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

EVALUATION OF THE SAFETY OF FOOD ADDITIVES USED IN FOOD FOR INFANTS AND YOUNG CHILDREN: STATE OF PLAY

Stefania Barmaz (Scientific Officer)

Food Ingredients and Packaging Unit (FIP)

Food Additives and Flavourings Team

EUROPEAN FOOD SAFETY AUTHORITY

BACKGROUND

- In accordance with Regulation (EU) No 257/2010, EFSA is currently **re-evaluating** the safety of **food additives** already permitted in the European Union before 20 January 2009 and issuing scientific opinions on their safety when used in food as per Annexes II and III to Regulation (EC) No 1333/2008
- A number of additives are permitted in the food categories 13.1.1 (**Infant formulae**) and 13.1.5.1 (**Dietary foods for infants for special medical purposes and special formulae for infants**) and consumed by infants below 16 weeks of age.
- Until the beginning of 2018, the risk assessment approach followed by the former ANS Panel in the re-evaluation of food additives did not cover these uses.
- A **scientific guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age** was developed by the EFSA Scientific Committed (Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age (wiley.com)).

LIST OF FOOD ADDITIVES

- The availability of this guidance document **allowed to start the re-evaluation of the safety of FAs permitted for use in foods** intended for infants below 16 weeks of age already evaluated by the former ANS Panel
- A specific **working group** of the Food Additives and Flavouring (FAF) Panel- WG on the re-evaluation of food additives permitted in foods for infants below 16 weeks of age - was charged with this task.

E-number	Food additive name
E 170	Calcium carbonate
E 304i	Ascorbyl palmitate
E 306	Tocopherol-rich extract
E 307	α-Tocopherol
E 308	γ-Tocopherol
E 309	δ-Tocopherol
E 322	Lecithins
E 414	Acacia gum
E 551	Silicon dioxide
E 407	Carrageenan
E 410	Locust bean gum
E 412	Guar gum
E 415	Xanthan gum
E 440	Pectins
E 466	Sodium carboxy methyl cellulose
E 471	Mono-and diglycerides of fatty acids
E 472c	Citric acid esters of mono- and diglycerides of fatty acids
E 473	Sucrose esters of fatty acids
E 1450	Starch sodium octenyl succinate

METHODOLOGY

SCIENTIFIC OPINION

EFSA Journal

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Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Jean-Louis Bresson, Birgit Dusemund, Ursula Gundert-Remy, Mathilde Kersting, Claude Lambré, André Penninks, Angelika Tritscher, Ine Waalkens-Berendsen, Ruud Woutersen, Davide Arcella, Daniele Court Marques, Jean-Lou Dorne, George EN Kass and Alicja Mortensen

Abstract

Following a request from the European Commission to EFSA, the EFSA Scientific Committee (SC) prepared a guidance for the risk assessment of substances present in food intended for infants below 16 weeks of age. In its approach to develop this guidance, the EFSA SC took into account, among others, (i) an exposure assessment based on infant formula as the only source of nutrition; (ii) knowledge of organ development in human infants, including the development of the gut, metabolic and excretory capacities, the brain and brain barriers, the immune system, the endocrine and reproductive systems; (iii) the overall toxicological profile of the substance identified through the standard toxicological tests, including critical effects; (iv) the relevance for the human infant of the neonatal experimental animal models used. The EFSA SC notes that during the period from birth up to 16 weeks, infants are expected to be exclusively fed on breast milk and/or infant formula. The EFSA SC views this period as the time where health-based guidance values for the general population do not apply without further considerations. High infant formula consumption per body weight is derived from 95th percentile consumption. The first weeks of life is the time of the highest relative consumption on a body weight basis. Therefore, when performing an exposure assessment, the EFSA SC proposes to use the high consumption value of 260 mL/kg bw per day. A decision tree approach is proposed that enables a risk assessment of substances present in food intended for infants below 16 weeks of age. The additional information needed when testing substances present in food for infants below 16 weeks of age and the approach to be taken for the risk assessment are on a case-by-case basis, depending on whether the substance is added intentionally to food and is systemically available.

