coherent public health policy.

## 96      **Background to LCS and their regulatory approval process**

97  
98 All LCS have undergone an extensive safety evaluation process by international and  
99 national regulatory food safety bodies both before and after their approval for use in the  
100 market. The Food and Agriculture Organization (FAO)/World Health Organization (WHO)  
101 Joint Expert Committee on Food Additives (JECFA) (21), the US Food and Drug  
102 Administration (FDA) (22), and EFSA (9), have confirmed the safety of all approved LCS as  
103 food additives. Hence there is an extensive body of evidence from both animal models and  
104 human studies that support the safety of LCS. Each compound is considered individually as  
105 their characteristics, metabolism and metabolic fates are different (23). Furthermore, there is  
106 an ongoing review process to ensure that any new information on safety is evaluated, for  
107 example recent scientific opinions by EFSA on aspartame and sucralose (24) (25).

108  
109 As part of the LCS safety evaluations, the regulatory authorities establish the Acceptable  
110 Daily Intakes (ADI) for each sweetener (26). The ADI is defined as an estimate of the amount  
111 of a food additive, expressed per kg bodyweight, that can be ingested daily by individuals  
112 over a lifetime without appreciable risk to health. 'Without appreciable risk' means, based on  
113 the current knowledge, "certainty that no harm will result, even after a lifetime of exposure to  
114 the additive" (27). The current ADIs for LCS were established using the 'No Observed  
115 Adverse Effect Level' (NOAEL). The 'No Observed Adverse Effect Level' (NOAEL) This is  
116 the highest dietary level of an additive at which no adverse effects were observed in animal  
117 studies. The ADI is typically set at 1/100th of the NOAEL (10-fold reduction for inter-species  
118 variation and 10-fold reduction for intra-species variation) to give a large margin of safety for  
119 even the most sensitive consumer. The ADI refers to a lifelong exposure situation, not a  
120 single occasion, and thus infrequent consumption of levels higher than the ADI are not a  
121 health concern. Because of the large safety margin used in setting the ADI, it is likely that an  
122 ADI for a given additive would have to be exceeded by some considerable amount for an  
123 extended period of time for there to be any risk of harm to human health. However, if an  
124 intake estimate indicates that the ADI may be regularly exceeded by certain sectors of the  
125 population, the regulatory authority may advise a reduction of levels in foods, or to reduce  
126 the range of foods in which the additive is permitted for use (27). In some cases, the ADI  
127 may be "not specified" when the total potential intake from all possible sources does not  
128 represent a hazard to health, and hence no numerical ADI is needed. It should be noted that,  
129 in the future, the Benchmark Dose (BMD) will be the preferred approach for establishing a  
130 reference point (28). However, discussion of the expert considerations and data  
131 requirements for calculation of a BMD is beyond the scope of this paper.

132  
133 In relation to efficacy, EFSA has a system for evaluating dossiers of evidence submitted for  
134 the substantiation of health claims (29). In 2011, the EFSA Panel on Nutrition, Novel Foods  
135 and Food Allergens (NDA) concluded that there was sufficient scientific evidence to support  
136 the claims that intense sweeteners, like all sugar replacers, lead to a lower rise in blood  
137 sugar levels after meals if consumed instead of sugars, and maintain tooth mineralisation by  
138 decreasing tooth demineralisation; again if consumed instead of sugars. However at that  
139 time, EFSA's experts found no clear cause and effect relationship to substantiate the claims  
140 that intense sweeteners when replacing sugars maintain normal blood sugar levels, or  
141 maintain/achieve a normal body weight (30).

142  
143 There are currently various jurisdiction-specific restrictions on the use of LCS in foods and  
144 beverages. For example, under European legislation, sweeteners are only permitted if used  
145 to replace sugars for the production of energy-reduced food (i.e. with 30% less energy), non-  
146 cariogenic food, or food with no added sugars (31). This limits the options available to  
147 manufacturers for more modest reformulation or stepwise reduction of sugar content in food  
148 and drink through the use of sweeteners.

## 150 Methods

151  
152 The consensus workshop was designed to follow Workshop participants were speakers or  
153 chairs at a conference held by the International Sweeteners Association (ISA) in London on  
154 6th November 2018 entitled 'The science behind low calorie sweeteners: where evidence  
155 meets policy'. The panel members were all speakers or chairs at that conference, chosen for  
156 their international expertise in LCS science and policy. The participants were chosen for their  
157 expertise in different aspects of LCS science and policy and for their international  
158 experience. The workshop was held the following day and chaired and facilitated by two  
159 independent consultants in nutrition science, (MA and SG), who drafted the paper and  
160 coordinated responses from participants. The ISA provided funds for the venue and  
161 speakers' expenses. They were observers at the workshop but had no control over the  
162 paper. Disclosures of interest for all authors are given, who have drafted this paper  
163 and are joint authors with the panel of experts.

164  
165 The workshop leaders (MA and SG) identified 3 key Themes or topic areas for discussion at  
166 the workshop:

- 167  
168 1) Role of low calorie sweeteners in weight management and glucose control  
169 2) Consumption and safety of low calorie sweeteners and consumer perception  
170 3) Role of low calorie sweeteners in relation to nutrition policy

171  
172 As the workshop was time-limited the choice of themes was based on the pertinence in  
173 terms of current debates on LCS, and the available expertise represented by the panel.

174  
175 Prior to the workshop, each panel member was asked to provide feedback on 3 questions  
176 with respect to their own area of expertise:

- 177  
178 a. Statements of fact: what do we know?  
179 b. Questions and type of evidence needed (gaps: what do we still need to know?)  
180 c. How this might translate to further research work or policy (actions: what should we  
181 do?).

182  
183  
184 Comments were minimally edited by MA and SG to produce the Working Document (WD)  
185 with provisional statements/questions/actions for each Theme.

186  
187 At the workshop all the participants discussed the WD in detail. A scoring system (1=strongly  
188 disagree to 10=strongly agree) was used to evaluate level of agreement on the 'facts'.  
189 Statements that achieved a high level of agreement were discussed further. Participants  
190 refined the wording of each statement to reach consensus. Having established agreement  
191 on the facts, participants identified the major gaps or research questions. Finally,  
192 participants identified the most important 'actions' suggested in the WD and these were then  
193 summarised. Participants agreed to the process for further review and publication, i.e. that  
194 the workshop leaders would circulate the draft consensus document for comments, integrate  
195 responses and write the discussion before presenting the final article to all participants for  
196 review and approval. Table 1 shows the Timeline of the project.

