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Conflict of Interest Disclosure

I wish to declare a potential conflict of interest, and that I have received direct industry support from the International Life Sciences Institute (ILSI) in relation to all or part of the results presented here.

Global Safety and Regulatory Processes for the Evaluation of Low-Calorie Sweeteners

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Outline

- **Low-Calorie Sweetener Safety Evaluation**
  - Regulatory Requirements
  - Safety testing
  - ADI Derivation
  - Regulatory Outcomes
- **Typical Safety Related Questions**
- **Recent Controversies Regarding LCS**
- **Conclusions**

Low-Calorie Sweetener Safety Evaluation

- **All LCS undergo a thorough premarket safety evaluation**
- **Data independently reviewed by Worldwide 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 an ADI**

Safety Outcome Determined Through the Derivation of an ADI

- What is an ADI (Acceptable Daily Intake)
- 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
- JECFA and Government Agencies assign an ADI on the basis of the safety database
- Once approved LCS are added to a positive list of ingredients permitted for sale in that jurisdiction

What Constitutes the DataBase Necessary for Approval

- The scientific database is required to include the following:
  - Technical information (manufacturing, specifications, technological function) safety studies (toxicology) and an exposure analysis
- The safety data has to be generated to strict guidelines (FDA RedBook, OECD, EFSA) and performed to high quality standards (GLP)
- This information is submitted in the form of a dossier for review by the authorities who conduct the risk assessment

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)

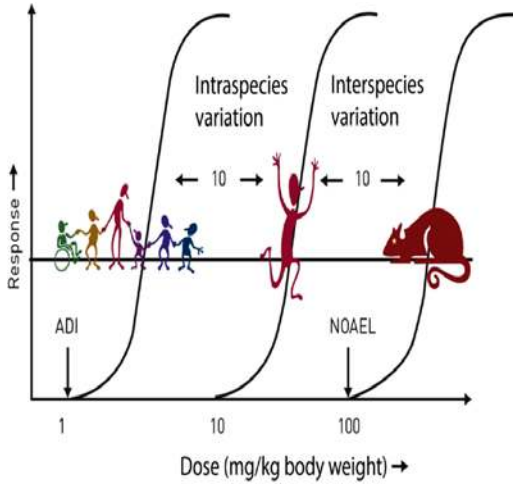
- All data from all studies must be submitted for review by regulatory authorities
- Not acceptable to only file the positive studies while ignoring negative data

The Purpose of Animal Toxicology Tests

- To provide Safety Assurance
- Animals given very high doses.
  - To produce potential adverse effects
  - To define a daily intake without adverse effects (NOAEL)
- LCS are some of the least toxic compounds which allow dosages up to 10% of the diet in some cases to replace the basal diet
- The NOAEL is derived from studies provided the sweetener chronically (2 year carcinogenicity studies)

How do Regulatory Authorities Calculate an 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)



