THE EU SAFETY ASSESSMENT OF FOOD CHEMICAL MIXTURES

FOCUS ON FOOD ADDITIVES AND THEIR POTENTIAL COMBINED USES

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This paper complements EU Specialty Food Ingredients' statement titled "The EU assessment of food chemical mixtures" (2022) with a focus on food additives.

As underlined by the European Food Safety Authority (EFSA), "*understanding how combined chemicals behave is complex and the number of combinations is potentially infinite*" [1]; yet the combination of food ingredients used to produce foodstuffs shall not raise safety issues.

Food additives are subject to an assessment of their safety before they are permitted for use in foods and beverages. The assessment shall be carried on single additives, in accordance with the EU legislative requirements [2]. However, **this should not be interpreted as the EU legislator failing to address combined exposures appropriately**.

1. https://www.efsa.europa.eu/en/press/news/190325
2. Regulation (EC) 1331/2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1331-20210327&qid=1742919679223

FOOD ADDITIVES CAN BE MIXTURES

Firstly, it is important to remember that food additives can be simple mixtures themselves, i.e., a mixture whose components can be fully characterised, or complex mixtures, i.e., mixtures containing a substantial fraction of unidentified components (for which not all the components have been chemically, fully identified)[3]. These complex mixtures are typically derived from e.g., plants, macroscopic fungi, macroalgae, animals, or their parts. EFSA adapts the risk assessment strategy to the nature of the additive, as exemplified in the Guidance on the preparation of an application for authorisation of a food additive (2025)[4].

EXAMPLES

- **Steviol glycosides (E 960)**, when extracted from the leaves of the plant *Stevia rebaudiana Bertoni*, are mixtures of stevioside, rebaudioside A, rebaudiosides B, C, D, E and F, steviolbioside, rubusoside and dulcoside A.[5]
- **Candelilla wax (E 902)** is obtained from the leaves of the candelilla plant, *Euphorbia antisyphilitica*. Its average composition has been reported as consisting of paraffins, alkenes, wax, resin, sitosteroyl esters, lactones (6% w/w), free wax resin acids, resin alcohols.[6]

3. https://doi.org/10.2903/j.efsa.2019.5519
4. Under adoption
5. https://doi.org/10.2903/j.efsa.2010.1537
6. https://doi.org/10.2903/j.efsa.2012.2946

GROUP ADI: AN ADEQUATE SCIENTIFIC APPROACH TO THE COMBINATION OF ADDITIVES EXPECTED TO HAVE CUMULATIVE EFFECTS BECAUSE OF SIMILAR CHEMICAL STRUCTURE OR TOXICITY

When EFSA evaluates the safety in use of a substance as a food additive, it establishes an Acceptable Daily Intake (ADI), i.e. an estimate of the amount of this substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health. It is usually expressed as milligrams of the substance per kilogram of body weight per day.

The ADI normally specifies the maximum acceptable intake for a single chemical substance, but there are a number of situations in which a modified approach is considered appropriate. **A group ADI may be set for compounds that are expected to have additive effects because of similar chemical structure or toxicity**. If ten such compounds were all consumed at the level specified by an individual ADI, the combined result would be equivalent to consuming ten times the ADI of just one of them, with the possibility of producing harmful effects. It is therefore considered necessary to control the overall intake of the group.[7]

EXAMPLES

EFSA derived:

- a group ADI of 10 mg/kg body weight per day expressed as sorbitan for sorbitan esters (E 491, E 492, E 493, E 494 and 495) singly or in combination.[8]
- a group ADI of 40 mg/kg body weight per day expressed as phosphorus for phosphates (E 338, E 339, E 340, E 341, E 343, E 450, E 451, E452).[9]

7. ILSI Europe Concise Monographs Series. The Acceptable Daily Intake - A Tool for ensuring food safety ILSI CM ADI for pdf
8. https://doi.org/10.2903/j.efsa.2017.4788
9. https://doi.org/10.2903/j.efsa.2019.5674

MAXIMUM PERMITTED LIMITS FOR THE COMBINED USE OF FOOD ADDITIVES

The group ADI approach is implemented in the food additive legislation[10] by setting **maximum permitted limits for groups of food additives** instead of for single additives.

Irrespective of whether a group ADI has been assigned or not, where a combination of food additives may be expected in food and beverage applications to deliver a specific technological function, permitted maximum levels for the sum of these additives may be set in the food additive legislation.

EXAMPLES

Benzoic acid (E 210), Sodium benzoate (E 211), Potassium benzoate (E 212) and Calcium benzoate (E 213) are assigned a group ADI of 5 mg/kg bw. They may be added individually or in combination in olives and olive-based preparations at a maximum level of 500 mg/kg, and this maximum level is applicable to the sum and the levels are expressed as the free acid.