## 198 Results

199

200 The results are given below in the form of the consensus statements for the three Themes  
201 and the three questions relating to each Theme. The panel agreed the most pertinent  
202 references to cite for each consensus statement.

203 **Theme 1: Role of low calorie sweeteners in weight management and  
204 glucose control: the scientific evidence**

206 **1a Facts - What we know**

- 208 1. When substituted for sugars to reduce energy density of foods and drinks, LCS  
209 reduce net energy intake and assist weight management (3; 5) (12) (13).
- 210 2. Intervention studies have shown that beverages containing LCS have at least a  
211 similar effect on appetite and energy intake to water (5; 32).
- 212 3. The collective evidence supports the conclusion that LCS have no adverse effect on  
213 blood glucose and insulin regulation (HbA1c, fasting and post-prandial glucose and  
214 insulin levels) in people with, and without, diabetes (2; 33) (34).
- 215 4. The potential value of LCS in dietary management of diabetes derives from their role  
216 as substitutes for sugars, and hence carbohydrates. (19).
- 217 5. Confounding by adiposity, and reverse causality can explain the positive association  
218 between LCS and T2DM and other cardiometabolic diseases, reported in some  
219 observational studies. (35) (36) (37).
- 220 6. Regarding effects involving the human gut microbiota, ~~current evidence is data are~~  
221 ~~limited and do does~~ not provide adequate evidence ~~that LCS influence of effects of~~  
222 ~~LCS-gut health at doses relevant to human use(either negative or positive~~  
223 ~~effects)~~ (38).

225 **1b Gaps: What we don't know**

- 231 1. What are the long-term effects of LCS on glucose tolerance, gut function,  
232 cardiometabolic effects, gut microbiota and weight management?
- 233 2. How are these effects altered according to personal factors, such as age, sex,  
234 ~~ethnicity~~, socio-economic status, health status, diet and lifestyle?
- 235 3. How do these effects differ according to dietary context (ad lib vs. weight-control diet)  
236 and form of LCS (in liquids or solids), and type or blend of LCS?
- 237 4. Does reducing exposure to sweetness have consequences for food choice and  
238 intake in the medium-to-long term?
- 239 5. Can LCS help improve long term Type 2 diabetes (T2DM) management, when part of  
240 standard dietary and lifestyle approaches?

241 **1c Actions - What should be done?**

- 250 1. There is a need for a portfolio of well-designed RCTs (with appropriate time frame of  
251 a year or more) with different comparators and different carriers of LCS (food and  
252 beverage matrices). The trials should be conducted by level of 'free sugar' intake in  
253 different populations; they should use multiple endpoints (diet quality, gut microbiota  
254 function and metabolomics, and wider health and quality of life measures). They  
255 should be done in the context of weight-control diets, including for T2DM and also in  
256 non-restrictive diets.  
257
- 258 2. There is a need for population cohort studies to model changes in weight/  
259 cardiometabolic risk in the context of changes in LCS consumption, not baseline LCS  
260 values. The studies should include substitution analysis (e.g. LCS beverages for  
261 caloric beverages, water, etc.) and adjustment for adiposity. Their data should be  
262 made available for further analysis.  
263
- 264 3. There is a need for a collation of evidence to support future health claim submissions  
265 for LCS and body weight control, as data become available.  
266

267

## Theme 2 - Consumption and safety of low calorie sweeteners and consumer perception

268 2a Facts - What we know

- 269 1. The safety of LCS is demonstrated by a substantial body of evidence [as well as continued review by independent regulatory agencies/committees including: JECFA/Codex, FDA and EFSA](#) (21) (22) (9). [These organisations have taken into account of the decades of both positive and negative human and animal studies to draw their conclusions.](#) Continual monitoring and modelling of LCS exposures is undertaken and this demonstrates that intakes of LCS, even among high consumers, are within ADIs (39: 40) (41).
- 270 2. Currently, the major sources of LCS in the Western diet are beverages and table top sweeteners (39: 40: 42).
- 271 3. LCS can be used to reduce the sugar and energy content of beverages and some foods whilst maintaining a similar sensory profile. The potential for energy reduction is more limited in foods and depends on the options for reformulation and what replaces the bulk of sugar (43). LCS can be used synergistically in blends to achieve the desired sensory profile at lower levels of use.
- 272 4. The collective evidence supports the conclusion that there is no relationship between adiposity and liking/ preference for sweet taste in either adults or children(44).
- 273 5. Consumer perceptions vary with regard to LCS, with some people having concerns about their potential health effects (14: 20).

274 2b Gaps - What we don't know

- 275 1. Which factors (including knowledge, attitudes and behaviours) influence consumer perception of risks and benefits of LCS consumption? Are these the same for health professionals?

- 301 2. There is a need for in-depth data relating to current patterns ~~on-of~~ LCS consumption  
302 at multiple levels, and across countries and regions, to strengthen the evidence base.  
303
- 304 3. There is a need for more reliable measures of LCS exposure, such as biomarkers.  
305 Further development of these and better linkage of food composition and dietary  
306 databases is needed to help monitor changing use and consumption of LCS.

307 **2c Actions - What should be done?**

- 309 1. There is a need to research and develop evidence-based strategies to communicate  
310 ~~all of the above~~ to consumers, health professionals and policy makers. The extensive  
311 body of scientific evidence that backs regulatory approval and the on-going safety  
312 assessment of LCS can then encourage better informed public health decisions. The  
313 media orf other organisations could be signpostedprovided, for example, with simple  
314 explanations of the ADI.
- 315 2. There is a need to develop communications to foster more informed public attitudes  
316 towards LCS, for example by emphasizing the potential health gains associated with  
317 sugar (and energy) intake reduction and the role of LCS in achieving this. It is  
318 important to explain that the overall impact of LCS will depend on the amount of  
319 sugars replaced in the diet and the overall reduction in calorie (energy) intake that  
320 ensues. Use of LCS alone cannot be expected to act as a 'silver bullet' for weight  
321 loss.
- 322 3. Research into biomarkers for individual LCS is needed to complement the exposure  
323 assessment based on consumption records. There is a need to improve linkage of  
324 databases and to model intakes in future scenarios.