Keywords: infants, neonates, ADI, health-based guidance values, development

Requestor: European Commission

Question number: EFSA-Q-2016-00489

Correspondence: SCER@efsa.europa.eu

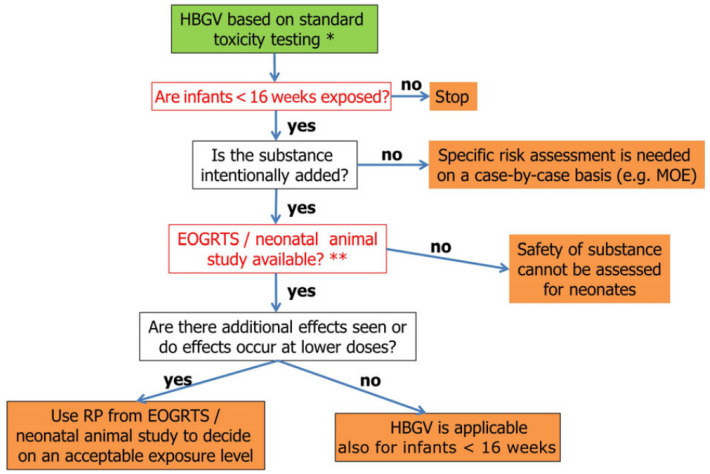


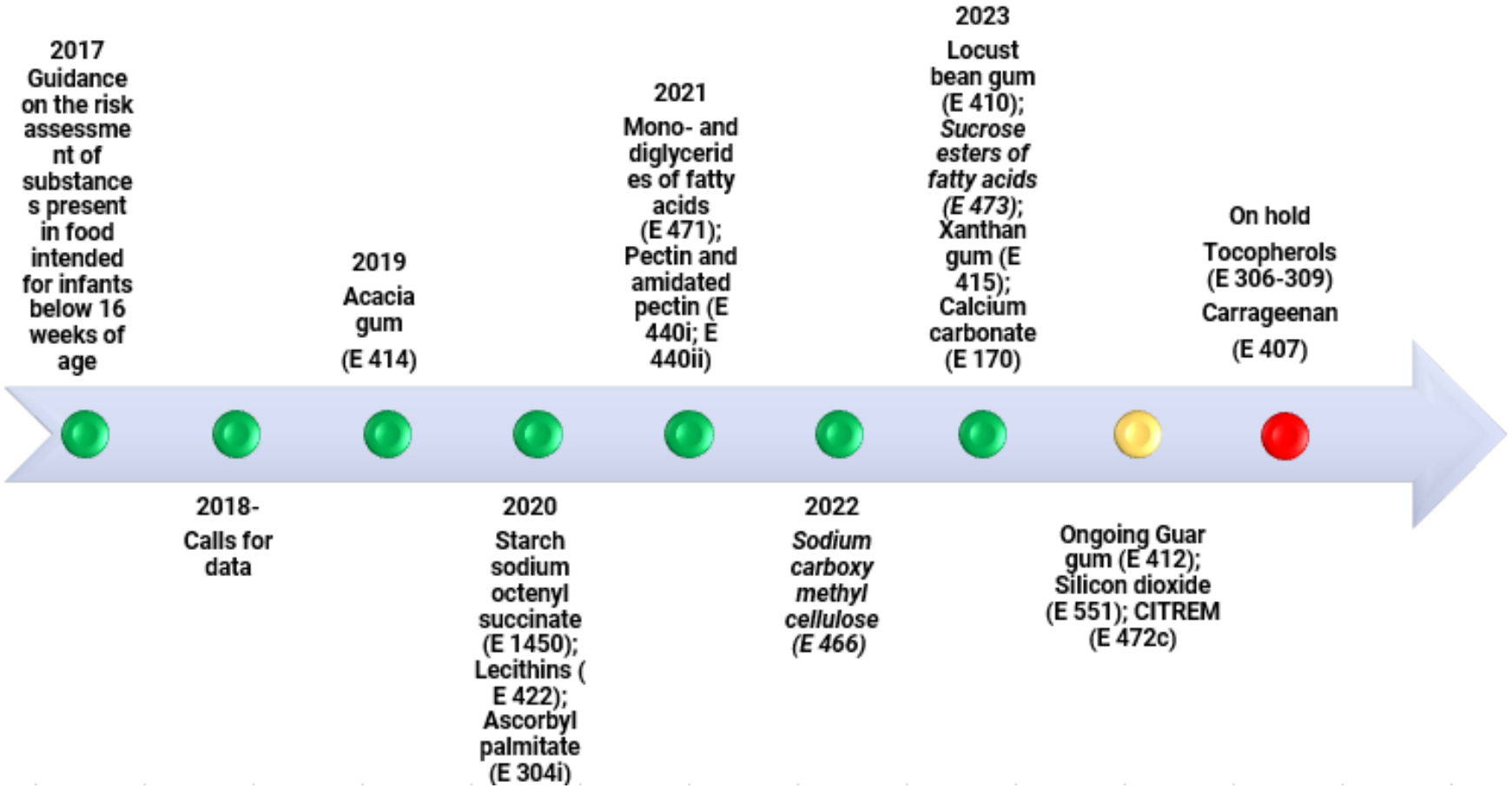
Figure 7: Decision tree approach for the risk assessment of substances present in food intended for infants below 16 weeks of age
RP: reference point
*: This decision tree assumes that a standard chemical risk assessment has already been performed on the substance of interest. Note that standard toxicity testing varies in the different areas within the remit of EFSA.
**: Extended one-generation reproductive toxicity study (EOGRTS) if the substance is systemically available, neonatal animal study if the substance is not absorbed from the gastrointestinal tract and is not systemically available. In case scientific justification is given, it is possible to deviate from the guidance given here (see Section 6).

