The Director General

Maisons-Alfort, 9 January 2015

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety
of 19 November 2014, revised on 9 January 2015[1]

on the assessment of the nutritional benefits and risks related to intense sweeteners

ANSES undertakes independent and pluralistic scientific expertise.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 19 November 2014 shall prevail.

On 30 June 2011, ANSES issued an internal request to assess the nutritional benefits and risks related to intense sweeteners.

1. BACKGROUND AND PURPOSE OF THE REQUEST

1.1 Scientific and regulatory background

In 2011, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) published an opinion reviewing two new studies on the potential health effects of aspartame and acesulfame potassium (K), two intense sweeteners. Further to this opinion, ANSES deemed it necessary to continue the assessment by taking it in two directions. It first asked the European Food Safety Authority (EFSA) to bring forward the re-evaluation of the Acceptable Daily Intake (ADI) of aspartame initially planned for 2020 by Regulation (EU) No 257/2010. The results of this re-evaluation were published in December 2013 (EFSA, 2013), and concluded that there was no need to revise the previously established ADI. At the same

[1] Cancels and replaces the opinion of 19 November 2014
Editorial corrections: “s” added to “sugar”
Correction of CES validation dates in paragraph 2

time, seeing that beyond these toxicological questions, there remained recurring uncertainties as to the nutritional benefits and risks related to intense sweeteners, ANSES set up a Working Group (WG) to study these questions. The initial assessment of artificial sweeteners, undertaken in the framework of Regulation (EU) No 257/2010 by EFSA, covered only the toxicological challenges and risks associated with their consumption; this initial assessment did not evaluate the possible nutritional benefits.

The term 'Intense sweeteners' (ISs) refers to various substances of plant origin or obtained by chemical synthesis, used in the food industry for their sweetening power that is tens to thousands of times higher than that of sucrose.
ISs are food additives whose marketing and use in foods are regulated at European level.

1.2 Consumption of artificial sweeteners in France

On the basis of several food surveys, ANSES estimated dietary intakes of the ISs currently used in France (acesulfame K, aspartame, cyclamate, saccharine, sucralose, aspartame-acesulfame K salts) for the general population (adults and children over the age of three), pregnant women and young diabetics. The methodology and full results of this work appear in the collective expert appraisal report of the WG.

These estimates show that in all of the study populations, irrespective of the IS taken into consideration, the mean and 95th percentile intakes are lower than the ADIs.

For a given population, focusing on the IS with the highest intake in relation to the ADI, the following mean (95th percentile) values are observed for the whole population:

- in adult men, intake of 4% (16%) of the ADI for acesulfame K;
- in adult women, intake of 2.6% (13%) of the ADI for cyclamate;
- in children aged three to ten years, intake of 2.1% (12%) of the ADI for cyclamate;
- in children aged 11 to 17 years, intake of 1.4% (8%) of the ADI for cyclamate;
- in young diabetics, intake of 11.5% (39%) of the ADI for cyclamate;
- in pregnant women, intake of 6.3% (24%) of the ADI for cyclamate.

1.2 Scope of the expert appraisal

The substances covered in this assessment are the ISs currently authorised in Europe, after scientific review: aspartame (EFSA, 2013), acesulfame potassium (K) (SCF, 2000b), cyclamic acid and its salts (SCF, 2000c), rebaudioside A (EFSA, 2010), neohesperidin dihydrochalcone (SCF, 1988), neotame (EFSA, 2007), saccharine and its salts (SCF, 1995), sucralose (SCF, 2000a), aspartame-acesulfame salt (SCF, 2000b) and thaumatin (SCF, 1988). The scientific opinions issued in the context of marketing authorisation applications have exclusively dealt with these substances' safety of use. Their potential benefits were evaluated by EFSA in an assessment of health claims. To date, two claims related to ISs have received a favourable opinion from EFSA and been authorised by the European Commission: "consumption of foods/drinks containing intense sweeteners instead of sugar contributes to the maintenance of tooth mineralisation" and "consumption of foods/drinks containing intense sweeteners instead of sugar induces a lower blood glucose rise after their consumption compared to sugar-containing foods/drinks" (EFSA, 2011b, EFSA, 2011a). The "weight control/management is helped by using foods and beverages sweetened with aspartame in place of foods and beverages sweetened with sugar", "intense sweeteners help to maintain a healthy body weight", "intense sweeteners help to control calorie intake", "table top sweetener can help slimming as part of a calorie controlled diet" and "intense sweeteners have no effect on carbohydrate metabolism, short or long term blood control glucose or insulin secretion" claims received unfavourable opinions from EFSA (EFSA, 2011b, EFSA, 2011a) and have not been authorised by the European Commission.

