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Perspective:

Standards for research and reporting on low-energy (“artificial”) sweeteners

David J. Mela, Valkenswaard, The Netherlands

John McLaughlin, Faculty of Biology, Medicine and Health, University of Manchester,
Manchester UK

Peter J. Rogers, School of Psychological Science, University of Bristol, Bristol UK

Corresponding author: David J. Mela, Hofstraat 18, 5554 EB Valkenswaard, The Netherlands; +31 6 2909 2318; djmela@djmela.eu

Last names for PubMed: Mela, McLaughlin, Rogers

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Nonstandard abbreviations:

ADME Absorption, distribution, metabolism, and excretion

LES Low energy sweeteners

RCT Randomized controlled (intervention) trial

1 **Abstract**

2 Widely differing views exist amongst experts, policy makers and the general public, regarding
3 the potential risks and benefits of reduced- or low-energy sweeteners (LES) in the diet.

4 These views are informed and influenced by different types of research in LES, with differing
5 hypotheses, designs, interpretation and communication. Given the high level of interest in

6 LES, and the public health relevance of the research evidence base, it is important that all
7 aspects of the research process are framed and reported in an appropriate and balanced

8 manner. In this perspective, we identify and give examples of a number of issues relating to
9 research and reviews on LES, which may contribute toward apparent inconsistencies in the

10 content and understanding of the totality of evidence. We conclude with a set of

11 recommendations for authors, reviewers and journal editors, as general guidance to improve
12 and better standardize the quality of LES research design, interpretation, and reporting.

13 These focus on clarity of underlying hypotheses, characterization of exposures, and the
14 placement and weighting of new research within the wider context of related prior work.

15

16 **Key words:** Energy, sweetness, guidance, communication, recommendations

17 Research and review papers convey a range of differing conclusions about the potential
18 impact of low-energy ('artificial' or nature-derived) sweeteners (LES) on public health,
19 ranging from harmful to neutral to beneficial. Some commentators have highlighted concerns
20 that use of LES may raise risks for obesity and metabolic disorders (1-4), while others are
21 equally clear in expressing likely benefits of LES with regard to many of these same
22 outcomes (5, 6). This has not been resolved by recent systematic reviews with meta-
23 analyses (7-9), which generated differing conclusions.

24 There is consistent international guidance to industry and the public to reduce sugars intakes
25 (10), and LES are a major alternative to sugars in many products, making this is an important
26 public health issue to resolve. Furthermore, given that LES and LES-containing products
27 receive a high level of attention from media and consumers, there is additional responsibility
28 for experts to frame and communicate their views and research data in an appropriate
29 context. As such, high standards for research designs and the representation and weighting
30 of evidence are needed to ensure a balanced interpretation, context and reporting in
31 research and reviews on LES.

32 A recent expert stakeholder panel proposed a number of research priorities for LES and
33 health outcomes (11). While that panel did not specifically address issues relating to the
34 execution of research and reporting on LES, others have highlighted issues in experimental
35 design and interpretation that can magnify apparent inconsistencies in the evidence base
36 (12-14). In this commentary, we highlight specific practices which can be considered as part
37 of guidance to improve the design, reporting and interpretation of research on LES. We
38 illustrate the issues with examples, and conclude with some recommended practices for
39 authors, reviewers and journal editors.

40

41 **Be clear about the hypothesis: What question is being tested?**

42 From a public health perspective there is need for an evidence base of research that
43 decisively addresses the benefits and risks of LES, i.e. generating reliable data and analyses
44 on how the use of LES, as a replacement for sugars or on their own, influence metabolic
45 health. Research on LES and non-communicable disease risks fit broadly under 3 underlying
46 *a priori* hypotheses, reflecting questions about exposure to energy reduction, sweetness or
47 LES-specific (metabolic or safety) effects. The design of studies, particularly in terms of the
48 exposure and relevant comparators, should follow from and correspond to the underlying
49 hypothesis and primary research question being posed.

50

51 1) Energy reduction: Testing effects of low-/non-caloric vs caloric sweeteners

52 Where the research question tests exposure to LES as a generic low- or non-caloric
53 source of sweetness, the hypothesis as stated is usually independent of the specific
54 sweetener(s) considered. The appropriate comparator will be the same test product
55 (usually food or beverage) vehicle(s) or dietary regimen with caloric sweeteners, tested
56 against LES with a significantly lower energy content per unit consumed, and similar in
57 sweetness and other sensory attributes.

