Info session: (Re-)Evaluating Food Additives
DAY 1: 19 March 2024
SESSION 1 | Food additives re-evaluation: taking stock

INTEGRATING EPIDEMIOLOGICAL EVIDENCE IN RISK ASSESSMENT – THE CASE OF ERYTHRITOL

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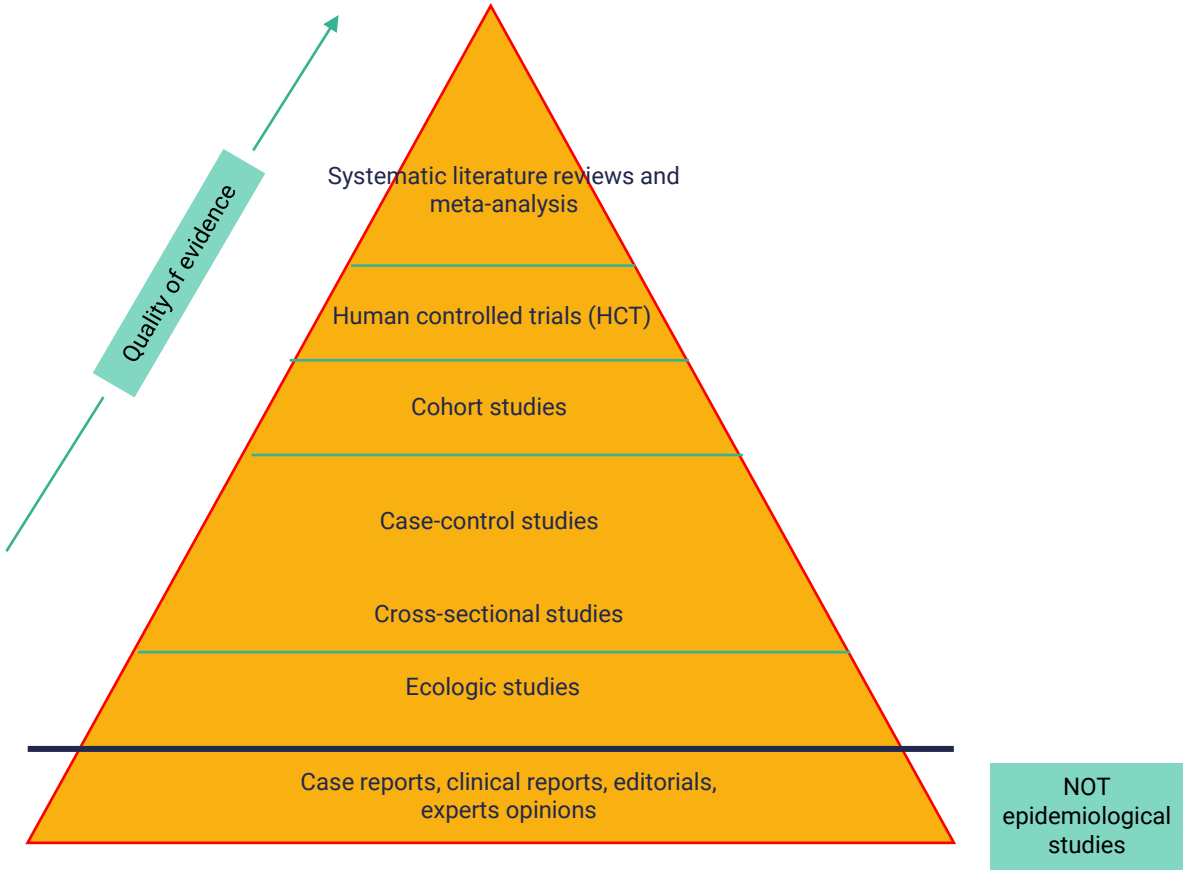
TYPE OF EPIDEMIOLOGICAL DATA

- **Experimental studies**: where the exposure conditions are modified by the researcher to examine what effect an intervention may have on the population under study

- **Non-experimental (observational) epidemiological studies**: researcher has no control over the circumstances or amount of exposure. Instead, the researcher observes the outcome of interest in a given population, whose members may have been exposed to certain factors, inadvertently or by choice

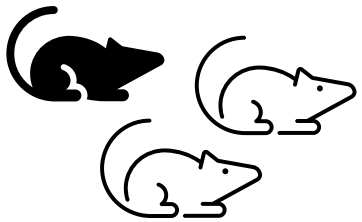


Both evidence streams have their strengths and weaknesses

INTEGRATION OF HUMAN EPIDEMIOLOGY IN RISK ASSESSMENT – WHY?