This assessment deals with both the specific effects of ISs and their effects as sugar substitutes. Historically, ISs have been developed to satisfy the appetite for sweetness while supplying few or no calories. They have been used to reduce sugar consumption and energy intake in weight-loss diets and to help regulate blood glucose levels and improve the acceptability of a low-sugar diet for diabetics. Associations of diabetes patients also point out the benefits of IS consumption in a social context but this parameter was not taken into account in this assessment.

The main beneficial effects expected by users are related to weight management and metabolism.

Therefore, this assessment primarily covers the effects of IS consumption on the following:

- eating behaviour (energy compensation) and food preferences (development of a taste for sweets and habituation to sweetness);
- weight :
- carbohydrate metabolism.

This assessment did not examine the animal studies required for IS marketing applications. However, other potential effects of ISs covered in these studies are also mentioned in the WG's report.

First, the nutritional benefits and risks related to ISs were specifically studied in pregnant women, following the publication of a study reporting an association between the consumption of beverages containing ISs and the frequency of pre-term delivery (Halldorsson *et al.*, 2010). This assessment gave rise to a progress report by ANSES (ANSES, 2012).

The assessment was then broadened to the general population, i.e. healthy adults as well as some specific populations (children, people with diabetes or at risk for diabetes, overweight and obese people) when there were specific data.

2. ORGANISATION OF THE EXPERT APPRAISAL

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise – General Requirements of Competence for Expert Appraisals (May 2003)".

It falls within the sphere of competence of the Expert Committee (CES) on Human Nutrition. ANSES entrusted the expert appraisal to the Working Group on Intense Sweeteners, established based on a public call for applications. A systematic and exhaustive literature review was undertaken on the health effects of IS consumption. The search methodology is described in the WG's expert appraisal report. Exposure to intense sweeteners in the French population was estimated by ANSES's Food Risk Assessment Division. The estimation method and all of the results are annexed to the collective expert appraisal report. Several stakeholders were interviewed in the context of this expert appraisal (the hearing reports are available on ANSES's website) and several scientific figures were consulted.

The methodological and scientific aspects of this group’s work were regularly submitted to the Expert Committee. The report produced by the Working Group takes account of the observations and additional information provided by the Committee members. It was adopted by the Expert Committee (CES) on Human Nutrition, which held meetings on 10 April, 11 April and 12 September 2014.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.
Expert declarations of interests are made public on ANSES's website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE CES AND WG

The discussion and conclusions presented below summarise the collective expert appraisal report of the WG on Intense Sweeteners and the Expert Committee on Human Nutrition. This summary presents data corresponding to the main issues identified by the WG (eating behaviour and dietary preferences, weight, blood sugar metabolism). Other fields of study identified through the systematic literature review, including cancers, cardio-vascular diseases and cognitive processes, were also taken into account by the WG. All of these potential effects were analysed and are presented in the WG's collective expert appraisal report.

3.1. Effects on eating behaviour and taste preferences

ISs are often consumed as sugar substitutes, particularly in beverages, in order to respond to a hedonic appetite for sweetness while avoiding energy intake from sugars. The expert appraisal assessed whether there were metabolic consequences of this separation of sweetness and calorie intake, particularly in terms of:

- body's ability to associate a taste with an energy value and therefore regulate its energy balance,
- consequences of IS consumption on appetite for sweetness and the consumption of sweet products.

3.1.1. Data in adults

A meta-analysis covering studies undertaken before 2006 along with around ten randomised experimental studies were identified to address these points.

The meta-analysis of 15 randomised experimental studies (De la Hunty *et al.*, 2006) assessed the effects of aspartame consumed alone or with other (unspecified) ISs on food and energy intake during the course of a day in adults. These measurements covered a limited number of subjects (less than 30) and highly variable time periods of a few days to 16 weeks. The main inclusion criterion for studies in this meta-analysis was the measurement of food intakes for at least 24 hours, to assess the full extent of any compensatory effects of the various meals consumed over the day.
The authors conclude that consuming aspartame as a sugar substitute results in daily energy intake to decrease by 220 Kcal on average. Moreover, the authors indicate that this substitution may be more efficient in beverages than in solid foods, since the energy supplied by liquids leads to less satiety than that supplied by solid foods. In fact, the estimated compensation rate is thought to be lower for sugars consumed in liquid form than in solid form (Almiron-Roig *et al.*, 2013). Therefore, according to these authors, the reduction in energy intake due to the replacement of sugar with sweeteners is greater with artificially sweetened beverages than with artificially sweetened solid foods.
However, the conclusions of this meta-analysis should be treated with caution, due to several methodological limitations, particularly a lack of essential information on the study selection process, the assessment of their quality and the statistics applied to assess the heterogeneity of the data taken into account.