58

59 2) Sweetness: Testing effects of sweetness (sweet stimuli) exposure *per se*

60 Where the research question tests exposure to LES as a 'pure' (non-caloric) sweet
61 stimulus, the hypothesis as stated is usually independent of the specific sweetener(s)
62 considered. The main exception to this would where the hypothesis is based on to
63 interactions of a specific LES structure and sweet taste receptor(s). The appropriate
64 comparison is to exposure to the same or similar delivery vehicle(s) or dietary regimen, at
65 the same energy and nutrient density, with and without LES.

66 Depending on the hypothesis, the research may test oral exposure to LES as sweet
67 stimulus, or LES as chemical stimuli for receptors sensitive to 'sweet' tastants in the gut or
68 internal tissues. For oral exposure, the most common comparison would be LES-

69 sweetened beverages vs water, but this has also been tested with solid foods (15). To
70 isolate the post-oral gastrointestinal or systemic exposures, LES in capsules would
71 typically be used, or perhaps nasogastric intubation (16) .

72 In order to interpret whether any putative effects are a response to LES specifically vs
73 sweet stimuli in general, these studies should optimally include an additional comparison
74 of sweet vs non-sweet caloric stimuli, such as glucose (sweet) vs pure short-chain
75 maltodextrin (non-sweet, rapidly hydrolyzed glucose polymer).

76

77 3) Sweetener-specific: Testing specific post-ingestive (metabolic, physiological, toxicologic)
78 effects of a specific LES or group of LES

79 These types of research questions are clearly based around one or more specific LES,
80 with the underlying hypothesis relating to unique physiological effects that may arise from
81 their particular characteristics. In this case the appropriate comparison is to the same test
82 product (food, beverage, capsule) vehicle(s) or dietary regimen with no LES or, to sharpen
83 the interpretation, preferably a different LES lacking the characteristic(s) of interest.

84 Because sweeteners differ markedly in their absorption, distribution, metabolism and
85 excretion (ADME), they can also differ in the potential presence of the intact material or
86 metabolites in different body sites (17, 18). This point is often overlooked, yet may be
87 highly relevant for the interpretation and extrapolation of experimental and population
88 data, and is considered further in the next section.

89

90 Differences in the (stated or unstated) hypotheses, lack of clarity or mixing of hypotheses can
91 have important consequences. Examples of this can be seen in the assessment of effects of
92 LES intervention trials on outcomes relating to energy balance in 3 recent systematic reviews
93 with meta-analyses. Rogers et al (8) separately analyzed and reported comparisons of LES
94 vs sugars, LES vs water, and LES vs placebo capsules. In contrast, Azad et al. (7) and
95 Toews et al. (9) did not make this distinction between comparators. For energy intake and
96 weight change, a benefit of LES is more plausible when compared to a caloric than a non-

97 caloric alternative (19), so the decision of whether to make this distinction can significantly
98 impact the combined effect sizes and conclusions (as can be seen in those reviews). There
99 may be valid arguments for either approach in meta-analysis; however, the primary research
100 studies invariably differentiate these comparisons in their hypotheses and designs.
101 A further consideration is whether the underlying hypotheses are or should be sweetener-
102 specific. This has implications for study selection and the interpretation (extrapolation) of
103 results. For example, the protocol and objectives for the systematic review of Toews (9) are
104 framed in a way that is independent of the specific sweetener, although the review only
105 included studies where the sweetener was specified. This criterion largely excludes studies
106 where free-living subjects consume a mix of commercial LES-containing 'diet' products,
107 generating much smaller evidence base than other contemporary systematic reviews for
108 similar outcomes (7, 8, 20).