Animal data

- Well established procedures and guidelines on use of controlled animal experiments for chemical risk assessment
- Fit for purpose for assessing safety pre-marketing
- Several limitations



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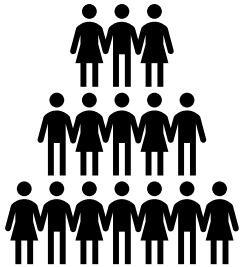
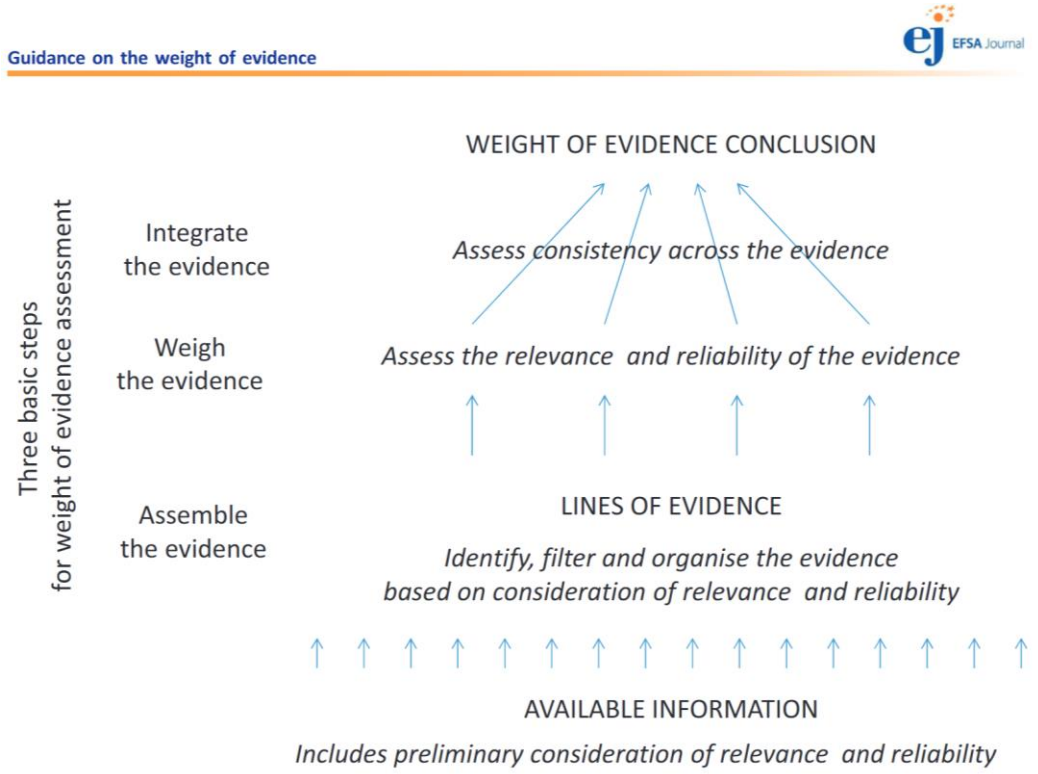
Human data

- Controlled human trials sometimes serve the same purpose
- For chemical risk assessment, observational epidemiological studies are conducted post-marketing
- Several (but different) limitations



TO IMPROVE EXISTING RISK ASSESSMENT FRAMEWORK

- Different **lines of evidence** need to be integrated
  - Animal data
  - Human data
  - Mechanistic data (biological plausibility)
- Weight of Evidence (**WoE**) is key

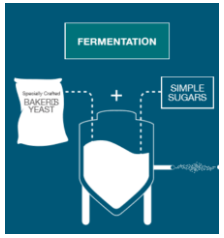


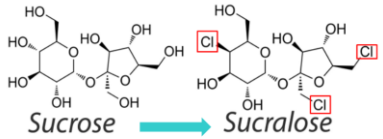
RE-EVALUATION OF SWEETENERS AS FOOD ADDITIVES