Other experimental studies (that were not included in the meta-analysis since they covered periods of less than 24 hours) analysed the effects of ISs on appetite and food intake. These studies used an IS preload approximately one hour before a meal, generally in beverage form (rarely in solid form, i.e. in a food), and measured food intake and calorie intake during the next meal.
All of these studies showed that irrespective of the nature of the tested IS, a preload reduced the sensation of hunger and the desire to eat, with a maximum effect immediately after its consumption. However, this effect tended to disappear before the start of the meal, which explains why most studies did not observe reduced food intake during the meal after the preload.

Regarding food preferences, several studies assessed the effect of ISs on the perception of sweetness (gustatory stimuli) and/or taste preferences for foods. Several studies showed that preference for a sweet food was independent of the sweetening agent (i.e. no difference between an IS and sucrose), but their results differed as to the repercussions of this preference on consumption of this food.
However, these studies had extremely variable protocols and objectives, to the extent that it is difficult to compare their results and draw an overall conclusion as to the effect of ISs on food preferences.

Overall, on the basis of studies dealing with occasional exposure to an IS before a meal, it is not possible to determine the effect of regular IS consumption on sweetness habituation or increased cravings for sweetened products.

Most experimental studies show that the occasional consumption of ISs before or during a meal has no effect on food intake or energy intake during the next meal. Occasional IS consumption before a meal reduces the sensation of hunger and the desire to eat, just like caloric sweeteners, but this effect is temporary and disappears before the start of the meal.

In most cases, the use of ISs as sugar substitutes results in a decrease in short-term energy intake due to their low calorie content and the lack of compensation. However, the available data cover insufficient time periods to guarantee the maintenance of this effect over the medium or long term.

3.1.2.Data in children

Preference for sweetness is innate. It is strong at birth and then tends to decrease. However, it seems to be maintained by the repeated consumption of sweetened foods or beverages during early childhood (Liem and Mennella, 2002).

A study (Wilson, 1994) showed that adding aspartame or sucrose to milk favoured its consumption. Moreover, the work of Birch *et al.* revealed that children preferred flavours associated with calorie intake, suggesting that sweetness itself is not sufficient to generate food preferences, and that energy density, just as much as (or even more than) sweetness, can determine food preferences (Johnson *et al.*, 1991, Birch and Fisher, 1998). However, there are no data showing whether ISs have a specific effect, in relation to caloric sweeteners, on the development of taste and food preferences.

A study compared the effects of consuming 250 mL daily of artificially sweetened beverages *vs* sugar-sweetened beverages on the satiety and desire to eat of children aged seven to 11 years for 18 months (de Ruyter *et al.*, 2013). The level of satiety was the same, irrespective of the beverage consumed.

Based on the available studies, it is not possible to determine whether ISs consumed during early childhood have a specific effect on the development of taste and food preferences or on the short- and medium-term regulation of food intake.

3.2. Effects on body weight and composition

ISs are commonly used by consumers as sugar substitutes as part of weight-loss diets or to control energy intake and avoid weight gain.

3.2.1. Data in adults

Experimental data

A meta-analysis (De la Hunty *et al.*, 2006), a systematic review (Wiebe *et al.*, 2011) and several original articles examined the relationship between IS consumption and changes in body composition and weight.

In the meta-analysis by De la Hunty (2006), eight studies on very heterogeneous populations (people with energy restrictions and unrestricted diets, normal-weight and obese people, in normal living conditions and in metabolic chambers) were included. According to the authors, the effect of ISs on weight loss is significant. They extrapolate the theoretical reduction of 220 kcal/day related to the replacement of sugars with aspartame over the long term, and by postulating its maintenance over time, calculate that this reduction could result in weight loss of 0.2 kg per week.
The WG once again emphasises the methodological weaknesses of this meta-analysis, particularly the lack of essential information related to the study selection process and the statistics applied to assess heterogeneity.

The systematic review by Wiebe *et al.* (2011) cites two intervention studies comparing the effects of artificially sweetened drinks and sugar-sweetened drinks on BMI (Raben *et al.*, 2002, Reid *et al.*, 2007). These studies, focusing on different populations (normal-weight women in one and overweight women in the other), had different results (no effect in normal-weight women, reduced weight in overweight women).

Five other randomised controlled trials (Maersk *et al.*, 2012, Raben A, 2011, Reid *et al.*, 2010, Sorensen *et al.*, 2005, Tate *et al.*, 2012) were identified. They were all undertaken in overweight subjects and the majority focused on very small populations (between 20 and 50 subjects). Two demonstrated modest weight loss of 1.2 and 1.5 kg on average, but the other three, including the one with the largest study population (n=318), did not show any effects on weight loss related to the consumption of artificially sweetened beverages compared to the consumption of sugar-sweetened beverages or water.