Decision tree

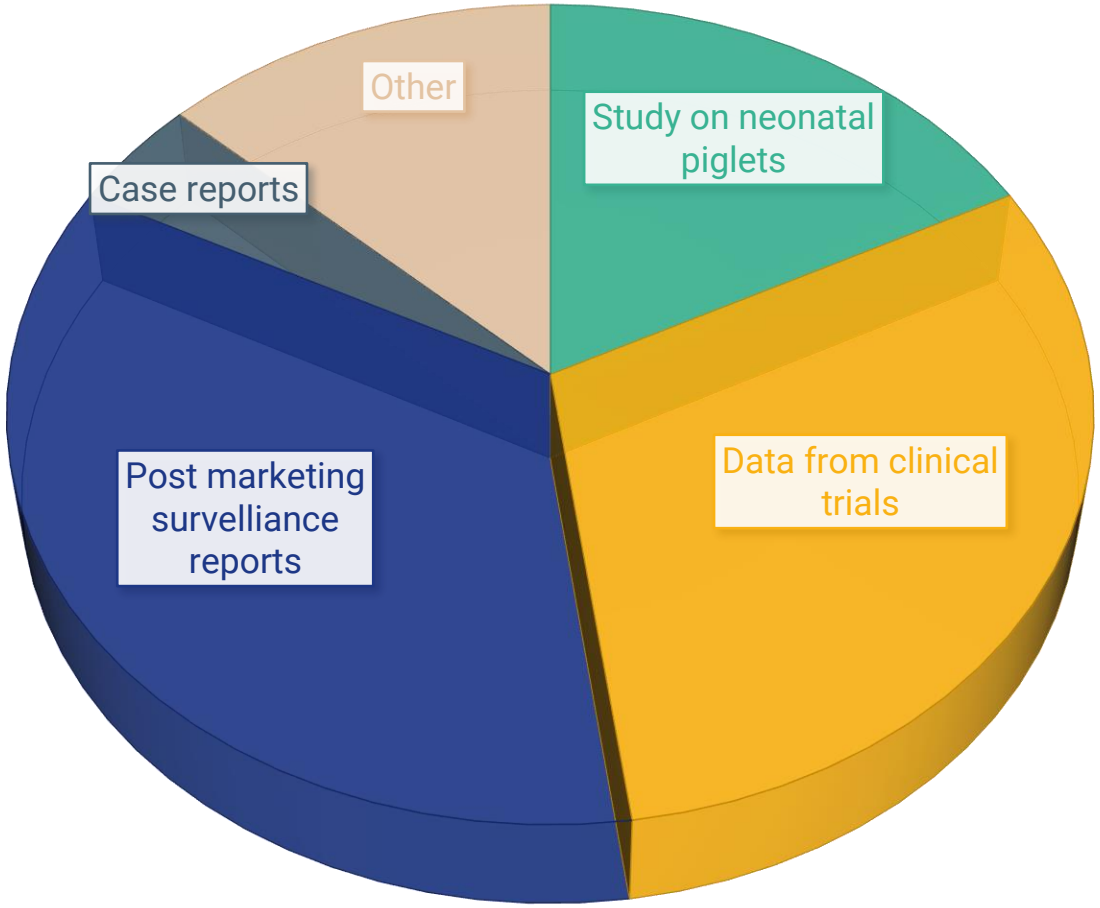
Exposure assessment

Taking into account all of the available information, the EFSA SC recommends values of 200 and 260 mL/kg bw per day as conservative mean and high level consumption values to be used for performing the risk assessments of substances which do not accumulate in the body present in food intended for infants below 16 weeks of age. These values are derived from data for infants aged 2–4 weeks, when formula consumption is highest, expressed on a body weight basis.