325 **Theme 3 - Role of low calorie sweeteners in relation to nutrition policy**

326 **3a Facts - What we know**

- 327 1. Reduction in the intake of 'free sugars' and 'added sugars' is being recommended  
328 around the world to reduce the risk and prevalence of obesity, which is a major public  
329 health concern ([10](#)) ([45](#)) ([46](#)). LCS is one of the strategies to consider.
- 330 2. LCS can be useful in dietary approaches to both prevent and manage diabetes and  
331 obesity. Benefit will depend on how foods and beverages containing LCS are  
332 substituted, as well as on the overall quality of the diet and the overall energy  
333 provision ([16](#)).
- 334 3. Despite repeated and consistent reassurances from food safety authorities, there is  
335 still some distrust of LCS among health professionals and policy makers. ([47](#))
- 336 4. Some policies acknowledge LCS consumption as a useful strategy to reduce sugars  
337 intake ([12](#)). However, there are discrepancies with other national and international  
338 policies ([10](#):[11](#)) and regarding use in children.

339 **3b Gaps - What we don't know**

- 350 1. Can LCS help individuals meet the population level dietary recommendations for  
351 reduction of sugars intake (e.g. to 5% (average) (48) or 10% (for individuals) (10 45)?  
352 If so, how can this be achieved?  
353
- 354 2. How does a dietary approach that includes LCS-sweetened foods and drinks affect  
355 dietary quality compared to low-sugar diets?  
356
- 357 3. What are the best strategies to communicate LCS safety and efficacy to interested  
358 parties such as health professionals and the general public?  
359
- 360

361 **3c Actions - What should be done?**

- 362 1. There is a need to model the potential for LCS to reduce sugar content and sugar  
363 intakes whilst ensuring that other dietary recommendations can also be met in the  
364 overall diet.  
365
- 366 2. Trends in dietary intake of LCS need to be monitored, linked with food and beverage  
367 reformulation and ultimately with health outcomes.  
368
- 369 3. Policies relating to LCS from different countries should be reviewed to compare their  
370 remit, priorities, evidence base and interpretation.  
371
- 372 4. To help reconcile policy discrepancies, policy-makers, scientists and regulatory  
373 affairs experts should agree on their understanding of the role of LCS in the diet.  
374
- 375 5. In the context of sugar reduction and obesity, it would be helpful to review the  
376 regulatory and public health policy hurdles that prevent wider use of LCS in food  
377 products for those sweeteners where dietary intake is very low compared to the ADI.  
378
- 379

380 **DISCUSSION**

381 **Strengths and limitations of approach**

382 The methodology followed a planned and transparent process. All 17 experts were  
383 requested ahead of the workshop to generate a summary of their topic in the form of  
384 answers to the three questions. These were then collated under three Themes by the  
385 workshop leaders and combined for the working document, which was circulated prior to the  
386 workshop. At the start of the group discussion, scoring was used as a consensus-forming  
387 technique to allow participants to indicate the strength of their agreement with each  
388 statement. Alternative forms of wording suggested by participants were considered in order  
389 to improve clarity of each statement. The resulting statements were circulated after the  
390 workshop, with supporting references, to allow for further reflection and improvement. A  
391 strength of the process was the expertise represented on the panel in many aspects of LCS  
392 (including toxicology, regulation, food science, medicine, microbiology, psychology,  
393 epidemiology, public health nutrition and dietetics). Finally, holding the workshop  
394 immediately after a scientific conference on the topic ensured that all experts were fully  
395 prepared and engaged to discuss the issues and formulate consensus.  
396

397 The workshop was wide in scope but was not intended to be exhaustive; the themes were  
398 selected as being pertinent to current debate on LCS and within scope of the expertise of the

400 panel. Consensus was based on expert opinion and key references [including systematic](#)  
401 [reviews; the group did not](#) review all the [primary literature on these themes](#). Other possible  
402 limitations of the methodology were that all our participants were scientists or public health  
403 experts, unlike the broader stakeholder panel used by Bright et al. [\(49\)](#). The workshop was  
404 instigated and funded by ISA; however, ISA had no control over the choice of Themes, and  
405 no role in the discussion or this paper. Participants all acted completely independently to  
406 express their views in open debate and to contribute to the resulting paper.  
407

## 408 Comparison with other consensus papers relating to LCS

### 409 Goals and methodology

410 To our knowledge, there have been three previous papers published in English that contain  
411 consensus statements about LCS [\(14\)](#) [\(15\)](#) [\(49\)](#). In addition, there have been a number of  
412 position papers and evidence reviews whose methodology and scope differ from that of the  
413 present report and these are discussed later.

414 The goal of the consensus report by Gibson et al. [\(14\)](#) was to summarise the role and  
415 potential benefits of LCS on appetite, energy intake, body weight, diabetes and dental health  
416 to give clarity to health professionals and educators on use of LCS. The goal of the Ibero–  
417 American Consensus on LCS [\(15\)](#) was “to develop a consensus on the use of low- and no-  
418 calorie sweeteners as substitutes for sugars and other caloric sweeteners in line with current  
419 international public health recommendations, in the context of the prevention and treatment  
420 of obesity and related diseases in Latin American countries”. The report [\(15\)](#) also provides a  
421 comprehensive overview of the position of international and national regulatory bodies on  
422 LCS safety and efficacy studies on individual LCS. Both these consensus reports [\(14\)](#) [\(15\)](#)  
423 were compiled by panels limited to international scientists and public health experts.

424 The report by Bright et al. [\(49\)](#), focused on future research needs, and involved a wider  
425 stakeholder panel who participated in interactive webinars, surveys and interviews with the  
426 research team and generated a list of 18 questions across 5 broad research areas, ranking  
427 them in order of priority. The stakeholder panel was recruited according to the “7 P’s” of  
428 stakeholder engagement i.e. patients, providers, researchers, policymakers, product  
429 makers, payers, and purchasers [\(50\)](#). It therefore included policymakers, lay audience  
430 members, health providers, a research funder, individuals with food industry experience, and  
431 researchers of several different specialties.

### 432 Content and conclusions

433 The consensus statements agreed by our expert panel were produced independently but  
434 have been compared with previous consensus statements in Table 2. Further details can be  
435 found in supplementary Tables S1 and S2. Some topics were not covered in other reports:  
436 for example, the statements in this paper have included association between sweetness  
437 preference and obesity, effects of LCS on gut bacteria and sources of LCS, which were not  
438 covered by Gibson et al. [\(14\)](#) or Serra-Majem et al. [\(15\)](#); conversely, this panel did not  
439 consider the effects of LCS on dental health.