Observational data

There are seven prospective observational epidemiological studies with highly heterogeneous results. One study did not show any association between IS consumption and changes in body composition (Parker *et al.*, 1997); four studies reported a positive association, i.e. a significantly higher body weight or waist size in IS consumers (Colditz *et al.*, 1990, Duffey *et al.*, 2012, Fowler *et al.*, 2008, Stellman and Garfinkel, 1988); and two studies reported a negative association (Mozaffarian *et al.*, 2011, Schulze *et al.*, 2004).

Observational and intervention studies report contradictory associations between IS consumption and weight loss.

Therefore, no conclusions can be drawn as to the long-term effect of replacing caloric sweeteners with ISs on the weight of regular adult consumers of sweet products.

A meta-analysis (Miller and Perez, 2014), published after the WG's literature search, took into account observational studies (with nine articles included) and randomised controlled trials (RCTs, with 15 articles included) in adults and children. The section on observational studies showed no relationship between IS consumption and changes in body weight or fat mass but showed a slight increase in BMI (+0.03 kg/m² on average). The section on RCTs showed that replacing sugars with ISs in sweet products resulted in moderate weight loss (with an estimated average effect of 0.8 kg) and a decrease in BMI (-0.24 kg/m² on average) for time periods ranging from three weeks to 18 months.
This meta-analysis, of good methodological quality, highlights the extreme variability of results from studies with a similar design (whether RCT or observational) and the differences in results between observational studies and RCTs. This finding, which does not call into question the conclusions previously issued by the WG, supports the idea that, while RCTs remain the most methodologically conclusive studies, the experimental designs used in RCTs do not reflect actual modes of IS consumption as seen in observational studies.

3.2.2.Data in children

Experimental data
Four studies focusing on the relationship between IS consumption and body composition were identified.
In three of these studies, changes in weight and BMI did not differ between IS consumers and non-consumers (Ebbeling *et al.*, 2006, Knopp RH, 1976, Williams *et al.*, 2007). These studies focused on overweight or obese children and had methodological limitations.
The fourth study, of good methodological quality, examined the effects of consuming 250 mL/day of an artificially sweetened drink in 641 normal-weight children (aged four to 12 years), who were regular consumers of sugar-sweetened drinks, for 18 months (de Ruyter JC, 2012). This study showed a significant decrease in the BMI z-score (the most relevant criterion to assess changes in corpulence in growing children) in the group that consumed artificially sweetened drinks. The change in body weight between the two groups differed by 1 kg on average.

Epidemiological data
Of the seven prospective epidemiological studies in children, five (Brown *et al.*, 2010, Vanselow *et al.*, 2009) observed a positive relationship between IS consumption (primarily in beverage form) and weight over time, while two (Brown *et al.*, 2010) did not find any relationship.

To explain these findings, the authors of these studies assumed that subjects 'at risk for weight gain' or with less healthy food profiles were those who consumed the most ISs with the aim of reducing their energy intake.

Most of the prospective observational studies undertaken in children show that IS use is paradoxically associated with weight gain, although the causality of this relationship has not been established. The four available controlled trials showed conflicting results but none reported weight gain.
No conclusions can be drawn from all of these studies as to the significance of ISs for weight management in children and adolescents.

3.3. Effects on blood glucose and type 2 diabetes

This section presents data on the effects of IS consumption on glucose homeostasis and risk of diabetes, in healthy subjects, type 1 diabetics (T1D) and type 2 diabetics (T2D).

Thirty-one clinical trials and two reviews assessed the short-term effects (less than one week) of IS consumption on glucose homeostasis. To date, the data on the long-term risk of developing diabetes are still limited and have been taken from seven observational epidemiological studies.

3.3.1.Effects on glucose homeostasis

Acute effects (less than 24 hrs.)

The available studies did not show any effects related to the consumption of aspartame on an empty stomach (Burns *et al.*, 1991, Horwitz *et al.*, 1988, Moller, 1991, Rodin, 1990, Smeets *et al.*, 2005, Stegink *et al.*, 1990), saccharine (Goldfine ID, 1969) or sucralose (Ma *et al.*, 2009, Ma *et al.*, 2010) on blood glucose levels and insulin levels.

Other studies assessed this effect on post-prandial glycaemic parameters after a test meal (Abdallah *et al.*, 1997, Anton *et al.*, 2010, Brown *et al.*, 2009, Ford *et al.*, 2011, Gregersen *et al.*, 2004). These studies generally showed that consuming ISs before a test meal did not modify post-prandial glycaemic and insulin responses compared to a placebo, and reduced these responses compared to a sucrose preload. These effects were reported irrespective of the tested IS (aspartame, stevia extract, sucralose, beverage containing acesulfame K and sucralose).
It should also be noted that the parameters of these studies were highly variable with differences in the composition of test meals, the time between the preload and the meal, the studied subject groups (age, sex, healthy overweight or obese subjects) and the preload form (solid or liquid).

