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APPROACHES TO THE SAFETY ASSESSMENT OF LOW CALORIE SWEETENERS & GLOBAL REGULATORY DEVELOPMENT STATUS

Ashley Roberts, PhD
Senior Vice President, Food & Nutrition
Health, Environmental & Regulatory Services (HERS)

ILSI-India Conference on Sweetness: Role of Sugar & Low Calorie Sweeteners
Innovations, Safety, Regulations Benefits, & Consumer Communication
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OUTLINE

- **Overview of Safety of Sweeteners**
  - Safety Assurance and the ADI
  - Risk assessment paradigm
  - Safety studies
  - Regulatory Processes
- **Safety & Regulatory Development Status**
  - JECFA
  - Recent safety concerns
- **Conclusions**

PREMARKET SAFETY EVALUATION

- Data independently reviewed by Regulatory Authorities
  - Joint FAO/WHO Expert Committee on Food Additives (JECFA)
  - European Food Safety Authority (EFSA)
  - Food and Drug Administration (FDA) in U.S.
  - Health Canada (HC)
  - Food Safety Australia/New Zealand (FSANZ)
- Regulatory Authorities establish ADI

SAFETY ASSURANCE AND THE ADI

- The ADI has been defined by JECFA as
  - "An estimate of the amount of a food additive, expressed on a bodyweight basis, that can be ingested over a lifetime without appreciable health risk"
- The ADI is usually expressed as a numerical value in mg/kg bw/day
- The ADI has been used for the past 50 years to establish safe intakes of food additives including LCS
- While JECFA determines ADI's, food additives such as LCS are on a positive list that have to be formally approved to be on that list.
- These additives are reassessed when new data becomes available (*e.g.,*Ramazzini) or as part of a cyclic review such as is going on in the EU now for LCS

THE DATABASE NECESSARY FOR APPROVAL

- Prior to approval and authorization a comprehensive database has to be developed and presented to the Regulatory Authority for independent evaluation
- Generated by the Company who adhere to strict guidelines (FDA RedBook, OECD, EFSA)
- Technical (manufacturing, specifications, technological function and case for need), toxicological requirements and exposure analysis provide the core of the data
- This information is submitted in the form of a dossier on which the risk assessment is conducted

TOXICOLOGY TESTS

- Comprehensive battery of studies are conducted in multiple species
  - Acute, sub-chronic, long-term toxicity
  - Pharmacokinetics
    - (Absorption, distribution, metabolism and excretion)
  - Genetic toxicity
  - Carcinogenicity
  - Reproductive toxicity and teratogenicity (birth defects)
  - Human studies (diabetes)

- All data from all studies must be submitted for review by regulatory authorities
- Not acceptable to only file the positive studies while ignoring negative data

TOXICOLOGY TESTS

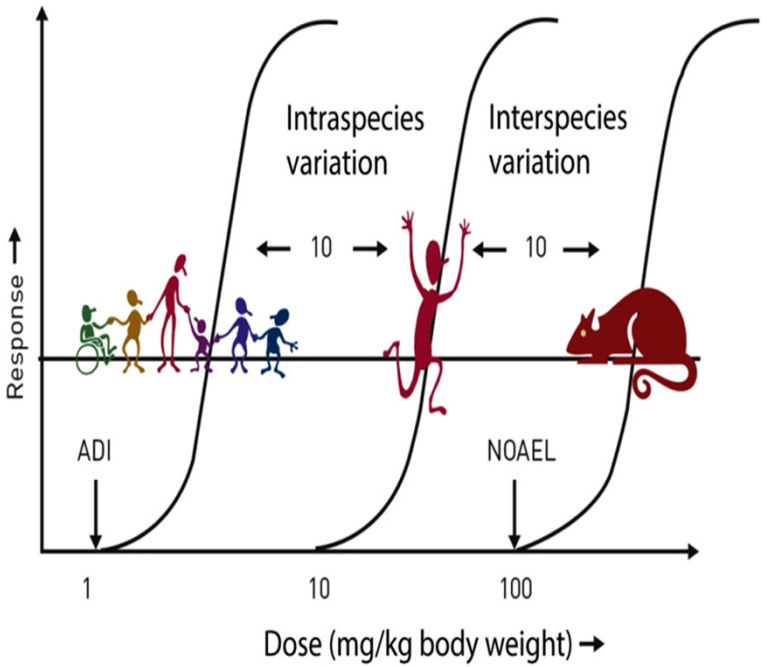
- Safety assurance is based on studies in animals given very high doses.
- Two aims
  - To produce potential adverse effects
  - To define a daily intake without adverse effects (NOAEL)
- Low Calorie Sweeteners are some of the least toxic compounds which allow dosages up to 10% of the diet in some cases to replace the basal diet
- While such dosages are equivalent to very high human exposure levels they are considered important for human safety assurance
- From all approved intense sweeteners the NOAEL is derived from chronic administration to animals