109

110 **Control and specify exposures where relevant**

111 There are research hypotheses and designs where the nature of the exposure and specific
112 LES may be important. By definition, LES all share the characteristics of being sweet and low
113 in energy when used in place of sugars. For hypotheses based on exposure to energy or
114 sweetness, effects are usually assumed to be related to variation in the energy content or
115 taste attributes of the test materials (19, 21). In the absence of other hypotheses, it is
116 generally reasonable to presume that similar results would be seen using other LES to
117 achieve the same calorie reduction or taste profile. Nevertheless, specific LES may differ
118 with regard to their stimulation of different "sweet taste" receptors, digestion or uptake in the
119 gut, and appearance and pharmacokinetics in different body pools, which results in differing
120 potential for interactions with specific gut or systemic receptors and systemic or gut
121 (including microbiota) metabolism (14, 17, 18, 22, 23). For example, protein or peptide
122 sweeteners are rapidly digested and absorbed as their constituent amino acids, so will not
123 enter the colon. Sucralose is usually reported to be almost completely excreted intact in
124 feces (70-90%), although this has recently been questioned (24). Steviol glycosides on the

125 other hand are actively metabolized by the colonic microflora, bacterial cleavage of the
126 glycoside component allowing absorption of steviol which is systemically available after
127 hepatic glucuronidation and renally excreted.

128 There is currently considerable interest in the possible effects of LES on the gut microbiota
129 composition, which has been reported for saccharin, sucralose and steviol glycosides in
130 humans (25). The plausibility of these observations is directly linked to the molecular and
131 thus ADME properties of the specific LES, and cannot be generalized. Moreover, as the
132 functional capacity of the microbiota may be more relevant than purely taxonomic accounts
133 of composition, the extrapolation from these observations to health implications must also
134 take account of the nature and properties of the specific LES exposures. The majority of
135 these studies have also been in rodents, which have been valuable in generating new
136 hypotheses, especially where these are not amenable to direct testing in humans (e.g., 26).

137 However, important differences in specific animal research models and test conditions
138 contribute to many inconsistencies in this literature (12, 27), and direct relevance to human
139 nutrition and metabolism cannot simply be assumed. Approaches in animal studies such as
140 very excessive dose loading may be appropriate for some safety and toxicological research
141 but can have distorting consequences for nutrition-related outcomes. A further issue for
142 interpretation and replication is that many studies have fed animals commercial 'tabletop'
143 LES preparations which are of unknown, impure or variable composition, where the
144 sweetener comprises perhaps only a small percentage of the total content (28-30). Notably,
145 the non-LES filler material or bulking agents in these compositions may also include
146 fermentable carbohydrates.

147 Exposures in studies may be short- or long-term, and hypotheses should also logically relate
148 to this. Despite *in vitro* evidence of variation in stimulation of oral, gut and systemic receptors
149 by LES, a large body of short-term physiological studies in humans find no consistent generic
150 or LES-specific effect on acute postprandial responses (31-33). However, there is more
151 limited evidence testing potential variation in chronic LES-specific exposure effects on
152 glycemic or gut hormone responses. Here it would be crucial that hypotheses relate to the

153 metabolic fates of specific LES, which might differentially affect physiology in the long-term, a
154 different and possibly more important question than what single-dose acute studies can
155 address. Measurable differences in physiological responses to different LES, mediated by
156 mechanisms independent of their actions at sweetness receptors, may be almost inevitable
157 given their extreme chemical diversity. It is important to confirm whether these differences
158 produce consistent and meaningful variation in health-related outcomes (34).

159 Depending on the hypotheses, human research studies may also need to take account (e.g.
160 by selection or pre-planned statistical analyses) of participant characteristics, particularly
161 whether they are habitually high or low consumers of LES. It is likely that these groups also
162 differ in regard to other habitual dietary and other lifestyle behaviors or personal
163 characteristics (e.g. microbiome), which may significantly influence responses to
164 interventions or their interpretation (14, 18). Establishing the nature of prior LES exposures of
165 populations may also have important implications for the interpretation of cross-sectional and
166 prospective observational studies measuring birth or long-term health outcomes. It seems
167 essential (and yet is rare) that researchers consider which particular LES were available to
168 the cohort at the time and place of data collection or index events (such as conception,
169 pregnancy), so the plausibility of causal interpretations can be placed in the context of the
170 relevant ADME properties and prior physiological or safety studies. For example, as noted
171 above, LES differ substantially in their uptake and access to systemic circulation or tissues.