Several studies also showed that consuming ISs before a meal resulted in increased secretion of GLP1 (Glucagon-like peptide), a gastro-intestinal hormone that usually increases insulin secretion, slows down gastric emptying and reduces glucagon secretion (Brown *et al.*, 2012). This increase in GLP1 may be induced by ISs activating sweetness receptors, as suggested by data in rats (Berthoud *et al.*, 1981).

Short- and medium-term effects

Several studies assessed the effect of regular IS intake (one to three times per day, for a few days to several weeks), in capsule form or in beverages, on maintaining blood sugar control (glucose and insulin levels measured after a night of fasting, glycated haemoglobin HbA1c).

For type 2 diabetics, the consumption of sucralose (Grotz *et al.*, 2003) or aspartame (Colagiuri *et al.*, 1989, Nehrling *et al.*, 1985, Stern *et al.*, 1976) for periods of up to 18 weeks did not affect metabolic control of diabetes (no change in fasting glucose levels) compared to sucrose or a placebo. Furthermore, glucose homeostasis was not modified in non-diabetic

obese subjects who had consumed a beverage sweetened with aspartame for six months compared to groups who had consumed sugar-sweetened drinks, water or milk (Maersk *et al.*, 2012). Other studies covering unspecified ISs compared to sucrose in obese or overweight subjects (Njike *et al.*, 2011, Raben A, 2011) confirm these results.

Regarding stevia extracts, the data show either a lack of effect on glucose control in healthy (Barriocanal *et al.*, 2008, Geuns *et al.*, 2007) or diabetic (Barriocanal *et al.*, 2008, Maki *et al.*, 2008) subjects or a slight decrease in blood glucose levels in healthy subjects (Curi *et al.*, 1986) or hypertensive subjects (Ferri *et al.*, 2006).

Overall, the vast majority of studies do not show any acute effects of IS intake on blood glucose or insulin levels measured on an empty stomach or after a test meal, in healthy subjects or in diabetics. Some studies reported a slight change in GLP-1 secretion, but with no repercussions on insulin secretion or blood glucose.

IS consumption has no effect on short- and medium-term blood glucose parameters in healthy subjects or in diabetics.

3.3.2.Effects on the risk of type 2 diabetes (T2D)

The seven observational studies dealing with IS consumption and the incidence of T2D showed diverging results.

Four cohort studies (three undertaken in North American populations and one in a European population), over periods of nine to 24 years, did not show any relationship between the consumption of artificially sweetened beverages and the risk of developing T2D after adjustment for BMI and the energy intake of subjects (2013, Bhupathiraju *et al*., 2013, de Koning *et al*., 2011, Schulze *et al*., 2004).

Three other cohort studies suggested a positive association between the consumption of artificially sweetened beverages and the incidence of T2D (Fagherazzi G, 2012, Nettleton JA, 2009, Sakurai *et al*., 2014). In the study undertaken in France (Fagherazzi G, 2012), the incidence of T2D was significantly higher in the group of women consuming the largest amounts of artificially sweetened beverages (over 600 mL per week) who were monitored for 14 years, and the authors specify that the relationship was linear and dose-dependent. The second study, undertaken in the United States for seven years, reported an increase in the incidence of T2D in subjects consuming more than one artificially sweetened beverage per day in a model with adjustment for the primary confounding factors. The third study, which reported an increased incidence of T2D in subjects consuming more than one artificially sweetened beverage per week, focused on a limited-sized Japanese population not representative of the general population, that was monitored for seven years.

It is important to underline the heterogeneity of these data, particularly in terms of the characteristics of the populations and the monitoring periods (from seven to 24 years). Furthermore, in these studies, the consumption of artificially sweetened beverages was recorded when the subjects were first included, often through self-administered frequency questionnaires, with no updating of dietary data over time.

The long-term epidemiological studies on the risk of developing T2D show heterogeneous results, but the most robust studies do not report any effects.

3.4. Other effects

3.4.1.Effects on lipid parameters

Of the 20 analysed experimental studies, the majority focused on aspartame or stevia extracts. Compared to a placebo, aspartame consumption had no effects on triglycerides or cholesterol (total, HDL, LDL or VLDL) in various populations (healthy, T2D and overweight subjects) for periods ranging from 13 to 28 weeks. Compared to a caloric sweetener (sucrose, glucose or fructose), of the five identified studies, two showed a slight improvement in lipid profile in the group that received aspartame, still with no differences compared to the placebo. The three studies that assessed the effect of stevia extracts on lipid parameters showed no differences compared to a placebo. Studies using other types of ISs (cyclamate, sucralose, IS mixture or unspecified IS) also showed no effects on the assessed lipid parameters.