Daily Exposure Analysis

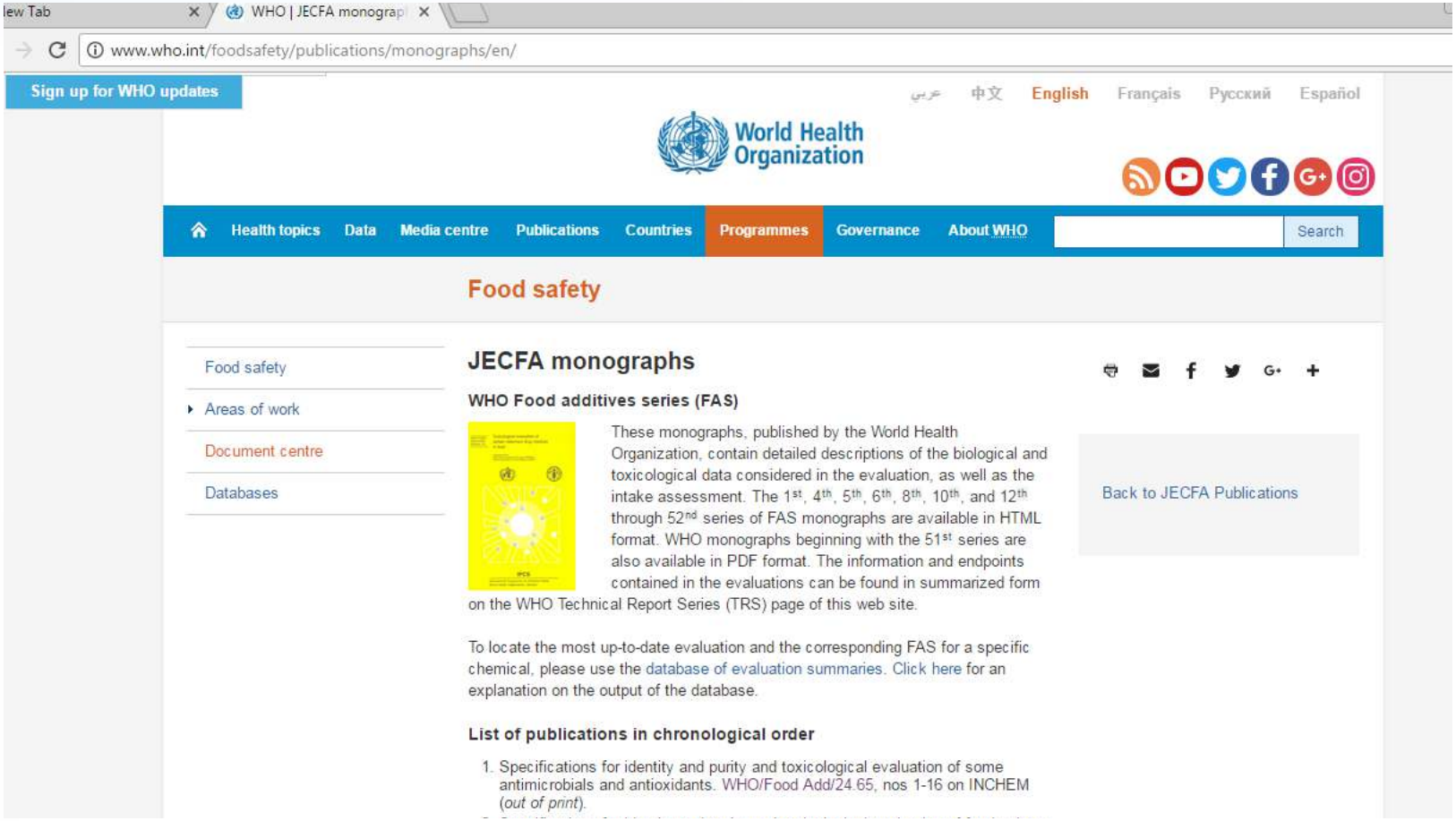
- The daily human exposure level is required to be below the ADI
- A daily intake analysis is therefore required
- Based upon a theoretical exercise using local food survey databases
  - NHANES in the U.S. and
  - The Comprehensive Database in the EU
- Requires the types of food category and inclusion levels
- Calculates exposures for specific population groups (*e.g.*, demographics) and ages and takes account for high consumers (90th to 95th percentile)
- Assumes that the additive is present in all foods and beverages
- Typically overestimates actual consumption over longer time periods

International Regulatory Outcomes

- Approvals may specify the permitted use categories and use levels (termed conditions of use)
- In the U.S. many LCS are classified as "general purpose sweeteners"
  - Permitted on the basis of cGMP (no limit on use, based upon safety)
- Leads to a change in legislation (CFR; Sweetener Directive)
- In the U.S. LCS can be Food Additives or GRAS Ingredients (same safety standard)
  - Approved Food Additives:
    - Aspartame, neotame, advantame, acesulfame potassium (ace-K), saccharin, sucralose
  - HISs that are FDA-listed Generally Recognized as Safe (GRAS) Ingredients:
    - Steviol glycosides, lo han guo

LCS ADI Values Derived by JECFA

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



Typical Questions

- **Are they safe for children?**
- **Are they safe for pregnant and lactating mothers?**
- **What happens if I exceed the ADI?**

Applicability of the ADI to Children and Pregnant and Lactating Mothers

- Toxicological protocols adopted for LCS cover all periods of human exposure including:
  - Rapid growth and development, maturation and aging
  - Reproduction (2 generations)
  - Birth defects (teratogenicity)
- Exposure during reproduction as well as the juvenile period is taken into account and so the ADI does apply to children and pregnant and lactating mothers
  - 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

What Happens if I Exceed the ADI Exceeding the ADI

- The ADI is not a lower bound of toxicity as we have at least a 100-fold safety margin
  - Not a toxic threshold
- 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*"
- As LCS are some of the least toxic substances and show little if any acute toxicity
  - Day to day variations in intake above the ADI are not relevant for human health and safety

Recent Controversies Regarding LCS

- **Do they cause cancer?**
- **Do they affect the gut microbiome leading to adverse health consequences?**

Does Aspartame and Sucralose Cause Cancer?