CALCULATION OF THE ADI

- **ADI (mg/kg/day) = NOAEL/safety factor**
- NOAEL = No-Observed-Adverse-Effect Level
  - From long-term studies
  - For the most sensitive endpoint in the most sensitive species
- **Apply "safety factor" (usually 100) to account for**
  - differences between individuals (10 X)
  - differences between humans and animals (10 X)

ADI DERIVATION USING CLASSICAL DEFAULT APPROACH

- Default safety/uncertainty factors for risk assessment purposes have been in use for greater than 50 years
- A 100-fold uncertainty factor is normally used by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) based upon a no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) from a chronic animal study



APPLICABILITY OF THE ADI TO CHILDREN

- Toxicological protocols adopted for LCS cover all periods of rapid growth and development maturation and aging and therefore all circumstances of human exposure are covered.
- Exposure during the juvenile period is taken into account and so the ADI does apply to children
  - One exception is for infants below 3 months of age
  - Due to lower levels of metabolising enzymes and studies do not mimic babies receiving infant formula in a unitary diet

EXCEEDING THE ADI

- It is important to remember that the ADI is not a lower bound of toxicity as we have at least a 100-fold safety margin
- The JECFA has indicated "*Because…data are extrapolated from lifetime animal studies, the ADI relates to lifetime use and provides a margin of safety large enough for toxicologists not to be concerned about short term exposure levels exceeding the ADI, providing the average intake over longer periods does not exceed it*"
- In reality the risk associated with the ADI being exceeded can only be assessed based upon the NOAEL and the dose response curve
- Given as stated previously that LCS are some of the least toxic substances and show little if any acute toxicity and so day to day variations in intake are not relevant for human health and safety

INTAKE ESTIMATES AND THE ADI

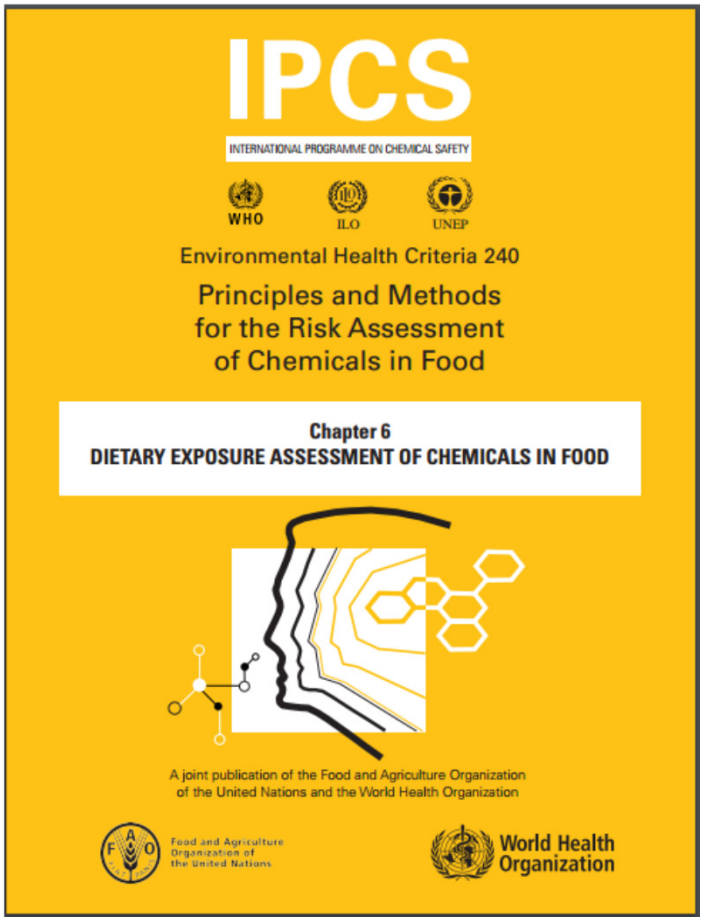
- A judgement can only be made on the safe use and approvability of a LCS when the daily intake based upon the food categories and level of use do not exceed the ADI
- Usually a theoretical exercise based upon food survey databases such as NHANES in the U.S. and The Comprehensive Database in the EU
- provides information for specific population groups (*e.g.*, demographics) and ages
- Takes in to account consumption of different types of food and makes allowance for high consumers (90^{th} to 95^{th} percentile)
- Assumes that the additive is present in all foods and beverages for which it is approved
- Typically overestimates actual consumption over longer time periods