440 Table 2 shows there was broad agreement between the sentiments expressed in our  
441 statements and these two reports.

442

443 The gaps identified by our panel have been compared with the research priorities from Bright  
444 et al. (49) (Table S3). Most of the important future research questions identified by their  
445 stakeholder panel were also selected by our panel as areas in need of study. In the case of  
446 effects of LCS beverages on appetite and energy intake (Bright et al. (49) Q2), our panel  
447 considered the evidence to be sufficiently strong for 'no effect or at least similar effect'  
448 compared to water to be classed as fact, and for a reduction in energy intake compared to  
449 sugar also to be classed as fact. Research gaps identified by our panel and not identified by  
450 Bright et al. (49) included research on biomarkers of LCS consumption to aid intake  
451 assessments, research on communication with consumers and other stakeholders about  
452 LCS and more research on issues related to policy. Conversely Bright's (49) questions on the  
453 sensing of LCS by the brain and the impact of LCS on the fetus, did not feature directly in  
454 our workshop discussion.

#### 455 Comparison with other reviews and position statements

456  
457 In 2011 EFSA was also of the opinion that a cause and effect relationship had not been  
458 established between the use of intense sweeteners and maintenance of normal body weight  
459 or blood glucose, but several high quality studies and reviews have since been published  
460 (51) (52) (53; 54) and others are currently underway: the SWITCH project (55) and the SWEET  
461 project;(available at <https://sweetproject.eu>) . A number of reviews and position statements  
462 have addressed the evidence for and against health benefits of LCS. Our panel observed  
463 that differences between the positions and policies of different organisations with regard to  
464 LCS are a cause of confusion. Reasons for discrepancies may include different remits and  
465 approaches and different interpretations of the evidence base. With regard to the science,  
466 the data are insufficient to answer some questions conclusively, given the multiple  
467 components involved.—The goal of systematic review and meta-analysis is frequently  
468 hampered by differing study designs that make comparison difficult and meta-analysis  
469 unreliable; hence the need for cautious wording, which may be interpreted as a negative  
470 statement. Reviews differ in scope and the precise research question asked, resulting in  
471 differences in study selection that lead to different conclusions. It is important to clearly  
472 establish that LCS are food additives and, as such cannot provide health benefits, except in  
473 relation to the reduction of sugar within an adequate diet and lifestyle. Our panel concluded  
474 that, when used to replace dietary sugar, the use of LCS use facilitates reduction in energy  
475 intake and weight loss. This was based on evidence from RCTs of 6m to 2 years in length  
476 and recent systematic reviews that pay careful attention to appropriate comparators. The  
477 panel also stated the need for studies of longer-term effects. By contrast, a recent wide-  
478 ranging review on health effects of non-sugar sweeteners (which in practice was were LCS  
479 as it-polylols were excluded. polylols) concluded that "there were no significant or clinically  
480 important effects on most outcomes" (8). However due to very strict inclusion and exclusion  
481 criteria, their analyses omitted some notable studies on body weight (51; 52); (53) (54) and  
482 combined studies with different comparators, potentially diluting the effect size (56). Another  
483 recent review (57) has been criticised on the same grounds (37). Toews et al. (8) also stated  
484 that "potential harms from the consumption of non-sugar sweeteners could not be excluded".  
485 a statement which relates to lack of evidence, not evidence of harm. Our panel took a harm-  
486 reduction approach, where LCS are a desirable substitute for sugar and one route to helping  
487 achieve sugar and energy reduction whilst still maintaining dietary diversity and pleasure.

488 Other position statements, particularly those published before 2014, have offered cautious  
489 conclusions on potential benefits of LCS. For example, the 2012 joint scientific statement  
490 from the American Heart Association and the American Diabetes Association (AHA/ADA)  
491 (37) concluded that "at present there are insufficient data to determine conclusively that non-  
492 nutritive sweeteners (NNS) benefit appetite, energy intake or body weight" (20). However, the  
493 AHA/ADAis document also stated that "when used judiciously, NNS could facilitate  
494 reductions in added sugars intake, thereby resulting in decreased total energy and weight  
495 loss/weight control and promoting beneficial effects on related metabolic parameters".

Commented [sg1]: moved from further down this section

497  
498 In 2011 EFSA was also of the opinion that a cause and effect relationship had not been  
499 established between the use of intense sweeteners and maintenance of normal body weight  
500 or blood glucose, but several high quality studies and reviews have since been published  
501 '51-'52,'53-'54 and others are currently underway: the SWITCH project '55' and the SWEET  
502 project; <https://sweetproject.eu>. The latest AHA advisory statement '19' (which focussed on  
503 LCS beverages and cardiometabolic outcomes) concluded that the use of LCS beverages  
504 may be an effective strategy to help control energy intake and promote weight loss.  
505 Nonetheless, due to the lack of long-term trials in children, the AHA, but thought it prudent  
506 to advise against prolonged consumption of LCS beverages by children, preferring water,  
507 other unsweetened beverages or milk as the primary drink. Policy statements from  
508 professional bodies of dietitians and nutritionists have generally been pragmatic, seeing LCS  
509 as a helpful tool in helping people reduce their sugar intake and manage their weight, whilst  
510 stressing the importance of the context, namely in the context of a healthy balanced diet that  
511 meets other dietary recommendations '16' '17' '18'.

### 512 Extension of our consensus statements to actions and policies

513 The main strategy of our consensus workshop was to stimulate forward thinking as well as to  
514 restate principles. The consensus statements on actions put the focus firmly on what is  
515 required to deliver. For example, the panel made recommendations for further long-term  
516 randomised controlled trials of LCS with different comparators and multiple endpoints, for  
517 prospective studies that control for adiposity and other confounders, and for better estimates  
518 of LCS exposure. Such recommendations may help research funding bodies select priorities.  
519 Clarity and consistency of policy would be improved by a comprehensive evaluation of all the  
520 evidence on effects of LCS. Others have also called for larger and longer clinical trials with  
521 careful selection of comparators '7' '37' '44' '58'. The review by Toews et al. '8' was also  
522 critical of the size, short duration, and methodological and reporting quality of studies. It also  
523 called for more data on benefits and risks of non-sugar sweeteners in doses and patterns  
524 more akin to real life consumption '8'. Our expert panel considered the safety data to be  
525 incontrovertible robust but agreed that there is a continued need for ongoing exposure  
526 assessment to account for changing LCS use, and also consideration of any new evidence  
527 that might emerge. Novel recommendations made by the panel included better strategies  
528 and methods to improve communications about the safety and efficacy of LCS, modelling of  
529 the effect of LCS on sugar reduction and diet quality, relaxing regulation to increase the  
530 potential for reformulation using LCS, and review and reconciliation of policy differences on  
531 the use of LCS.