EXAMPLES

Food category 4.2.5 Jam jellies and marmalades and similar products:

E 400 (alginic acid), E 401 (Sodium alginate), E 402 (Potassium alginate), E 403 (Ammonium alginate), E 404 (Calcium alginate), E 406 (agar), E 407 (carrageenan), E 410 (locust bean gum), E 412 (guar gum), E 415 (xanthan gum) and E 418 (gellan gum)

→ permitted at maximum level of 10000 mg/kg individually or in combination

Food category 5.1 Cocoa and chocolate products:

E 500 (Sodium carbonates), E 501 (Potassium carbonate); E 503 (Ammonium carbonates), E 504 (Magnesium carbonates), E 170 (calcium carbonate), E 524 - 528 (hydroxides) and E 530 (magnesium oxide):

→ permitted at maximum level of 70000 mg/kg individually or in combination.

10. Regulation (EU)1129/2011 amending Annex II to Regulation (EC) 1333/2008 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02011R1129-20131121&qid=1742920223301

The food additive legislation also establishes a list of 16 food colours with combined maximum limits.

E-number	Name
E 100	Curcumin
E 102	Tartrazine
E 104	Quinoline Yellow
E 110	Sunset yellow FCF/Orange yellow S
E 120	Cochineal, Carminic acid, Carmines
E 122	Azorubine, Carmoisine
E 124	Ponceau 4R, Cochineal red A
E 129	Allura red AC
E 131	Patent Blue V
E 132	Indigotine, Indigo carmine
E 133	Brilliant Blue FCF
E 142	Green S
E 151	Brilliant black BN, Black BN
E 155	Brown HT
E 160e	Beta-apo-8'-carotenal (C 30)
E 161b	Lutein

More generally, the food additive legislation lays down a list of food additives that may be regulated combined, namely:

- E 200-203: Sorbic acid, sorbates (SA)
- E 210-213 Benzoic acid, benzoates (BA)
- E 200-213: Sorbic acid — sorbates; Benzoic acid — benzoates (SA + BA)
- E 200–219: Sorbic acid — sorbates; Benzoic acid — benzoates; p-hydroxybenzoates (SA + BA + PHB)
- E 200–203; 214–219: Sorbic acid — sorbates; p-hydroxybenzoates (SA + PHB)
- E 214–219: p-hydroxybenzoates (PHB)
- E 220–228: Sulphur dioxide — sulphites
- E 249–250: Nitrites
- E 251–252: Nitrates
- E 280–283: Propionic acid — propionates
- E 310–320: Gallates, TBHQ and BHA
- E 338–341, E 343 and E 450 — 452: Phosphoric acid — phosphates — di-, tri- and polyphosphates
- E 355–357: Adipic acid — adipates
- E 432–436: Polysorbates
- E 473–474: Sucrose esters of fatty acids, Sucroglycerides
- E 481–482: Stearoyl-2-lactylates
- E 491–495: Sorbitan esters
- E 520–523: Aluminium sulphates
- E 551–559: Silicon dioxide — silicates
- E 620–625: Glutamic acid — glutamates
- E 626–635: Ribonucleotides.

IS THE CURRENT SCIENTIFIC AND REGULATORY FRAMEWORK FOR THE COMBINED USE OF FOOD ADDITIVES SUFFICIENT?

In 2000, ILSI Europe stated that "a recent analysis considered whether there might be a need to take into account possible interactions between different additives that do not share common metabolites or structural similarities. A review of the toxicity data on the additives approved in the EU showed very few examples where interactions were theoretically possible. The few that were identified included substances having similar effects on the liver (curcumin, thiabendazole, propyl gallate and butylated hydroxytoluene), on the kidney (diphenyl, o-phenylphenol and ferrocyanide salts) and on the blood (azorubine and propyl gallate). These might be of theoretical concern in exposure situations where the intake of each additive was close to the ADI. However, such situations were not likely to arise, because of low levels of intake, particularly where the additives are alternatives for the same application." [7]

Twenty-five years after this conclusion, the continuous re-evaluation of food additive safety, the advancement of EFSA scientific methodologies for assessing chemical mixtures and the sensible legislative approach ensure that risk assessors and risk managers are adequately prepared to address combinations of food additives where necessary.

DISCLAIMER

The document is designed to provide insights about the EU safety assessment of food chemical mixtures, with a focus on food additives and their potential combined uses. As such this document is not, and should not be construed as a guarantee or warranty, nor a part of any contractual or other legal obligations on behalf of EU Specialty Food Ingredients and its member companies. This information is offered solely for the consideration, investigation and verification of interested parties.

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