INTAKE ESTIMATES AND THE ADI

- An understanding is required of the types of food category to which the sweetener will be added and the inclusion level.
- This is dependent on both the sweetness level in relation to sugar and stability.
- Also sensory analysis is taken in to consideration
- Approvals in some jurisdictions including the European Union specify the permitted use categories and use levels (termed conditions of use).
- Many LCS in the United States are permitted on the basis of cGMP
  - Effectively means that there is no limit on use based upon safety

EXPOSURE LEVELS ARE VERY LOW DUE TO HIGH SWEETNESS POTENCIES

Sweetener	Sucrose sweetness equivalence	Examples of brand names containing sweetener	ADI (mg/kg bw/d)	Maximum daily mg intake based on 70kg person
Acesulfame K	200 x	Sweet One® Sunett®	15	1050
Aspartame	200 x	Nutrasweet® Equal® Sugar Twin®	40	2800
Saccharin	400 x	Sweet and Low® Sweet Twin® Sweet'N Low® Necta Sweet®	5	350
Sucralose	600 x	Splenda®	15	1050
Steviol Glycosides	~300 x	Truvia® PureVia® Enliten®	4	280


IPCS
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
WHO
ILO
UNEP
Environmental Health Criteria 240
Principles and Methods for the Risk Assessment of Chemicals in Food
Chapter 6
DIETARY EXPOSURE ASSESSMENT OF CHEMICALS IN FOOD
A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization
Food and Agriculture Organization of the United Nations
World Health Organization