### 532 Conclusion

533 The panel considered that the substantial body of evidence concerning LCS safety should  
534 be communicated in a consistent manner. More emphasis is required on the role of LCS in  
535 helping people reduce their sugar and energy intake, which is a public health priority.  
536

537 Research priorities should include

- 538 a. a dossier of the totality of evidence on LCS and body weight control,
- 539 b. studies to monitor and model LCS intakes and their impact on sugar reduction and  
540 diet quality,
- 541 c. effective communication strategies to inform consumers, non-governmental  
542 organisations (NGOs), health professionals, research funding bodies and the food  
543 and beverage industry

544 Efforts should be made to understand and, where possible, reconcile policy discrepancies  
545 between organisations and reduce regulatory hurdles that impede product development and  
546 reformulation designed to reduce sugars and/or calories.

550  
551 It is hoped that these consensus statements and recommendations arising from the expert  
552 workshop will assist policy makers, and other stakeholders including NGOs, health  
553 professionals, research funding bodies and the food and beverage industry.  
554

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560 All authors completed ICMJE Forms. All authors report personal or institutional honoraria and/or expenses from International  
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572 M. Ashwell: Sugar Nutrition UK, Global Stevia Institute.  
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579 M. Fantino: International Sweeteners Association, The Coca Cola Company.  
580 A. Gallagher: International Sweeteners Association.  
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591 Sweeteners Association.  
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593 W. Russell: International Sweeteners Association.  
594 J. Sievenpiper: Tate and Lyle Nutritional Research Fund, PepsiCo, International Sweeteners  
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597  
598

## 599 References

- 600
- 601 1. Mortensen A (2006) Sweeteners permitted in the European Union, Safety aspects. .  
Scandinavian Journal of Food and Nutrition **50**, 104-116.
- 602
- 603 2. Wiebe N, Padwal R, Field C *et al.* (2011) A systematic review on the effect of sweeteners  
604 on glycemic response and clinically relevant outcomes. *BMC Med* **9**, 123.
- 605
- 606 3. Miller PE, Perez V (2014) Low-calorie sweeteners and body weight and composition: a  
607 meta-analysis of randomized controlled trials and prospective cohort studies. *Am J Clin Nutr*  
**100**, 765-777.
- 608
- 609 4. Bellisle F (2015) Intense Sweeteners, Appetite for the Sweet Taste, and Relationship to  
Weight Management. *Curr Obes Rep* **4**, 106-110.
- 610
- 611 5. Rogers PJ, Hogenkamp PS, de Graaf C *et al.* (2016) Does low-energy sweetener  
612 consumption affect energy intake and body weight? A systematic review, including meta-  
analyses, of the evidence from human and animal studies. *Int J Obes (Lond)* **40**, 381-394.
- 613
- 614 6. Lohner S, Toews I, Meerpolh JJ (2017) Health outcomes of non-nutritive sweeteners:  
analysis of the research landscape. *Nutr J* **16**, 55.
- 615
- 616 7. Mosdol A, Vist GE, Svendsen C *et al.* (2018) Hypotheses and evidence related to intense  
617 sweeteners and effects on appetite and body weight changes: A scoping review of reviews.  
*PLoS One* **13**, e0199558.
- 618
- 619 8. Toews I, Lohner S, Kullenberg de Gaudry D *et al.* (2019) Association between intake of  
620 non-sugar sweeteners and health outcomes: systematic review and meta-analyses of  
randomised and non-randomised controlled trials and observational studies. *BMJ* **364**, k4718.
- 621
- 622 9. European Food Safety Authority Topics: Sweeteners.  
<https://www.efsa.europa.eu/en/topics/topic/sweeteners> (accessed 30 August 2019)
- 623
- 624 10. US Department of Agriculture (2015) Scientific report of the 2015 Dietary Guidelines  
Advisory Committee.  
<https://health.gov/dietaryguidelines/2015-scientific-report/> (accessed August 2019)
- 625
- 626 11. ANSES (French Agency for Food Environmental and Occupational Health & Safety)  
627 (2015) OPINION of the French Agency for Food Environmental and Occupational Health &  
Safety on the assessment of the nutritional benefits and risks related to intense sweeteners.  
revised on 9 January 2015. <https://www.anses.fr/en/content/opinion-french-agency-food-environmental-and-occupational-health-safety-19-november-2014> (accessed August 2019)
- 628
- 629
- 630
- 631 12. Public Health England (2015) Sugar Reduction: The evidence for action. *PHE*  
632 publications gateway number 2015391. <https://www.gov.uk/government/publications/sugar-reduction-from-evidence-into-action> (accessed August 2019)
- 633
- 634 13. Public Health England (2015) Sugar Reduction: The evidence for action. Annex 5: Food  
635 supply. *PHE* publications gateway number 2015391.  
<https://www.gov.uk/government/publications/sugar-reduction-from-evidence-into-action>  
(accessed August 2019)
- 636
- 637
- 638 14. Gibson S, Drewnowski A, Hill J *et al.* (2014) Consensus statement on benefits of low-  
calorie sweeteners. *Nutrition Bulletin* **39**, 386-389.
- 639
- 640 15. Serra-Majem L, Raposo A, Aranceta-Bartrina J *et al.* (2018) Ibero-American Consensus  
641 on Low- and No-Calorie Sweeteners: Safety, Nutritional Aspects and Benefits in Food and  
642 Beverages. *Nutrients* **10**, 818.
- 643
- 644 16. British Dietetic Association (2016) Policy Statement : the use of Artificial Sweeteners.
- 645
- 646 17. Diabetes UK (2018) The use of low and no calorie sweeteners: position statement  
<https://www.diabetes.org.uk/professionals/position-statements-reports/food-nutrition-lifestyle/use-of-low-or-no-calorie-sweetners> (accessed February 12, 2019)
- 647
- 648 18. Dyson PA, Twenefour D, Breen C *et al.* (2018) Diabetes UK evidence-based nutrition  
guidelines for the prevention and management of diabetes. *Diabet Med* **35**, 541-547.