Of the four identified cohort studies, most showed no effects on lipid parameters related to the consumption of artificially sweetened beverages. A single study reported a possible link between the consumption of these beverages and an increase in TG levels associated with a lowering of HDLc (Dhingra *et al.*, 2007).

The majority of observational studies showed no effects on lipid profile related to ISs. Two studies reported that replacing sugars with aspartame reduced plasma concentrations of triglycerides but the data are too limited to conclude that ISs have a beneficial effect on lipid profile.

3.4.2.Effects on pre-term deliveries

Two epidemiological studies are available.
In the first (Halldorsson *et al.*, 2010), a dose-effect relationship was observed, which meant that the risk of pre-term delivery was higher in the heaviest consumers of artificially sweetened beverages. In addition to this Danish study described in the ANSES progress report (ANSES, 2012), another study, methodologically similar and including over 60,000 pregnant women, suggested that the consumption of artificially sweetened beverages and sugar-sweetened beverages was associated with increased risk of spontaneous or induced pre-term delivery. However, although the association was stronger for sugar-sweetened beverages, the authors concluded that they could not determine whether this risk was caused by the effects of these beverages or by other dietary or socio-economic factors (Englund-Ögge L, 2012).

The data published since 2012 do not change the conclusions formulated in the ANSES progress report, i.e. that based on the available data, it is not possible to identify any benefits or draw any conclusions regarding the risk related to the consumption of intense sweeteners during pregnancy, in terms of maternal health, obstetrical parameters or newborn health.

A meta-analysis of two studies, published after the WG's literature search (La Vecchia, 2013), did not show any effects of artificially sweetened beverages on pre-term deliveries. The WG notes that this was not a real meta-analysis since no systematic review was undertaken and only the results of two studies were combined using a simple analytical method. The choice of the two studies taken into account, by Halldorsson *et al.*, 2010 and Englund-Ögge, 2012, which were also analysed by the WG, was not justified.

3.4.3.Effects on cancer

The relationship between IS consumption and cancer in humans was assessed in 55 scientific studies. Thirty-nine of these studies involved the urinary tract and 32 focused exclusively on bladder cancer. The other studies assessed the relationship between IS consumption and the risk of brain cancer (four studies), digestive system cancer (six studies) or other cancers (five studies). Except in the studies focusing on bladder cancer, the ISs in question were not identified by the authors.

The relationship between saccharine consumption and bladder cancer was the most commonly studied, given that data were available in rodents (Arnold *et al.*, 1977). The results of studies in humans are conflicting. Based on the analysis of data in humans, it is not possible to determine a relationship (whether for saccharine or for the other studied ISs), since the studies did not adjust their results for major confounding factors such as exposure to chemical pollutants.

Regarding kidney, brain, digestive system and breast cancers, the data are more limited and do not show any relationship with IS consumption.

A recent cohort study examining the risk of lymphoma and leukaemia suggested an increased risk of non-Hodgkin lymphomas and multiple myelomas in males consuming more than one serving (355 mL) per day of artificially sweetened beverages and in the heaviest consumers of aspartame (as a table-top sweetener and in beverages) compared to non-consumers (Schernhammer ES, 2012). No significant association was reported in women. The authors specified that due to the differences in the results by sex, the results should be interpreted with caution. Moreover, this study did not take into account exposure to chemical pollutants as a confounding factor. However, it is worth noting that this study attempted to take into account, in its statistical analysis, changes in the individual consumption of artificial sweeteners over time, although little information is available regarding the methodology.

On the whole, the epidemiological studies do not show any effects of IS consumption on cancer risk. Only one recent study suggested a relationship between the consumption of beverages containing ISs and the occurrence of non-Hodgkin lymphomas and myelomas, and additional studies are required.

3.4.4.Neurological effects

Regarding the potential neurological effects of ISs, only aspartame has been studied.

There are two studies in healthy adults (Lapierre *et al.*, 1990, Spiers *et al.*, 1998). No effects of aspartame on the measured parameters (reaction time, headaches, hunger, sedation, electroencephalographic parameters) were observed. The study undertaken in epileptic subjects (Rowan *et al.*, 1995) showed no statistically significant difference between aspartame and the placebo on the incidence of epileptic seizures.

The four available studies on migraine subjects (Koehler and Glaros, 1988, Lipton *et al.*, 1989, Schiffman *et al*., 1987, Van den Eeden *et al*., 1994) show conflicting results. However, no conclusion can be drawn due to their poor methodological quality (no adjustment) and the subjective nature of the measured effects (using non-validated self-questionnaires).

Regarding children, there are two studies, one in epileptic children (Shaywitz *et al.*, 1994a) and the other in hyperactive children (Shaywitz *et al.*, 1994b), showing no significant effects of aspartame.