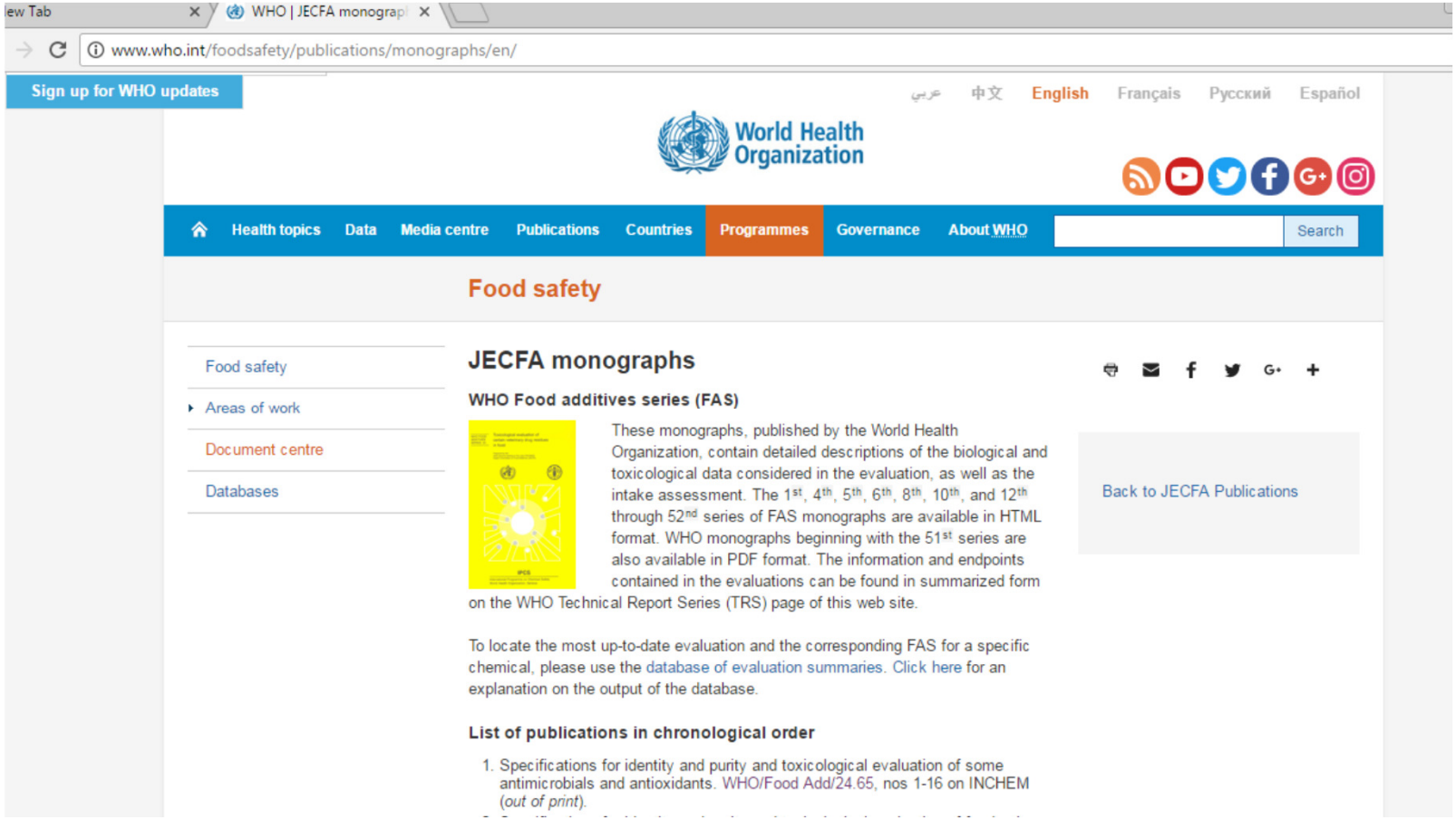
INTERNATIONAL REGULATORY PROCESSES

- **LCS are approved as Food Additives in many regulatory jurisdictions**
- **Formal approval leading to a change in legislation (CFR; Sweetener Directive)**
- **In the United States LCS can be Food Additives or GRAS Ingredients**
  - **HISs that are Approved Food Additives:**
    - Aspartame, neotame, advantame, acesulfame potassium (ace-K), sucralose
      - Use is permitted by and under conditions of a regulation
    - Saccharin
      - The Food and Drug (FDA) removed Generally Recognized as Safe (GRAS) status and issued an interim food additive regulation limiting use
  - **HISs that are FDA-listed GRAS Ingredients:**
    - Steviol glycosides, lo han guo
      - Use permitted through history of use and/or scientific procedures by Qualified Experts leads them to be GRAS