- 649 19. Johnson RK, Lichtenstein AH, Anderson CAM *et al.* (2018) Low-Calorie Sweetened  
650 Beverages and Cardiometabolic Health: A Science Advisory From the American Heart  
651 Association. *Circulation* **138**, e126-e140.
- 652 20. Gardner C, Wylie-Rosett J, Gidding SS *et al.* (2012) Nonnutritive sweeteners: current use  
653 and health perspectives: a scientific statement from the American Heart Association and the  
654 American Diabetes Association. *Circulation* **126**, 509-519.
- 655 21. Food and Agriculture Organisation of the United Nations Chemical risks and JECFA.  
656 <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/> (accessed 30 August  
657 2019)
- 658 22. US Food and Drug Administration Additional Information about High-Intensity  
659 Sweeteners Permitted for Use in Food in the United States. <https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states> (accessed 30th August 2019)
- 660 23. Magnuson BA, Carakostas MC, Moore NH *et al.* (2016) Biological fate of low-calorie  
661 sweeteners. *Nutr Rev* **74**, 670-689.
- 662 24. European Food Safety Authority (2013) Scientific Opinion on the re-evaluation of  
663 aspartame (E 951) as a food additive. *EFSA Journal* **2013**; . Available online:  
664 [www.efsa.europa.eu/efsajournal](http://www.efsa.europa.eu/efsajournal) (accessed August 2019)
- 665 25. European Food Safety Authority (2017) Statement on the validity of the conclusions of a  
666 mouse carcinogenicity study on sucralose (E 955) performed by the Ramazzini Institute.  
667 *EFSA Journal* **2017**; **15**.
- 668 26. Benford D (2000) The Acceptable Daily Intake: A Tool for Ensuring Food Safety. *ILSI Europe Concise Monograph*. <http://ilsi.org/publication/the-acceptable-daily-intake-a-tool-for-ensuring-food-safety/>  
669 (accessed August 2019)
- 670 27. European Food Information Council (EUFIC) (2013) Acceptable Daily Intakes (ADIs)  
671 <https://www.eufic.org/en/understanding-science/article/qas-on-acceptable-daily-intakes-adis>  
672 (accessed August 2019)
- 673 28. Haber LT, Dourson ML, Allen BC *et al.* (2018) Benchmark dose (BMD) modeling:  
674 current practice, issues, and challenges. *Critical Reviews in Toxicology* **48**, 387-415.
- 675 29. Buttriss JL (2015) Nutrition and Health Claims in Practice. *Proc Nutr Soc* **40**, 211- 222.
- 676 30. European Food Safety Authority (2011) Scientific Opinion on the substantiation of health  
677 claims related to intense sweeteners and contribution to the maintenance or achievement of a  
678 normal body weight (ID 1136, 1444, 4299), reduction of post-prandial glycaemic responses  
679 (ID 4298), maintenance of normal blood glucose concentrations (ID1221, 4298), and  
680 maintenance of tooth mineralisation by decreasing tooth demineralisation (ID 1134, 1167,  
681 1283) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal*; **9**(6):2229  
682 [26pp] *Online* [www.efsa.europa.eu/efsajournal](http://www.efsa.europa.eu/efsajournal) (accessed August 2019)
- 683 31. EUR-Lex (2008) Regulation (EC) No 1333/2008 of the European Parliament and of the  
684 Council of 16 December 2008 on food additives. *Official Journal of the European Union*,  
685 <http://data.europa.eu/eli/reg/2008/1333/oj> (accessed August 2019)
- 686 32. Fantino M, Fantino A, Matray M *et al.* (2018) Beverages containing low energy  
687 sweeteners do not differ from water in their effects on appetite, energy intake and food  
688 choices in healthy, non-obese French adults. *Appetite* **125**, 557-565.
- 689 33. Tucker RM, Tan SY (2017) Do non-nutritive sweeteners influence acute glucose  
690 homeostasis in humans? A systematic review. *Physiol Behav* **182**, 17-26.
- 691 34. Nichol AD, Holle MJ, An R (2018) Glycemic impact of non-nutritive sweeteners: a  
692 systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr* **72**, 796-  
693 804.
- 694
- 695
- 696
- 697

- 698 35. Imamura F, O'Connor L, Ye Z *et al.* (2015) Consumption of sugar sweetened beverages,  
699 artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic  
700 review, meta-analysis, and estimation of population attributable fraction. *BMJ* **351**, h3576.  
701 36. Romo-Romo A, Aguilar-Salinas CA, Brito-Cordova GX *et al.* (2016) Effects of the Non-  
702 Nutritive Sweeteners on Glucose Metabolism and Appetite Regulating Hormones: Systematic  
703 Review of Observational Prospective Studies and Clinical Trials. *PLoS One* **11**, e0161264.  
704 37. Sievenpiper JL, Khan TA, Ha V *et al.* (2017) The importance of study design in the  
705 assessment of nonnutritive sweeteners and cardiometabolic health. *CMAJ* **189**, E1424-E1425.  
706 38. Lobach AR, Roberts A, Rowland IR (2018) Assessing the in vivo data on low/no-calorie  
707 sweeteners and the gut microbiota. *Food Chem Toxicol*.  
708 39. Le Donne C, Mistura L, Goscinnny S *et al.* (2017) Assessment of dietary intake of 10  
709 intense sweeteners by the Italian population. *Food and Chemical Toxicology* **102**, 186-197.  
710 40. Buffini M, Goscinnny S, Van Loco J *et al.* (2018) Dietary intakes of six intense sweeteners  
711 by Irish adults. *Food Additives & Contaminants: Part A* **35**, 425-438.  
712 41. Martyn D, Darch M, Roberts A *et al.* (2018) Low-/No-Calorie Sweeteners: A Review of  
713 Global Intakes. *Nutrients* **10**, 357.  
714 42. Malek AM, Hunt KJ, DellaValle DM *et al.* (2018) Reported Consumption of Low-  
715 Calorie Sweetener in Foods, Beverages, and Food and Beverage Additions by US Adults:  
716 NHANES 2007-2012. *Curr Dev Nutr* **2**, doi: 10.1093/cdn/nzy1054.  
717 43. Gibson S, Ashwell M, Arthur J *et al.* (2017) What can the food and drink industry do to  
718 help achieve the 5% free sugars goal? *Perspect Public Health* **137**, 237-247.  
719 44. Wittekind A, Higgins K, McGale L *et al.* (2018) A workshop on 'Dietary sweetness-Is it  
720 an issue?'. *Int J Obes (Lond)* **42**, 934-938.  
721 45. World Health Organisation (2015) Guideline: Sugars intake for children and adults: WHO,  
722 Geneva. [https://www.who.int/nutrition/publications/guidelines/sugars\\_intake/en/](https://www.who.int/nutrition/publications/guidelines/sugars_intake/en/).  
723 46. Scientific Advisory Committee on Nutrition (2015) *Carbohydrates and Health*. Public  
724 Health England. available online <https://www.gov.uk/government/publications/sacn-carbohydrates-and-health-report>.  
725 47. Harricharan M, Wills J, Metzger N *et al.* (2015) Dietitian perceptions of low-calorie  
726 sweeteners. *Eur J Public Health* **25**, 472-476.  
727 48. Public Health England (2015) Why 5%? An explanation of the Scientific Advisory  
728 Committee on Nutrition's recommendations about sugars and health, in the context of current  
729 intakes of free sugars, other dietary recommendations and the changes in dietary habits  
730 needed to reduce consumption of free sugars to 5% of dietary energy. *PHE publications*  
731 *gateway number 2015193*. <https://www.gov.uk/government/publications/sacns-sugars-and-health-recommendations-why-5> (accessed August 2019)  
732 49. Bright OM, Wang DD, Shams-White M *et al.* (2017) Research Priorities for Studies  
733 Linking Intake of Low-Calorie Sweeteners and Potentially Related Health Outcomes:  
734 Research Methodology and Study Design. *Curr Dev Nutr* **1**, e000547.  
735 50. Concannon TW, Meissner P, Grunbaum JA *et al.* (2012) A new taxonomy for stakeholder  
736 engagement in patient-centered outcomes research. *J Gen Intern Med* **27**, 985-991.  
737 51. de Ruyter JC, Olthof MR, Seidell JC *et al.* (2012) A trial of sugar-free or sugar-sweetened  
738 beverages and body weight in children. *The New England journal of medicine* **367**, 1397-  
739 1406.  
740 52. Tate DF, Turner-McGrievy G, Lyons E *et al.* (2012) Replacing caloric beverages with  
741 water or diet beverages for weight loss in adults: main results of the Choose Healthy Options  
742 Consciously Everyday (CHOICE) randomized clinical trial. *The American journal of clinical*  
743 *nutrition* **95**, 555-563.  
744