STATE OF PLAY



DATA CONSIDERED IN THE SAFETY ASSESSMENTS



- In most cases data from clinical trials were submitted along with post-marketing surveillance reports, these were considered as supportive in the assessment in most of the cases
- Neonatal studies on piglets were available for the gums and SSOS (E 1450)
- In some cases, a scientific justification based on literature data to address the safety assessment was provided

OUTCOME OF THE ASSESSMENTS

Food additive	Outcome
Acacia gum (E 414)	Concerning the risk assessment for infants below 16 weeks of age, the Panel concluded that there is **no reason for health concern** considering the large MOE of roughly 2,000 and 8,000.
Locust bean gum (E 410)	The Panel identified a reference point of 1,400 mg/kg bw per day based on reduced blood zinc levels in a piglet study and applied the MoE for the safety assessment. A MoE above 1 was obtained when the average typical use levels reported by the IBO were considered (mean and 95th percentile). However, when exposure estimates are based on the maximum permitted level or on **the maximum use level reported by the IBO (mean and 95thpercentile)** MoEs below 1 were obtained.
Pectin (E 440i) and amidated pectin (E 440ii)	The results of the adequate piglet study could serve to derive a reference point. When calculating the MOE for pectins exposure, this was below 1 for some scenarios. The Panel concluded that **an MOE below 1 is too low**. Under the current exposure estimates at the MPLs, an internal methanol exposure (in the range of methylation given for pectin (E 440i)) would result that could lead to adverse health effects in infants below 16 weeks of age.
Xanthan gum (E 415)	The results of the adequate piglet study could serve to derive a reference point. When calculating the MOE for infants<16 weeks of age consuming FSMP (FC 13.1.5.1) for the highest xanthan gum exposure, this was 2.4. The Panel concluded that the MOE **does not raise concerns**
Starch sodium octenyl succinate (E 1450)	The Panel concluded that **at use levels of SSOS in food for infants below 16 weeks within the range reported in the clinical studies** (up to 2,725 mg/kg bw per day), there is **no indication for safety concern.**

Conclusion based on the margin of exposure approach

Conclusion based on the outcome of the animals and clinical studies

OUTCOME OF THE ASSESSMENTS

Food additive	Outcome
Lecithins (E 322)	For the reason that choline is a precursor of the neurotransmitter acetylcholine, the Panel considered appropriate to address the safety of lecithins (E 322) in food for IYC by comparing the **concentration of choline in human milk with that in the formula**. The Panel concluded that the intake of lecithins (E 322) as a food additive in infant formula belonging to FC 13.1.1 or in food for special medical purposes belonging to FC13.1.5.1 does not raise safety concerns up to the MPL of lecithins (E 322
Mono-and diglycerides of fatty acids (E 471)	The Panel based its approach to assess the safety of mono and diglycerides of fatty acids (E 471) for infants below 16 weeks of age on a comparison of the daily intake of mono-and diacylglycerides (and the fatty acids released from them) **from human milk** and **from infant formula** containing E 471. After reviewing the available data, the Panel concluded that the exposures are in the same order of magnitude. Overall, the Panel concluded that there is no reason for a safety concern when E 471 is used as food additive in FC 13.1.1 and 13.1.5.1 and according to the Annex III to Regulation (EC) No 1333/2008.
Ascorbyl palmitate (E 304i)	Ascorbyl palmitate fully hydrolyses pre-systemically to ascorbic acid and palmitate, the Panel concluded that the intake of both metabolites, at the MPLs for ascorbyl palmitate as a food additive in FC 13.1.1 or 13.1.5.1 **does not raise safety concerns**
Calcium carbonate (E 170)	The Panel concluded that there is no need for a numerical acceptable daily intake (ADI) for calcium carbonate and that, in principle, there are no safety concern with respect to the exposure to calcium carbonate per se at the currently reported uses and use levels in all age groups of the population, including infants below 16 weeks of age. With respect to the calcium intake resulting from the use of E 170 in food for the general population and infants < 16 weeks of age, the Panel concluded that it contributes only to a small part to the overall calcium dietary exposure. However, the unavoidable presence of aluminium in E 170 is of concern and should be addressed.

Conclusion based on a scientific justification

OUTCOME OF THE ASSESSMENTS

Food additive	Outcome
Sucrose esters of fatty acids (E 473)	Not used in food for infants below 16 weeks of age according to the information received in the call for data and following EFSA request and no data received to address the safety for this population group
Sodium carboxy methyl cellulose (E 466)	Not used in food for infants below 16 weeks of age according to the information received in the call for data and following EFSA request and no data received to address the safety for this population group

Assessment not performed in the absence of uses and relevant data

TOXIC ELEMENTS

- FAs **may be susceptible to contamination by toxic elements**. Of general interest are lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As). Other elements such as aluminium (Al) may be of interest for some FAs.