SAFETY & REGULATORY DEVELOPMENT STATUS

JECFA EVALUATION OF INTENSE SWEETENERS

Intense Sweeteners	INS	ADI	Year
Acesulfame potassium	950	0-15 mg/ kg bw	1990
Advantame	969	0-5 mg/kg bw	2013
Aspartame	951	0-40 mg/kg bw	1981
Aspartame-Acesulfame potassium	962	0-40-mg/kg bw; 0-15 mg/kg bw	2000
Alitame	956	0-1 mg/kg bw	1996
Cyclamate, Calcium	952 (III)	0-11 mg/kg bw	1982
Cyclamate, Sodium	952 (iv)	0-11 mg/kg bw	1982
Cyclamic acid	952 (i)	0-11 mg/kg bw	2009
Neotame	961	0-2 mg/kg bw	2003
Saccharin	954	0-5- mg/kg bw	1993
Saccharin, Calcium	954(ii)	0-5 mg/kg bw	1993
Saccharin, Potassium	954 (III)	0-5 mg/kg bw	1993
Saccharin, Sodium	954 (iv)	0-5 mg/kg bw	1993
Sucralose	955	0-15 mg/kg bw	1990
Steviol glycosides	960	0-4 mg/kg bw	2008
Thaumatin	957	Not specified	1985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JECFA monographs
WHO Food additives series (FAS)
These monographs, published by the World Health Organization, contain detailed descriptions of the biological and toxicological data considered in the evaluation, as well as the intake assessment. The 1st, 4th, 5th, 6th, 8th, 10th, and 12th through 52nd series of FAS monographs are available in HTML format. WHO monographs beginning with the 51st series are also available in PDF format. The information and endpoints contained in the evaluations can be found in summarized form on the WHO Technical Report Series (TRS) page of this web site.
To locate the most up-to-date evaluation and the corresponding FAS for a specific chemical, please use the database of evaluation summaries. Click here for an explanation on the output of the database.
Back to JECFA Publications
List of publications in chronological order
1. Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants. WHO/Food Add/24.65, nos 1-16 on INCHEM (out of print).

EU RE-EVALUATION PROCESS

- In the European Union LCS permitted/approved **before 20 January 2009 are required to undergo a thorough new risk assessment** by the European Food Safety Authority (EFSA).
- **Commission Regulation (EU) No 257/2010** set up a programme for the re-evaluation of approved LCS in accordance with Regulation (EC) No 1333/2008.
- Therefore other than aspartame, advantame and steviol glycosides all LCS including acesulfame K, alitame, cyclamate, neotame, NHDC, sucralose and thaumatin will be re-evaluated.
- The submissions for re-evaluation is required to be submitted by March 2018 and will be evaluated by 2020.

DOES ASPARTAME CAUSE CANCER?

The Ramazzini Institute has conducted 3 lifetime studies and concluded that aspartame has carcinogenic potential

- Only studies reporting positive results by Soffritti *et al.* (Soffritti et al. 2005; Belpoggi et al. 2006; Soffritti et al. 2006; Soffritti et al. 2010).

Detailed review of protocol and data of Soffritti by:

- EFSA, 2006 & 2013; Agence Franciase de Securite Santarie des Aliments (2006); U.S. National Toxicology Program; FDA, Health Canada; Expert panel (Crit Rev Toxicology, 2007)

All agreed that:

- "**there is no credible evidence that aspartame is carcinogenic"**
- "no need to further review the safety of aspartame"
- "no need to revise previously established ADI"