- 746 53. Peters JC, Wyatt HR, Foster GD *et al.* (2014) The effects of water and non-nutritive  
747 sweetened beverages on weight loss during a 12 week weight loss treatment program. *Obesity*  
748 **22**, 1415-1421.
- 749 54. Peters JC, Beck J, Cardel M *et al.* (2016) The effects of water and non-nutritive  
750 sweetened beverages on weight loss and weight maintenance: A randomized clinical trial.  
751 *Obesity (Silver Spring)* **24**, 297-304.
- 752 55. Masic U, Harrold JA, Christiansen P *et al.* (2017) EffectS of non-nutritive sWeetened  
753 beverages on appetiTTe during aCTive weigHt loss (SWITCH): Protocol for a randomized,  
754 controlled trial assessing the effects of non-nutritive sweetened beverages compared to water  
755 during a 12-week weight loss period and a follow up weight maintenance period. *Contemp*  
756 *Clin Trials* **53**, 80-88.
- 757 56. Malik VS (2019) Non-sugar sweeteners and health. *BMJ* **364**, k5005.
- 758 57. Azad MB, Abou-Setta AM, Chauhan BF *et al.* (2017) Nonnutritive sweeteners and  
759 cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials  
760 and prospective cohort studies. *CMAJ* **189**, E929-E939.
- 761 58. Sylvestsky AC, Rother KI (2018) Nonnutritive Sweeteners in Weight Management and  
762 Chronic Disease: A Review. *Obesity (Silver Spring)* **26**, 635-640.
- 763

Peer Review

764 **Table 1: Timeline of the project**  
765

January 2018	Identification of ISA conference speakers and chairs
April 2018	Workshop leaders (MA & SG) appointed
	Conference speakers and chairs invited to workshop
May 2018	Three key workshop Themes identified by workshop leaders
May 2018	Workshop leaders agree questions for experts and-based on the 3 Themes for workshop
July 2018	Experts asked to provide provisional answers to questions
September 2018	Workshop leaders collate expert comments into WDworking document
November 6 <sup>th</sup> , 2018	ISA Conference
November 7 <sup>th</sup> , 2018	Expert workshop
November 2018	Draft consensus statements agreed at workshop, circulated to experts
December 2018	Comments received from experts
December 2018- January 2019	Draft paper written by workshop leaders
January 2019	Draft paper circulated to experts for approval
February 2019	Paper finalised and submitted to journal
July and August 2019	Revisions to paper agreed by panel

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 771 **Table 2: Comparison of our consensus statements on LCS with those of**  
 772 **others.**

773 (+ = broad correspondence with our Consensus statements; blank = not (or not  
 774 fully) addressed)

<b>Theme 1:</b> <b>Role of low calorie sweeteners in weight management and glucose control: the scientific evidence</b>	Gibson et al (2014) ( <a href="#">14</a> )	Serra-Majem et al (2018) ( <a href="#">15</a> )
1. When substituted for sugars to reduce energy density of foods and drinks, LCS can reduce net energy intake and assist weight management.	+	+
2. Intervention studies have shown that LCS beverages have at least a similar effect on appetite and energy intake to water	+	
3. The collective evidence supports the conclusion that LCS have no adverse effect on blood glucose and insulin regulation (HbA1c, fasting and post-prandial glucose and insulin levels) in people with, and without, diabetes	+	+
4. The potential value of LCS in dietary management of diabetes derives from their role as substitutes for sugars. and hence carbohydrates.	+	+
5. Confounding by adiposity, and reverse causality can explain the positive association between LCS and T2DM and other cardiometabolic diseases, reported in some observational studies.		+
6. Regarding effects involving the human gut microbiota, current evidence is limited and does not provide adequate evidence <u>that LCS influence of effects of LCS-gut health at doses relevant to human use(either negative or positive effects)</u> .		
<b>Theme 2:</b> <b>Consumption and safety of low calorie sweeteners and consumer perception</b>		
1. The safety of LCS is demonstrated by a substantial body of evidence <u>as well as continued review by independent regulatory agencies/committees including: JECFA/Codex, FDA and EFSA</u> . <u>These organisations have taken into account of the decades of both positive and negative human and animal studies to draw their conclusions.</u> Continual monitoring and modelling of LCS exposures is undertaken and this demonstrates that intakes of LCS, even among high consumers, are within ADIs		+
2. Currently, the major sources of LCS in the Western diet are beverages and table top sweeteners		
3. LCS can be used to reduce the sugar and energy content of beverages (and some foods) whilst maintaining a similar sensory profile. The potential for energy reduction is more limited in foods and depends on the options for reformulation and what replaces the bulk of sugar. LCS can be used synergistically in blends to achieve the desired sensory profile at lower levels of use	+	+