Some studies with significant methodological limitations suggested that aspartame consumption may be involved in triggering epileptic seizures and migraines but no conclusions can be drawn regarding the occurrence of such a risk from the data as a whole.

3.5. Conclusions and recommendations of the WG and CES

After an analysis of all of the scientific literature, it appears that, despite a large number of studies, the data are insufficient to determine any long-term nutritional benefits related to the consumption of products containing ISs as sugar substitutes.

- In most cases, the use of ISs as sugar substitutes results in a decrease in short-term energy intake due to their low calorie content and the lack of compensation. However, the available data cover insufficient time periods to guarantee the maintenance of this effect over the long term.
- No conclusions can be drawn from studies on weight management as to the benefits of IS consumption in children, adolescents or adults.
- In diabetics, no benefits of regular consumption of ISs as sugar substitutes on glucose control have been demonstrated.
- No benefits of IS consumption on preventing the occurrence of type 2 diabetes have been demonstrated.
- While two studies reported that replacing sugars with aspartame reduced plasma concentrations of triglycerides, the data are too limited to conclude that ISs have a beneficial effect on lipid profile.

The available data do not show any risks related to IS consumption.
However, due to the limited number of studies, it is not possible to rule out potential long-term risks related to IS consumption in specific populations, particularly adult daily consumers and children.

- As for habituation to sweetness, IS consumption has not shown any effects in adults. However, in children, there are no data that demonstrate whether ISs have an effect on taste development, food preferences or the control of food intake.
- Observational and intervention studies on weight management have reported conflicting associations. Some prospective observational studies show that IS use is paradoxically associated with weight gain, although the causality of this relationship has not been established.
- As for glucose regulation, short- and medium-term IS consumption does not result in the post-prandial elevation of blood glucose or insulin levels in healthy or diabetic subjects.
- The most robust epidemiological studies on type 2 diabetes do not show a higher or lower incidence of diabetes in daily IS consumers.
- Epidemiological studies on cancer do not show any link to IS consumption. However, a recent study suggests a relationship between the consumption of beverages containing ISs and the occurrence of lymphomas, and additional studies are required.

To conclude, no beneficial effects have been shown that provide grounds to recommend regular IS consumption for adults or children. Moreover, the available data do not show the occurrence of risk in occasional consumers. However, based on the epidemiological data currently available, it is not possible to completely rule out certain risks in the event of regular, prolonged consumption.

Therefore, for the general population, the overall assessment of potential risks and benefits does not justify the long-term use of ISs as sugar substitutes, particularly in beverages, which are their main vector. Thus, artificially sweetened beverages and sugar-sweetened beverages should not be consumed to replace water.

3.6. Research recommendations

The review of the scientific literature revealed some gaps that should be filled and areas of research that should be explored.

- There were differences between the results of randomised controlled trials and the results of observational studies. Furthermore, the studies assessing the effects of replacing sugars with ISs on eating behaviour or energy intake were undertaken over the short term and should be supplemented with long-term studies. Two types of additional studies seem necessary to clear up these differences. On the one hand, longer-term (at least one year) blind, placebo-controlled intervention studies would shed further light on the metabolic and physiological effects of ISs. On the other hand, intervention studies in which ISs are consciously consumed would help to understand potential changes in eating behaviour related to the replacement of sugars with ISs in near-real-life conditions.
- There are also very few data on the long-term impact of ISs on food preferences. Therefore, it appears necessary to study the effects of IS consumption on dietary choices.
- In most of the cohort studies, the consumption of artificially sweetened beverages was reported only when the subjects were first included, and subsequent consumption was not taken into account. These studies assessed only the consumption of artificially sweetened beverages, and not the total consumption of artificial sweeteners. It is also difficult to distinguish between the effects of the various ISs consumed alone and their effects when combined with other ISs. Future cohort studies should be capable of taking into account qualitative and quantitative changes in the consumption of artificially sweetened products and adapted dietary questionnaires, to accurately and specifically assess IS consumption.
- Specific populations such as pregnant women, children, diabetic subjects and regular IS consumers have not been adequately studied. It appears necessary to further study the effects of ISs in these populations. Likewise, it appears necessary to determine the repercussions of IS consumption during the peri-natal phase on offspring (under the 'foetal programming' assumption).
- Most of the cohort studies were undertaken in the United States where the characteristics of IS consumption are different from those observed in France. It appears necessary to supplement the information provided by these studies with the results of national studies.
- Some data suggested that the potential effects of ISs on changes in weight or the incidence of diabetes may vary depending on initial corpulence. Due to the increasing prevalence of obesity, it appears necessary to study potential interactions between corpulence and IS consumption in terms of the risk of weight gain or diabetes.