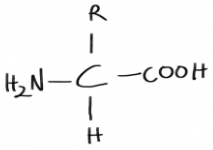
- Many different types of sweeteners used broadly across food products
- Highly scrutinized substances
- Really diverse
- Emerging literature → **observational epidemiological studies**

E Number	Food additive(s)
E 420	Sorbitols
E 421	Mannitols
E 950	Acesulfame K
E 951[(a)]	Aspartame[(a)]
E 952	Cyclamates
E 953	Isomalt
E 954	Saccharin and its Na, K and Ca salts
E 955	Sucralose
E 957	Thaumatin
E 959	Neohesperidine dihydrochalcone
E 961	Neotame
E 962	Salt of aspartame-acesulfame
E 965	Maltitols
E 966	Lactitol
E 967	Xylitol
E 968	Erythritol

(a) In May 2011, EFSA was asked by the European Commission to bring forward the full re-evaluation of the safety of aspartame (E 951). That re-evaluation was completed by EFSA in 2013 (EFSA ANS Panel, 2013).







Scientists find consuming artificial sweeteners may be linked to a higher risk of depression

Sucralose, a Common Artificial Sweetener, May Increase Cancer Risk

Sources:
https://www.theguardian.com/society
https://www.euronews.com/health/2023/09/21/consuming-artificial-sweeteners-linked-to-a-higher-risk-of-depression-study
https://www.healthline.com/health-news/sucralose-a-common-artificial-sweetener-may-increase-cancer-risk
https://www.cbsnews.com/miami/news/erythritol-an-ingredient-in-stevia-linked-to-heart-attack-and-stroke-study-finds/
https://www.toxicology.org/events/shm/fda/docs/2023-Dec/2-Scott-SOT-FDA-Colloquium-2023-Sweeteners.pdf

RE-EVALUATION OF SWEETENERS – PROTOCOL FOR HI&HC

Problem formulation	• Is there a dose-response relationship between the dietary exposure to sweeteners and adverse effects in **humans**/experimental animals?
Extensive **Literature Searches**	• Open-ended searches; from last SCF/EFSA opinion
Screening the studies for relevance	• Two steps: Ti/Ab_full text • Setting of **inclusion/exclusion criteria**
Evaluation of the **Risk of Bias**	• Adapted from the OHAT rating tool (NTP, 2019); 3 tiers
Weighing the **Body of Evidence**	• Modified version of the OHAT (NTP.-OHAT, 2019) and EFSA Guidance on WoE (2017)

Table 5: Inclusion/exclusion criteria related to human studies

Study type	**In**	Human data (observational and interventional studies) Case reports (narrative approach) Toxicokinetic studies (narrative approach) Studies on gut microbiota in humans (narrative approach)

Table 8: Evaluation of risk of bias in human studies (adapted from the OHAT risk of bias rating tool)[8]

Number	Question	Applies to study type	Domain of bias	Rating (++, +, -, --)
1	Was the administered dose or exposure level adequately randomised?	HCT	Selection	
2	Was the allocation to study groups adequately concealed?	HCT	Selection	
3	Did the study population allow for appropriate comparisons?	Co, CaCo, CrSe	Selection	
4	Did the study design or analysis account for important confounding and modifying variables?	Co, CaCo, CrSe	Confounding	

[8] The Panel make reference to the explanatory notes from the US National Toxicology Program (NTP) Handbook for conducting a literature-based health assessment using the OHAT approach for systematic review and evidence integration (NTP-OHAT, 2019).

Number	Question	Applies to study type	Domain of bias	Rating (++, +, -, --)
5	Were the research personnel and study participants blinded to the study group during the study?	HCT	Performance	
6	Were the outcome data complete without attrition or exclusion from analysis?	HCT, Co, CaCo, CrSe	Attrition/exclusion	
7	Can we be confident in the exposure characterisation?	HCT, Co, CaCo, CrSe,	Detection	
8	Can we be confident in the outcome assessment (e.g. missing outcome)?	HCT, Co, CaCo, CrSe,	Detection	
9	Were all the measured outcomes reported?	HCT, Co, CaCo, CrSe,	Selective reporting	
10	Were the statistical methods appropriate?	All	Other sources of bias	

CaCo: case–control; CrSe: cross-sectional; Co: cohort; HCT: human controlled trial.