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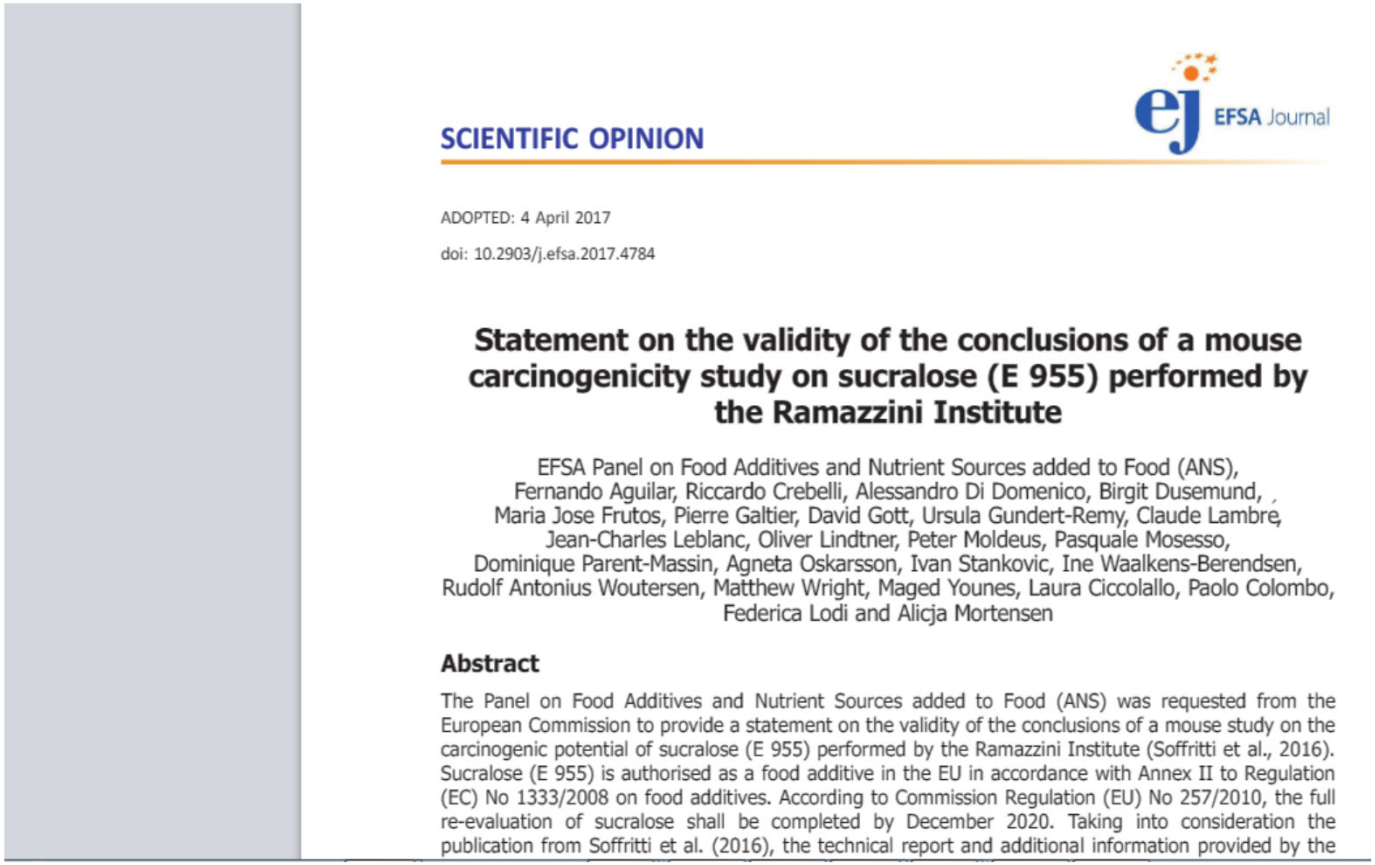
EFSA completes full risk assessment on aspartame and concludes it is safe at current levels of exposure
Press Release
10 December 2013
Aspartame and its breakdown products are safe for human consumption at current levels of exposure, EFSA concludes in its first full risk assessment of this sweetener. To carry out its risk assessment, EFSA has undertaken a rigorous review of all available scientific research on aspartame and its breakdown products, including both animal and human studies.
"This opinion represents one of the most comprehensive risk assessments of aspartame ever undertaken. It's a step forward in strengthening consumer confidence in the scientific underpinning of the EU food safety system and the regulation of food additives", said the Chair of EFSA's Panel on Food Additives and Nutrient Sources Added to Foods (ANS Panel), Dr Alicja Mortensen.
Experts of ANS Panel have considered all available information and, following a detailed analysis, have concluded that the current Acceptable Daily Intake (ADI) of 40mg/kg bw/day is protective for the general population. However, in patients suffering from the medical condition phenylketonuria (PKU), the ADI is not
See also
Aspartame homepage
Food Ingredients and Packaging Unit
Panel on Food Additives and Nutrient Sources Added to Food (ANS)
FAQ on aspartame

DOES SUCRALOSE CAUSE CANCER?