172 Lastly, a limitation noted in a recent systematic review of the relationship between sweet
173 taste exposure and subsequent liking and preference for sweet stimuli was that few studies
174 had made any quantitative assessments of the perceived sweetness of test materials or diets
175 (21). Instead, the content or even just the presence of sugars or sweeteners in foods or diets
176 was often used as a proxy indicator of exposures to sweetness. While matching of test
177 materials should be relatively easy in laboratory-based trials, the characterization of
178 exposures to sweetness is more challenging where the subjects or cohort are consuming a
179 range of commercially available foods. Recent efforts to generate “sensory-diet” databases
180 (35, 36) are an important development, as they can provide a basis for objectively quantifying

181 and comparing exposures to sensory attributes of foods and diets in large populations. For
182 both behavioral and physiological research focused on the effects of orosensory exposure to
183 sweetness in foods or beverages, it seems essential that some effort is made to verify the
184 actual exposures.

185 Considering all these potential sources of variability in research materials or exposures,
186 design and outcomes, it is vital that the hypotheses, design and interpretation of research are
187 consistent with the specific LES source(s), the doses and means of delivery, and the putative
188 mechanisms or sites of action, which may primarily be oral, gastrointestinal or systemic.

189 Effects of specific sweeteners may be independent of sweetness, even where this is the
190 main attribute of LES that underpins the reason to design and undertake the study.

191 Depending on the hypothesis, the range of potential “off-target” effects may make it
192 inappropriate to aggregate LES studies together and test for a class effect.

193

194 **Place new research in the context of the totality of evidence**

195 New or different types of research will have differing contributions to the overall totality of
196 evidence, and should be viewed within this context (37). The impartial and balanced
197 representation and dissemination of the evidence base can however be undermined by
198 selective citation and citation distortion (citation bias and amplification) in biomedical
199 research (38, 39). These practices include systematically ignoring data conflicting with prior
200 beliefs, conveying hypothesis as fact, and preferential reference to statistically significant vs
201 “neutral” outcomes (or vice-versa).

202 Reporting of research on LES is not immune to these issues. An extreme example is the
203 pattern of citations to Suez et al (29), who proposed that consumption of intense sweeteners
204 may alter the intestinal microbiota leading to adverse effects on glucose tolerance. As of
205 November 2019 that publication had been cited over 1000 times, usually to highlight this as a
206 potential or even confirmed risk of LES (2, 4, 40). In contrast, a 2013 systematic review of
207 controlled human trials of LES effects on markers of glycemc control (41), with a differing
208 conclusion, had been cited only 5 times. Similarly, reviews of the LES-microbiota-glycemia

209 hypothesis (e.g., 42) may also make little or no reference at all to the primary research
210 papers and reviews of controlled human trials that have specifically tested sustained
211 exposure to LES on glycemic control (32, 43, 44), nor the regulatory and safety reviews
212 where these outcomes have been considered in depth for specific sweeteners (18, 45-49).
213 The choice of this example is not to question the results of Suez et al (29) or whether LES
214 affect microbiota or glycemic control. It is simply to illustrate where new research with
215 provocative results needs to be placed in the context of the totality of prior evidence. In this
216 case, the record of citations indicates a pattern of giving disproportionate weight to
217 hypothesized adverse effects, relative to a large body of empirical evidence to the contrary
218 (18). In other cases, hypothesized effects of LES are simply assumed, with seemingly no
219 apparent need to consider the evidence at all. For example, a common argument against the
220 use of LES as an approach to reduce sugars intakes, rests on the view that sweetness
221 exposure 'drives' sweetness preferences. This idea is plausible and commonly expressed,
222 and even appears in relatively high-level policy documents (50). Yet there seems to be little
223 objective support for this view, and possibly even more evidence favoring the alternative that
224 sweetness exposure satisfies (rather than drives) preferences (21).