RE-EVALUATION OF SWEETENERS – EXAMPLES

- **Thaumatin (E 957)**: human studies available but only HCT (experimental)

- **Neohesperidine DC (E 959)**: no human studies available

- **Erythritol (E 968)**: human studies available → HCTs + observational studies

3.5.4.2. Human studies

Three human intervention studies conducted in healthy volunteers (non-peer-reviewed reports) examining possible effects of oral exposure to thaumatin on blood chemistry and allergenicity were submitted through the call for data (Tompkins and Enticknap, 1984; MacLeod et al., 1981; Eaton et al., 1981 in Documentation provided to EFSA nr: 7). These studies were conducted in the early 1980s when conduct and reporting were considerably different from current standards. No signs of overt toxicity were observed in a study assigning 15 subjects to 280 mg thaumatin/day to thaumatin over 13 weeks and comparing them to same number of controls (Tompkins and Enticknap, 1984). No sign of allergenicity assessed by skin prick test after oral exposure to thaumatin was observed in two studies

3.5.4.2. Human studies

No human studies on neohesperidine dihydrochalcone were received by the interested parties through the call for data and none were retrieved in the literature.

TABLE 11 Summary of human studies considered under the GI effects HOC.

Authors (year) (RefID[a])	Type of HCT	Dose (g/person or g/kg bw)[b]	Administration	Number of subjects	Population (mean age in years)	RoB tier
Teysseire et al. (2022) (4355)	Cross-over trial	50 g	Single dose, by a nasogastric tube	18 (5 M and 13 F)	Adults (24)	2
Meyer-Gerspach et al. (2021) (3859)	Cross-over trial	75 g	Single dose, by a nasogastric tube	20 (10 M and 10 F)	Adults (27.7)	1
Wölnerhanssen et al. (2021) (3850)	Cross-over trial	10 g, 25 g, 50 g	Single dose, by a nasogastric tube	12 (7 M and 5 F)	Adults (21.7)	2
Wölnerhanssen et al. (2016) (3759)	Cross-over trial	75 g	Single dose, by a nasogastric tube	20 (10 M and 10 F)	Adults (25)	1
Kim et al. (2011) (1242						
Biofortis (2010)[c] (Documentation to EFSA No. 6, 12)						
Storey et al. (2007) (7						
Tetzloff et al. (1996) (						

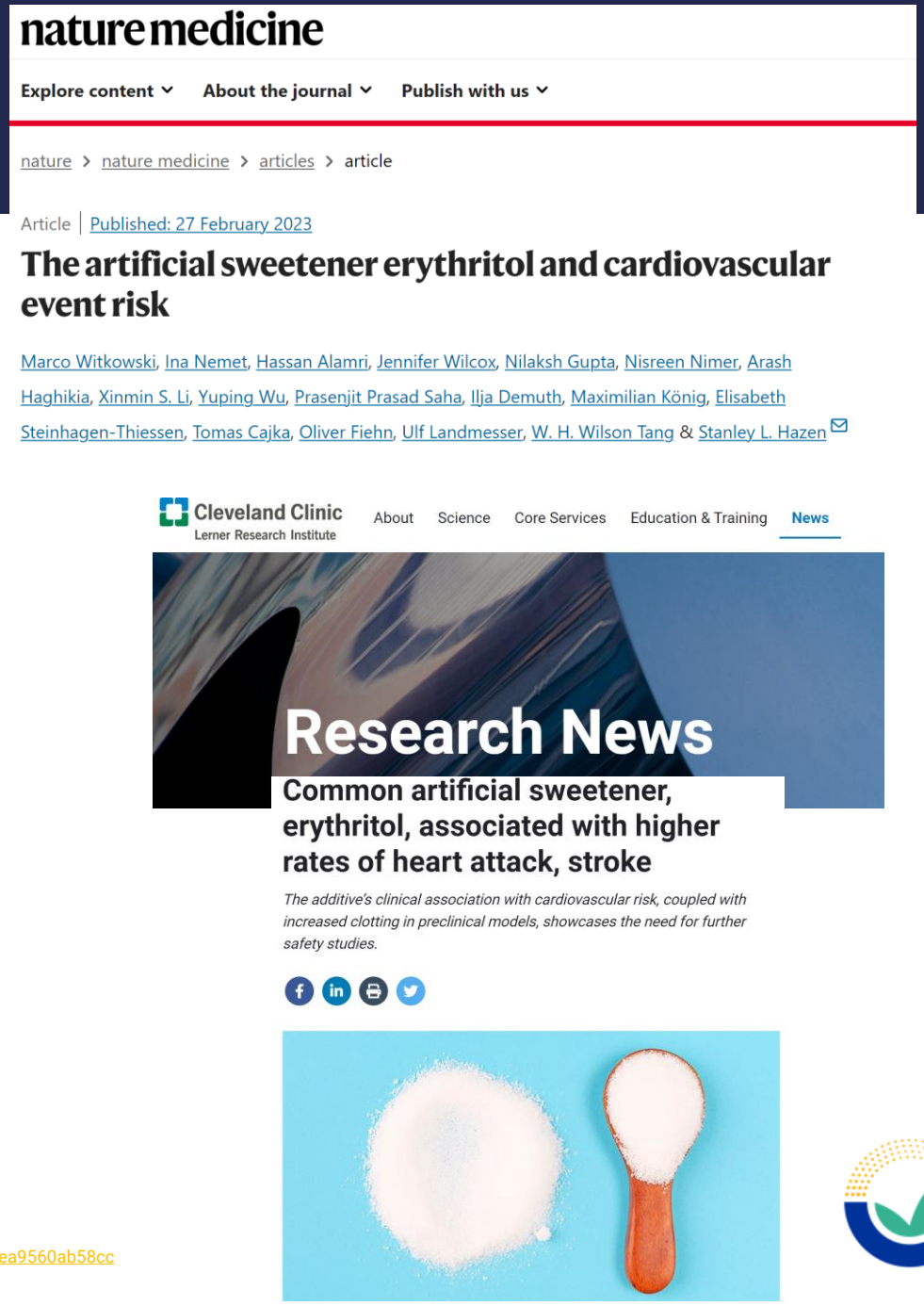
3.5.1.2 | *Studies on circulating erythritol*