4. The collective evidence supports the conclusion that there is no relationship between adiposity and liking/ preference for sweet taste in either adults or children		
5. Consumer perceptions vary with regard to LCS, with some people having concerns about their potential health effects	+	+
<b>Theme 3:</b> <b>Role of low calorie sweeteners in relation to nutrition policy</b>		
1. Reduction in the intake of 'free sugars' and 'added sugars' is being recommended around the world to reduce the risk of obesity, which is a major public health concern. LCS should be one of the strategies to consider.	+	+
2. LCS can be useful in dietary approaches to both prevent and manage diabetes and obesity. Benefit will depend on how foods and beverages containing LCS are substituted, as well as on the overall quality of the diet and the overall energy provision.	+	+
3. Despite repeated and consistent reassurances from food safety authorities, there is still some distrust of LCS among health professionals and policy makers	+	+
4. Some policies acknowledge LCS consumption as a useful strategy to reduce sugars intake. However, there are discrepancies with other national and international policies and regarding use in children.		+

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779 **Supplementary information**

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781 **Comparison of Consensus statements from others with the Consensus**  
 782 **statements in this paper**

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784 **Table S1: Conclusions from Gibson et al. (2014)**

	Relevant to our consensus statement Blank = not addressed
(1) LCS do not increase appetite and have no discernible effect on satiety	1a2
(2).LCS help to reduce energy when used in place of higher energy ingredients	1a1
(3).LCS can enhance weight loss under real-life conditions when used as part of a behavioural weight loss programme	1a1
(4).LCS may have a beneficial effect on post-prandial glucose and insulin in healthy individuals and in people with diabetes	1a3 1a4
(5).LCS have dental benefits when used in food, beverages, toothpaste and medications, provided other constituents are also non-cariogenic and non-erosive	

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787 **Table S2: Conclusions from Serra-Majem et al ( 2018)**

	Relevant to our consensus statement Blank = not addressed
1) LNCS are some of the most extensively evaluated dietary constituents, and their safety has been reviewed and confirmed by regulatory bodies globally including the World Health Organisation, the US Food and Drug Administration and the European Food Safety Authority;	2a1
2) Consumer education, which is based on the most robust scientific evidence and regulatory processes, on the use of products containing LNCS should be strengthened in a comprehensive and objective way;	2b1 2a5
3) The use of LNCS in weight reduction programmes that involve replacing caloric sweeteners with LNCS in the context of structured diet plans may favour sustainable weight reduction.  Furthermore, their use in diabetes management programmes may contribute to a better glycaemic control in patients, albeit with modest results.	1a1 1a3 1a4

LNCS also provide dental health benefits when used in place of free sugars	
4) It is proposed that foods and beverages with LNCS could be included in dietary guidelines as alternative options to products sweetened with free sugars;	2a3 3c1 3a4
5) Continued education of health professionals is required, since they are a key source of information on issues related to food and health for both the general population and patients. With this in mind, the publication of position statements and consensus documents in the academic literature are extremely desirable.	3a3 3c4

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790791 **Table S3: Conclusions from Bright (2018) on Future Research Needs**  
792 Blank = not addressed

	Relevant to our consensus statement
Q1. Do LCSs aid weight loss and/or weight maintenance?	1a1 1b1
Q2. Does LCS consumption modify appetite (hunger, fullness, desire to eat /prospective consumption) and/or total energy intake and, if so, how?	1a1, 1a2
Q3. Does the use of LCSs affect insulin secretion, carbohydrate metabolism, or the gut microbiota and its function? If so, where is this happening (cognition, sweet receptors on tongue, receptors in gastrointestinal tract, etc.) and does it have any physiologic consequences on health?	1b1
Q4. Are there potential long-term health risks (obesity, diabetes, cancer, CVD, etc.) of LCS consumption in humans? Are certain population groups (diabetics, children, pregnant women, those with genetic disease) more susceptible to the potential health risk(s)?	1b1, 1b2
Q5. Is LCS sweetness perceived by the brain as energy in the same way as other sweeteners? Do those who are overweight or obese sense LCSs differently than normal-weight people?	
Q6. Are there impacts of LCS consumption during pregnancy on the fetus?	
Q7. Do LCSs differentially affect long-term food intake, eating frequency, and portion sizes in children, adolescents, and adults? Is there an impact on dietary quality and adherence to recommended dietary patterns?	1b4? 3b1 3b2
Q8. In individuals with diabetes and prediabetes, does chronic consumption of LCSs have an impact on glycemic control, alter glucose transport, or invoke a cephalic phase response?	1b5
Q9. Does LCS consumption affect consumption of other sweeteners or sugars or total carbohydrate intake? Is the effect different than that from consumption of nutritive sweeteners?	1b4 2b3
Q10. Do LCSs affect energy metabolism and fat storage?	1b1
Q11. Should study findings be evaluated for each LCS individually or collectively? To which health outcome(s) are the findings from individual	1b3

LCSs generalizable to the class of ingredients?	
Q12. Is LCS intake accurately estimated in current dietary assessment tools?	2b3
Q13. Are there interactions between the combination of fat substitutes and sweetener substitutes on appetite (hunger, fullness, desire to eat or prospective consumption) and/or total energy intake?	related to 1b2
Q14. Is there any variation in how LCSs affect those of different ages, races, and ethnicities?	1b2
Q15. Do individuals with different dietary patterns (high protein vs. high carbohydrate, etc.) affect the metabolism of LCSs differently and, if so, how?	1b2
Q16. How do we design a system or methodology to address the differences in existing LCS compounds vs. compounds that will be emerging down the road?	2a1? 2b2 2b3
Q17. Do the effects of LCS consumption on body weight differ by sex? If so, what are the sex-specific mechanisms of the impact of LCS consumption on body weight?	1b2
Q18. Has there been a gradual increase in the overall sweetness in our diet?	related to 1b4

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