225 The persistent failure to present and consider research in the context of the totality of prior
226 evidence risks uncritically (re-)generating and sustaining hypotheses without adequately
227 acknowledging where these have previously been robustly tested and perhaps rejected (see
228 51). From recent headlines, commentaries and narrative reviews, non-experts might be
229 forgiven for being unaware that LES had been the subject of a substantial number of RCTs,
230 and systematic reviews and meta-analyses of these. As a general principle, it is poor practice
231 for professional papers to cite selected *in vitro*, animal and observational studies as the
232 primary evidence for putative effects of LES, without balanced reference to the large corpus
233 of human trials and safety assessments where the same markers and outcomes have been
234 considered (45-49). When the totality of information is considered a very different picture
235 may emerge. For example, animal data are often used to underpin the view that LES may
236 lead to disordered appetite and weight gain. However, in our systematic review of human

237 and animal studies of LES and body weight (8), we identified 90 relevant animal studies of
238 which only a small minority (mostly from one research group) reported increased body
239 weight. The corresponding human RCT data also showed beneficial effects on energy intake
240 and body weight. The impact of selective citation is reflected in the view of some members of
241 a recent expert stakeholder panel, that additional LES intervention trials for weight control
242 outcomes were mainly needed "...due to public perception and some vocal opposition" (11).

243

244 **Acknowledge the limitations of observational and animal data**

245 Even papers critical of LES acknowledge there are many discrepancies between the adverse
246 health impacts hypothesized by some animal and human observational studies, in contrast to
247 more often neutral or beneficial effects usually seen in human intervention trials (52).

248 Differences in the weighting given to evidence from these different research designs
249 contributes toward differing views of the perceived risks and benefits of LES. While there are
250 limitations to the suitability and interpretation of RCT data for certain research questions (37),
251 there is a need for particular caution in selective use and extrapolation from observational
252 and animal data. This can be illustrated by the interpretation of research on the relationship
253 between water intake and body weight, as an analogy to research on LES.

254 Water is a zero-energy food and beverage ingredient, widely recommended as a preferred
255 beverage choice in the context of obesity, despite inconsistent evidence around its influence
256 on weight management (53). Systematic reviews and meta-analyses of observational data
257 on water consumption in relation to weight management have reported limited evidence of
258 benefits, and even significant *adverse* associations of water consumption with body weight
259 outcomes in children and adolescents (54, 55). Other analyses have found that water
260 consumption was positively associated with all-cause mortality (56). The plausibility of
261 adverse effects of water consumption on weight control could be further supported by
262 reference to a considerable volume of animal research. It has long been known that greater
263 water intake is positively correlated with greater food intake in animals (57), and greater

264 weight gain with the addition of water to the diet has been reported in experiments with
265 several species (58-63).

266 This example shows the ease with which selective, uncritical reference to observational and
267 animal research could be used to underpin an apparently compelling but intentionally absurd
268 narrative. In the case of water, adverse effects suggested by the cited observational and
269 animal studies are readily dismissed, despite the absence of a robust body of contrary RCT
270 data. For LES, similar adverse effects suggested by observational and animal data are given
271 much more weight as a basis for causal inferences, even where there are substantial RCT
272 data to the contrary. There may be very valid reasons for this, but animal studies may lack
273 generalizability (27, 64), and the limitations of observational studies and risk of assuming
274 causation from association are well-known (65, 66). In the observational studies of water and
275 body weight, confounding and reverse causality are readily invoked and accepted as reasons
276 to conclude the observed relationships are spurious (54, 56, 67). Similar concerns have
277 repeatedly been raised regarding interpretation of epidemiological associations of body
278 weight and metabolic health with LES (3, 13, 68). LES may be disproportionately used in
279 place of sugar by individuals with a pre-existing history or elevated risk of weight gain or
280 diabetes, and this caveat is often highlighted in the original papers (e.g., 69). Moreover, in
281 the case of LES, the likelihood that epidemiological associations are spurious is reinforced
282 where the corresponding RCT data for related outcomes consistently indicate neutral or
283 beneficial effects (8, 41). As a result, several authors have expressed doubt about the weight
284 that should be placed on observational (and animal) studies in this area for outcomes where
285 data from sustained RCTs are available (8, 13, 70, 71).

286 This ultimately comes down to ensuring the research approach has been appropriately
287 designed to address a specific hypothesis, and that the limitations - including potential for
288 confounding or post-hoc use of the same data to answer other research questions - are
289 adequately acknowledged in drawing conclusions. All types of study designs have potential
290 weaknesses, and all can contribute in different ways to the totality of evidence (37).

291 Observational and animal research on LES can generate hypotheses and address questions

292 that cannot be directly tested in humans, such as longer-term disease outcomes and
293 toxicology, and potential multi-generational effects (26, 27, 72, 73). Nevertheless, such data
294 should be very cautiously interpreted, particularly where they conflict with results from robust
295 RCTs.