- Recently Soffritti *et al.* published a study in mice purporting to show sucralose is carcinogenic
- Soffritti stated that “Sucralose administered in feed over a lifetime induces hematopoietic neoplasms
- 2 Published carcinogenicity studies conducted using FDA Redbook guidelines (one in rats and one in mice) showed no evidence of carcinogenicity
  - These studies have been accepted by regulators around the word
- Detailed evaluation of study protocol by EFSA conducted
- Data did not support the conclusions of Soffritti



SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 4 April 2017

doi: 10.2903/j.efsa.2017.4784

Statement on the validity of the conclusions of a mouse carcinogenicity study on sucralose (E 955) performed by the Ramazzini Institute

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Fernando Aguilar, Riccardo Crebelli, Alessandro Di Domenico, Birgit Dusemund, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy, Claude Lambre, Jean-Charles Leblanc, Oliver Lindtner, Peter Moldeus, Pasquale Mosesso, Dominique Parent-Massin, Agneta Oskarsson, Ivan Stankovic, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen, Matthew Wright, Maged Younes, Laura Ciccolallo, Paolo Colombo, Federica Lodi and Alicja Mortensen

Abstract

The Panel on Food Additives and Nutrient Sources added to Food (ANS) was requested from the European Commission to provide a statement on the validity of the conclusions of a mouse study on the carcinogenic potential of sucralose (E 955) performed by the Ramazzini Institute (Soffritti et al., 2016). Sucralose (E 955) is authorised as a food additive in the EU in accordance with Annex II to Regulation (EC) No 1333/2008 on food additives. According to Commission Regulation (EU) No 257/2010, the full re-evaluation of sucralose shall be completed by December 2020. Taking into consideration the publication from Soffritti et al. (2016), the technical report and additional information provided by the

Therefore, the Panel concluded that the available data did not support the conclusions of the authors (Soffritti *et al*., 2016) that sucralose induced haemat opoietic neoplasias in male Swiss mice.

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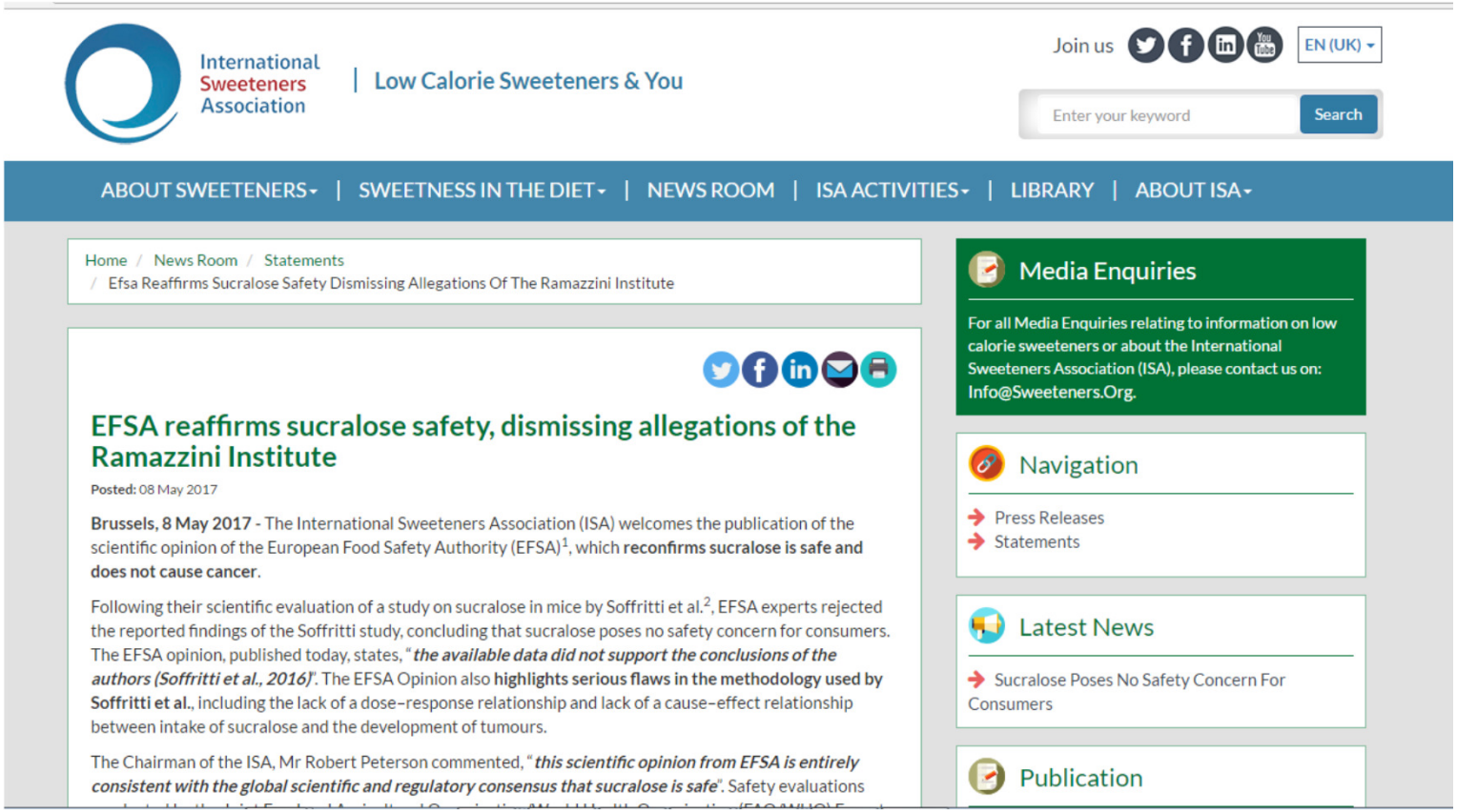