The Ramazzini Institute has conducted 3 lifetime studies in rodents with aspartame and 1 with sucralose

- 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; Soffritti *et al.,* 2016)
- Carcinogenicity studies conducted using FDA Redbook guidelines showed no evidence of carcinogenicity

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) for aspartame and EFSA 2017 for sucralose

All agreed that:

- **"there is <u>no credible evidence</u> that aspartame is carcinogenic"**

EFSA Concluded

- "Data did not support the conclusions of Soffritti"

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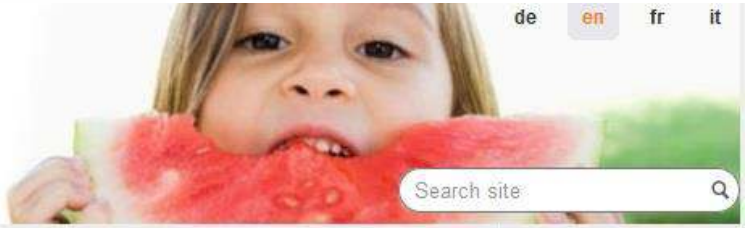

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EFSA completes full risk assessment on aspartame and concludes it is safe at current levels of exposure

Press Release
10 December 2013

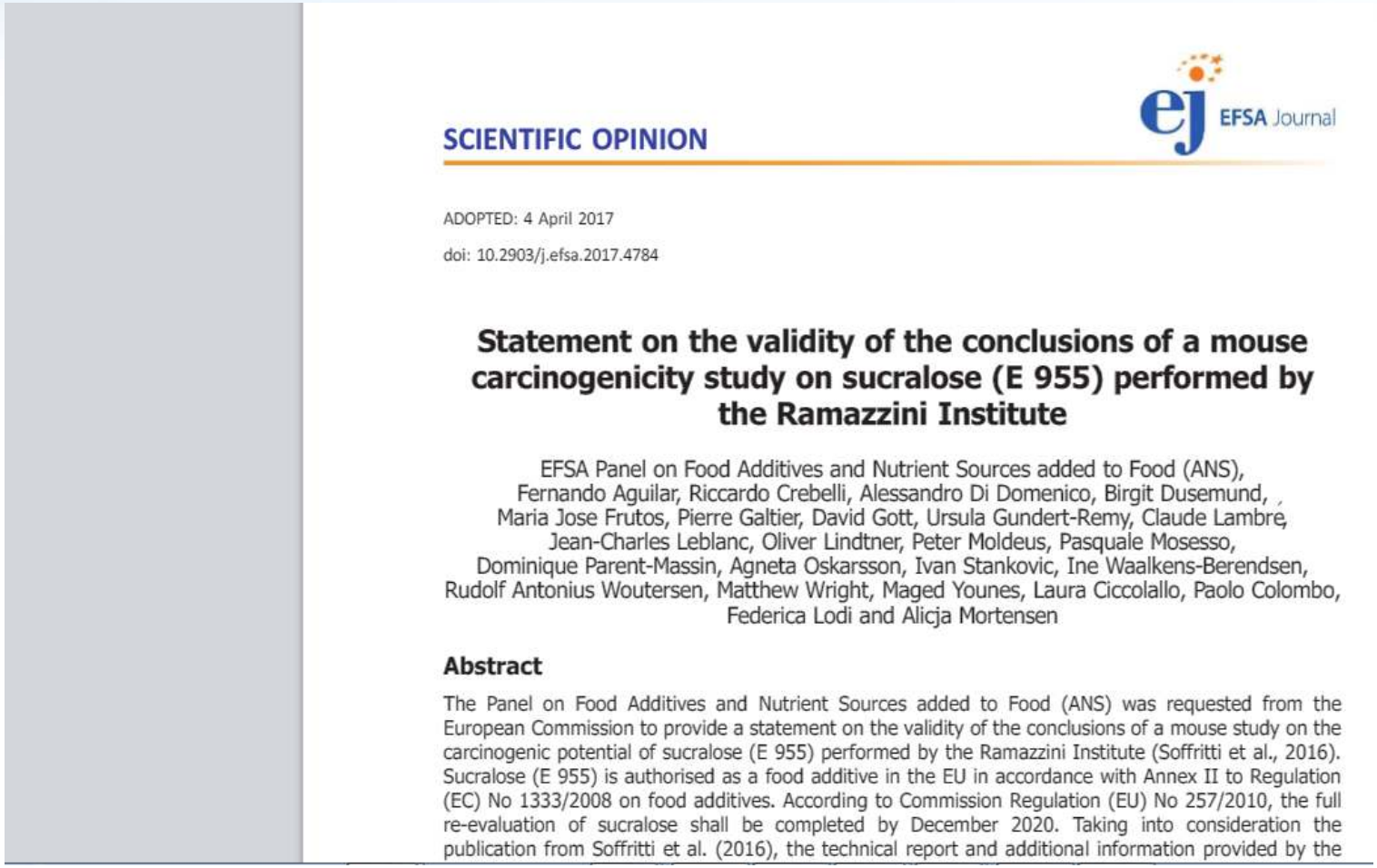
Aspartame and its breakdown products are safe for human consumption at current levels of exposure, EFSA concludes in its first full risk assessment of this sweetener. To carry out its risk assessment, EFSA has undertaken a rigorous review of all available scientific research on aspartame and its breakdown 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