- The literature on steviol glycosides is still sparse and should be enhanced, particularly given the recent growth in their use in beverages and foods.

4. CONCLUSION OF THE FRENCH AGENCY FOR FOOD, ENVIRONMENTAL AND OCCUPATIONAL HEALTH & SAFETY

ANSES adopts the conclusions of the Working Group and the Expert Committee on Human Nutrition.

The intense sweeteners currently authorised in Europe comprise ten compounds of various chemical natures. They are used in the formulation of foods and beverages, essentially for their sweetening role but also for their technological properties (stabilisers, texturisers). Their sweetening power is a hundred (acesulfame K, aspartame) to several thousand (neotame) times higher than that of sucrose. In France, the ISs most commonly used by the food processing industry are aspartame, acesulfame K and sucralose, in addition to stevia extracts in recent years.

Their overall use has sharply risen in the last 20 years[2]. These compounds are mainly used to formulate reduced-calorie products while maintaining sweetness. Their lower calorie content, a major sales argument used to promote these products, suggests a direct link to weight management for consumers. However, no claims related to the effects of intense sweeteners on weight management have been authorised.

The Agency estimated exposure to ISs in the French population[3]. These data show that, in a worst case scenario, the intakes of the heaviest consumers (95th percentile) are below the Acceptable Daily Intakes established at EU level for all of the ISs taken into consideration[4].

ANSES therefore wanted to undertake an extensive analysis of the literature in order to review the data currently available on the potential nutritional benefits and risks related to the consumption of products containing ISs, particularly since nutritional benefits were not examined in the context of the initial authorisation issued under Regulation (EU) No 257/2010. It should be noted however that while an overall assessment of the benefits of artificial sweeteners can be undertaken independent of their nature, considering their common purpose, which is to create a perception of sweetness, assessing the associated risks may require distinction in terms of the toxicological challenges related to each compound. That said, this assessment has been reviewed for the authorisation of each artificial sweetener.

Further to this work, ANSES considers that:

- regarding nutritional benefits, the available studies, while numerous, do not provide proof that the consumption of artificial sweeteners as sugar substitutes is beneficial in

[2] The market share of artificially sweetened products within a product class varies considerably depending on the sector; it is 95% for chewing gum, 20% for soft drinks (versus 7% in 1994) and 15% for table-top sweeteners. Given the consumption of these various products, the main vectors are beverages, “light” dairy products and compotes, confectionery and table-top sweeteners.
Internationally, total sales of reduced-sugar products were estimated in 2011 at $41 billion for beverages and $21 billion for foods (source: Euromonitor).
In terms of equivalent sweetness (i.e. the relative contribution of each product to the creation of a sweet taste), ISs contribute to approximately 10% of sweetness worldwide (source: LMC International).

[3] Based on the consumption data of the INCA 2 study cross-referenced with the IS composition data submitted by manufacturers.

[4] Aspartame, acesulfame K, cyclamate, saccharine, sucralose and aspartame acesulfame K salts

terms of weight management, blood glucose regulation in diabetic subjects or the incidence of type 2 diabetes;

- regarding nutritional risks (incidence of type 2 diabetes, habituation to sweetness in adults, cancers, etc.), it is not possible based on the available data to establish a link between the occurrence of these risks and the consumption of artificial sweeteners. However, some studies underline the need to improve knowledge of the links between IS consumption and certain risks.

ANSES particularly stresses the lack of relevant, conclusive studies on the supposed benefits of artificial sweeteners, in the context of their broad, long-standing use in nutrition.

In addition, considering the many issues raised by this assessment, the Agency underlines the need to undertake new research into the nutritional benefits and risks related to the consumption of artificial sweeteners, and particularly:

- for children, research into the development of taste and food preferences and the control of food intake;
- for the general population, research into weight management.

ANSES continues its scientific monitoring of the nutritional benefits and risks related to ISs. In the framework of this ongoing monitoring, it notes the emergence of work on new topics, such as the effects of ISs on the microbiota (Suez *et al.*, 2014). In the future, the Agency may therefore update this assessment as needed in light of new data.

In a nutritional policy context where one of the priority objectives is to reduce sugar intake in the general population, ANSES considers that there is no convincing scientific information providing grounds to encourage, in the framework of public policy, the systematic replacement of sugars with ISs in sweet products. This objective of reducing sugar intake should be achieved by reducing the overall sweetness of food, from a very early age. Therefore, regarding sweetened beverages (significant vectors of sugars and ISs), artificially sweetened beverages and sugar-sweetened beverages should not be consumed as substitutes for water.

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KEYWORDS

Intense sweetener; aspartame; acesulfame K; stevia; sucralose; diabetes; obesity; energy intakes; satiety; eating behaviour; compensation; weight

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