Recently, associations between increased erythritol blood levels and metabolic disorders and/or cardiovascular diseases have been reported (Rebholz et al., 2018; Wang et al., 2019; Witkowski et al., 2023). In addition, several metabolomic profiling studies reported that elevated circulating erythritol concentrations, together with other metabolites, were observed in patients with type II (T2) diabetes and related vascular and non-vascular complications (Chen et al., 2016; Duangkumpha et al., 2022; Menni et al., 2013; Moon et al., 2023; Shao et al., 2022) and/or cardiovascular disease (Fu et al., 2022).

Witkowski et al. (2023) examined the association between circulating blood erythritol levels and major adverse cardiovascular events (MACE): death, nonfatal myocardial infarction or nonfatal cerebrovascular accident (stroke) in one cohort (USA) consisting of 1157 stable patients aged 52–76 years and undergoing cardiac risk assessment for symptom evaluation. In this untargeted metabolomic study, circulating levels of multiple polyols, including erythritol, were associated with incident (3 years) risk for MACE.

ERYTHRITOL - CHALLENGES

- Observational studies retrieved in the literature, in particular a recent **cohort study**
- Health outcome investigated: cardiovascular disease
- **No information on dietary intake**
- Therefore, no distinction between **endogenous** and **exogenous** erythritol
- **Population**: population with suspected chronic coronary syndromes and high cardiovascular disease risk
- Animal studies not fully relevant for the investigated outcome



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Article | Published: 27 February 2023

The artificial sweetener erythritol and cardiovascular event risk

Marco Witkowski, Ina Nemet, Hassan Alamri, Jennifer Wilcox, Nilaksh Gupta, Nisreen Nimer, Arash Haghikia, Xinmin S. Li, Yuping Wu, Prasenjit Prasad Saha, Ilja Demuth, Maximilian König, Elisabeth Steinhagen-Thiessen, Tomas Cajka, Oliver Fiehn, Ulf Landmesser, W. H. Wilson Tang & Stanley L. Hazen

Cleveland Clinic Lerner Research Institute

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Research News

Common artificial sweetener, erythritol, associated with higher rates of heart attack, stroke

The additive's clinical association with cardiovascular risk, coupled with increased clotting in preclinical models, showcases the need for further safety studies.