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

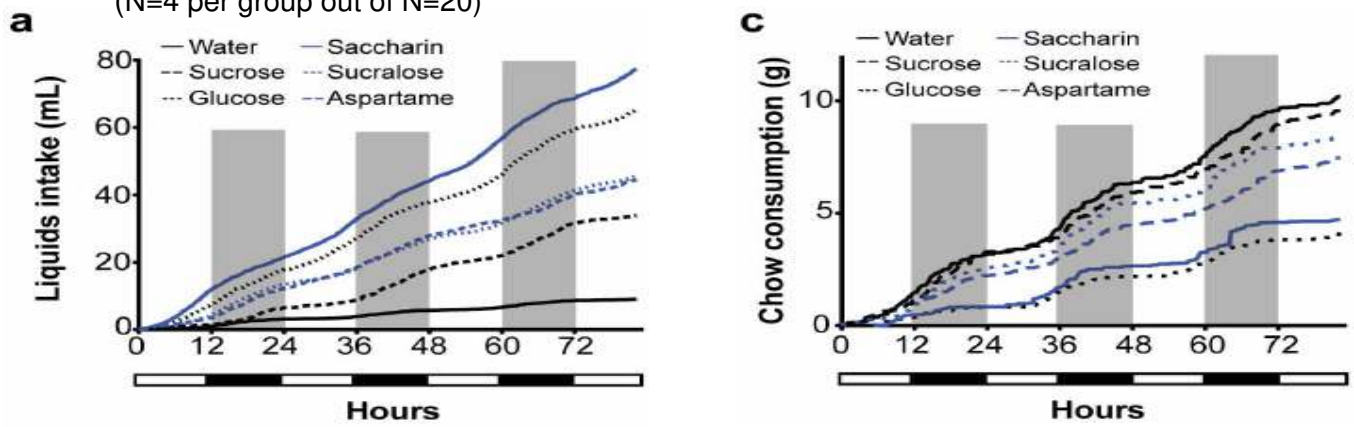
Therefore, the Panel concluded that the available data did not support the conclusions of the authors (Soffritti *et al*., 2016) that sucralose induced haemat opoietic neoplasias in male Swiss mice.

Do LCS Affect the Microbiome?

- Recent High Profile Article Concluded that Artificial Sweeteners Alter the Gut Microbiota
  (Suez *et al.,* 2014)
- Limitations were noted within this publication calling in to question the outcomes in the study
  - Lack of isocaloric control groups in the animal or human studies
  - Animal studies utilized sweetener doses significantly greater than the ADI
  - Difficulties translating microbiome findings in animals to humans

LCS Doses Were at Least 30-fold Higher than ADI

(N=4 per group out of N=20)



Reproduced from Suez *et al.,* 2014; Extended Data Figure 3a & c.

	Approx liquid intake/day (mL)	Daily exposure (mg/kg/day)	ADI (mg/kg/day)
Water	2	---	---
Aspartame	10	1333	40
Saccharin	20	3333	5
Sucralose	10	1666	15

Do LCS Affect the Microbiome?

OUTCOME:

- Currently the scientific literature provide no significant evidence that any LCS alters the gut microbiota in humans at permitted human intake levels
- **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 has been generated to support the safety of all currently permitted LCS
- The safety has been critically reviewed by numerous regulatory authorities and scientific bodies
- A number of controversies have been reported regarding LCS; However all regulatory authorities continue to support the safety of LCS

Thank You!

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