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Home / News Room / Statements / Efsa Reaffirms Sucralose Safety Dismissing Allegations Of The Ramazzini Institute

EFSA reaffirms sucralose safety, dismissing allegations of the Ramazzini Institute

Posted: 08 May 2017

Brussels, 8 May 2017 - The International Sweeteners Association (ISA) welcomes the publication of the scientific opinion of the European Food Safety Authority (EFSA)[1], which **reconfirms sucralose is safe and does not cause cancer**.

Following their scientific evaluation of a study on sucralose in mice by Soffritti et al.[2], EFSA experts rejected the reported findings of the Soffritti study, concluding that sucralose poses no safety concern for consumers. The EFSA opinion, published today, states, "***the available data did not support the conclusions of the authors (Soffritti et al., 2016)***". The EFSA Opinion also **highlights serious flaws in the methodology used by Soffritti et al.**, including the lack of a dose–response relationship and lack of a cause–effect relationship between intake of sucralose and the development of tumours.

The Chairman of the ISA, Mr Robert Peterson commented, "***this scientific opinion from EFSA is entirely consistent with the global scientific and regulatory consensus that sucralose is safe***". Safety evaluations

Media Enquiries

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- Sucralose Poses No Safety Concern For Consumers

Publication

DO LCS AFFECT THE MICROBIOME?

- Recent High Profile Article Concluded that Artificial Sweeteners Alter the Gut Microbiota (Suez *et al* 2014); However a number of limitations were noted within this study
  - Lack of isocaloric control groups to account for differences in caloric intake between sweetener and control groups
  - Human dietary relevance is limited because:
    - Utilizing sweetener doses that are significantly greater than the ADI
  - Difficulties translating microbiome findings in animals to humans
- The studies currently present in the scientific literature provide no significant evidence that any LCS alters the gut microbiota in humans at currently permitted human intake levels
    - Limitations in the experimental designs and selectivity in both the reporting and analysis of results call into doubt the conclusions raised within the Suez *et al*. (2014) publication
- **No adverse health effects mediated by gut microflora changes can be assumed based upon the available data**

CONCLUSIONS ON THE SAFETY OF LCS

- A large body of evidence is required to support safety, and is critically reviewed by regulatory authorities
- No evidence of adverse effects of LCS at levels of human consumption even within the highest users
- A number of controversies have been reported regarding LCS; However all regulatory authorities continue to support the safety of LCS

THANK YOU!

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Health, Environmental & Regulatory Services (HERS)
Intertek
2233 Argentia Rd., Suite 201,
Mississauga, Ontario L5N 2X7 CANADA

+1 905-542-2900

ashley.roberts@intertek.com

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