Sources:
https://www.nature.com/articles/s41591-023-02223-9
https://www.lerner.ccf.org/news/article/?title=Common+artificial+sweetener%2C+erythritol%2C+associated+with+higher+rates+of+heart+attack%2C+stroke&id=ea9560ab58cc87cd9bba43ff11bde112318d54f1

ERYTHRITOL – APPROACH AND CONCLUSIONS

- Some studies meeting the inclusion criteria were not included in the formal WoE and were addressed narratively
- This is often due to study limitations for relevance
- These studies may be used as supportive evidence

Conclusions

- Recent literature suggested a **possible association from human observational studies between higher circulating blood levels of erythritol and cardiovascular disease and related risk factors**.
- However, these preliminary results do not conclusively identify specific health concerns for the use of erythritol as a food additive.
- Overall, the Panel considered that a **causal relationship** between **dietary exposure to erythritol (E 968) and cardiovascular disease risk has not been demonstrated by the available studies**.
- the Panel considered that fasting erythritol serum levels may be a **biomarker of metabolic disturbances** (i.e. type 2 diabetes mellitus, central adiposity gain which are known risk factors for cardiovascular disease)
- Nevertheless, further research might be helpful to clarify the nature of the association found in some observational studies.

LESSONS LEARNT AND FUTURE

- Protocol cannot foresee all possible scenarios → case-by-case decision cannot be excluded
- Implementation of a protocol leads to revisions and amendments
- Body of evidence:
  - more than a few epidemiological (observational) studies
  - better epidemiological (observational) data regarding the **exposure characterization**
- Integration of lines of evidence:
  - comparable health outcomes

DRAFT GUIDANCE ON EPIDEMIOLOGICAL STUDIES

IN EFSA PIPELINE: The new draft EFSA guidance on Epidemiology

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: The document was endorsed for publication and testing on 24 June 2020

doi: 10.2903/j.efsa.2020.6221

Draft for internal testing
Scientific Committee guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments

EFSA Scientific Committee,
Simon More, Vasileos Bambidis, Diane Benford, Claude Bragard, Antonio Hernandez-Jerez, Susanne Hougaard Bennekou, Kostas Koutsoumanis, Kyriaki Machera, Hanspeter Naegeli, Soren Saxmose Nielsen, Josef R Schlatter, Dieter Schrenk, Vittorio Silano, Dominique Turck, Maged Younes, Tony Fletcher, Matthias Greiner, Evangelia Ntzani, Neil Pearce, Marco Vinceti, Laura Ciccolallo, Marios Georgiadis, Andrea Gervelmeyer and Thorhallur I Halldorsson

- EFSA has been and is working on multiple fronts to address this topic
- Further work and consensus are needed on how to integrate evidence from human epidemiological studies in chemical risk assessment that has been designed around use of experimental studies in animals
- New draft guidance currently for **public consultation** and final adoption in mid 2024

Public consultation (PC)
https://connect.efsa.europa.eu/RM/s/publicconsultation

CHALLENGES AHEAD

JOURNAL ARTICLE

Nitrites and nitrates from food additives and natural sources and cancer risk: results from the NutriNet-Santé cohort

Eloi Chazelas, Fabrice Pierre, Nathalie Druesne-Pecollo, Younes Esseddik,

Research

Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses

BMJ 2024 ; 384 doi: https://doi.org/10.1136/bmj-2023-077310 (Published 28 February 2024)

Research

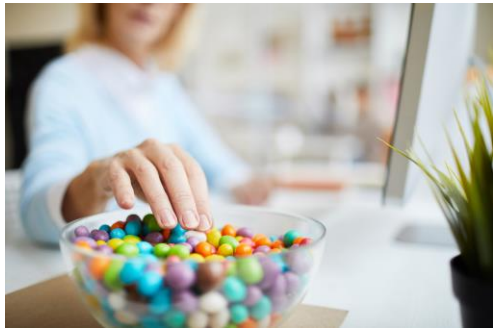
Food additive emulsifiers and risk of cardiovascular disease in the NutriNet-Santé cohort: prospective cohort study

BMJ 2023 ; 382 doi: https://doi.org/10.1136/bmj-2023-076058 (Published 06 September 2023)
Cite this as: *BMJ* 2023;382:e076058

Sources:
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1004338
https://academic.oup.com/ije/article/51/4/1106/6550543
https://www.bmj.com/content/384/bmj-2023-077310
https://www.bmj.com/content/382/bmj-2023-076058

STAY TUNED!

STAY TUNED FOR MORE SWEETENERS (AND EPI DATA) TO COME!



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