296

297 **A note on bias: white hats and black hats**

298 Application of the guidance proposed here would improve the quality of communication and
299 discourse on LES, independent of the views or interests of who is delivering the messages.

300 All stakeholders may potentially be guilty of “white hat bias”, the well-intentioned but biased
301 “distortion of information in the service of what may be perceived to be righteous ends” (74).

302 We as authors hold certain views based on our reading of the evidence and our own
303 research (8, 19, 21), and also acknowledge potential conflicts of interest such as funding
304 sources and collaborations. In research on LES, as in other areas of nutrition, the potential
305 for industry-related (“black hat”) bias has been widely discussed. Indeed, Mandrioli et al (75)
306 recently concluded that reviews of LES and health were biased by sponsorship and financial
307 conflicts of interest, although the risk of bias was mainly relevant to narrative rather than
308 systematic reviews. However, commercial associations are not the only possible source of
309 bias, and absence of such interests is no assurance of impartiality (39, 74, 76-79). The
310 personal reputation, conference invitations, and travel and research support for
311 “independent” researchers may also benefit from the particular views they take. A continued
312 flow of provocative research results and atmosphere of uncertainty around LES undoubtedly
313 also improves the chances for further funding of research on the topic.

314 These different biases can influence the design, interpretation, and reporting of research on
315 LES, undermining an impartial and balanced scientific and public consideration of the
316 possible benefits or risks of their use. This places even greater demand on authors and
317 journal editors to ensure the faithful representation and appropriate weighing of evidence.

318 With this in mind, we encourage others, and especially those with differing views, to offer

319 other examples from the current literature that would support further refinement of the
320 recommendations that follow here.

321

322 **Conclusions and recommendations**

323 There are significant issues in how the evidence base on LES is generated, interpreted and
324 communicated by the expert community, with implications for public health, industry and
325 future research needs. We have discussed a number of these, with examples, to illustrate
326 the need for a more consistent standard of practice in the conceptualization and reporting of
327 both primary research and reviews of that research. These issues also emphasize areas for
328 more careful and critical scrutiny of research publications by wider stakeholders, including
329 research end-users.

330 Importantly, in relation to public health, LES are not a case where the “precautionary
331 principle” necessarily applies. Where adverse effects of LES exposures are confirmed by
332 evidence-based expert risk assessment, these rightly should be considered in regulatory and
333 public health policies. However, there may also be value gained from the use of LES, for
334 example as a tool for maintaining the acceptability of foods, beverages and diets reduced in
335 sugar, facilitating progress towards widely-advised goals to reduce sugar intakes (80, 81). In
336 short, there are risks to be considered not just from exposure to LES but also from
337 prematurely advising the public to avoid them.

338 We believe it should be possible to formulate guidance to address the issues raised here,
339 which can be widely embraced by individual researchers, and those involved with the
340 funding, communication and use of research. Many of our concluding recommendations in
341 Table 1 apply to nutrition research in general, but they have particular relevance to research
342 with LES. We hope these can be broadly accepted by the expert community, and welcome
343 further their consideration and development.

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Table 1. Recommendations for research and reporting on LES

- Research hypotheses should be explicit, and the underlying research question(s) reflected in the choice of exposures, comparators and analyses.
- The justification and interpretation of primary research studies and their representation in reviews should reflect the stated hypotheses, with particular regard to caloric vs non-caloric comparators, and potential for extrapolation to LES in general vs specific LES.
- Where outcomes are not attributable to energy reduction or perceived sweetness, interpretation relies on the chemical and ADME properties of specific LES.
- The selection and citation of existing research should fairly represent the balance and weight of different types of evidence, particularly where there are data from RCTs with relevant exposures and populations.
- Animal research and other studies generating evidence related to safety and toxicology should specifically refer to that literature.
- Reporting of evidence on health associations with LES from observational studies, including prospective cohort studies, should be clear that these are subject to residual confounding including reverse causality, and may have been designed to answer a different research question.
- Hypotheses generated by observational and animal data must be interpreted in relation to the specific exposures, plausible causal pathways, and results of any related human intervention trials.