- **The source of toxic elements** might be that the FA is produced from environmentally **contaminated plant materials**. Other **potential sources** are **reagents and processing aids** used for manufacturing and the **contact materials used**, from which there may be metal pick-up.

- **Health base guidance values and reference points** for substances of concern, including the toxic elements, have been established in **previous opinions by EFSA**.

RISK ASSESSMENT FOR TOXIC ELEMENTS - METHODOLOGY

The potential exposure to impurities from the use of a food additive was calculated by assuming that **the impurity is present in the food additive up to a certain value** and then by calculation pro-rata to the estimates of **exposure to the food additive itself**

Depending on the available data and EU specifications, for the risk assessment the FAF Panel considered:

- the **potential presence of toxic elements in the FAs** at:
  - (i) the maximum current limit in the EU specification, if available;
  - (ii) limits proposed by the IBO, if applicable
  - (iii) at specific values proposed by the FAF Panel considering the available analytical data
- and **the dietary exposure estimates** (highest mean and 95th percentile) for infants below 16 weeks of age (and for the general population)

RISK ASSESSMENT FOR TOXIC ELEMENTS - METHODOLOGY

The resulting exposure was compared with the reference points (RPs) or health-based guidance values (HBGVs) for Pb, Hg, Cd and As from CONTAM Panel opinions.

The risk assessment for toxic elements contained in FAs **triggered in all cases** a recommendation **to reduce** the maximum limits for toxic elements and/or **to complement** the EU specifications by adding limits for certain toxic elements

Impurity/constituent/ HBGV/RP (ug/kg bw)	Basis/Reference
Lead (Pb)/ 0.5 ($BMDL_{01}$)	The reference point is based on a study demonstrating perturbation of intellectual development in children with the critical response size of 1 point reduction in IQ. The EFSA CONTAM Panel mentioned that a 1 point reduction in IQ is related to a 4.5% increase in the risk of failure to graduate from high school and that a 1 point reduction in IQ in children can be associated with a decrease of later productivity of about 2%. A risk cannot be excluded if the exposure exceeds the $BMDL_{01}$ (MOE lower than 1). EFSA CONTAM Panel (2010)
Mercury (Hg)/ 4 (TWI)	The HBGV was set using kidney weight changes in male rats as the pivotal effect. Based on the $BMDL_{10}$ of 0.06 mg/kg bw per day, expressed as mercury, and an uncertainty factor of 100 to account for inter and intra species differences, with conversion to a weekly basis and rounding to one significant figure, a TWI for inorganic mercury of 4 µg/kg bw per week, expressed as mercury was established. EFSA CONTAM Panel (2012)
Cadmium (Cd)/ 2.5 (TWI)	The derivation of the reference point is based on a meta-analysis to evaluate the dose-response relationship between selected urinary cadmium and urinary beta-2-microglobulin as the biomarker of tubular damage recognised as the most useful biomarker in relation to tubular effects. A group-based $BMDL_5$ of 4 µg Cd/g creatinine for humans was derived. A chemical specific adjustment factor of 3.9 was applied to account for human variability in urinary cadmium within each dose-subgroup in the analysis resulting in a reference point of 1.0 µg Cd per g creatinine. In order to remain below 1 µg Cd/g creatinine in urine in 95 % of the population by age 50, the average daily dietary cadmium intake should not exceed 0.36 µg Cd/kg bw, corresponding to a weekly dietary intake of 2.5 µg Cd/kg bw. EFSA CONTAM Panel (2009a)
Arsenic (As)/ 0.3-8 ($BMDL_{01}$)	The reference point is based on a range of benchmark dose lower confidence limit and 8 µg/kg bw per day identified for cancers of the ll as skin lesions. In general, the MOE should be at point is based on carcinogenicity in animal studies. is derived from human studies, an interspecies is not needed, i.e. a MOE of 1,000 would be sufficient. EFSA CONTAM Panel (2009b); EFSA Scientific Committee (2012)

Revised in 2024

HBGV: health-based guidance value; RP: reference point; $BMDL_{01}$: benchmark dose (lower confidence limit); bw: body weight; TWI: Tolerable Weekly Intake; MOE: margin of exposure.

OTHER ASPECTS CONSIDERED

Depending on the manufacturing process in some cases **additional impurities of toxicological concern** were assessed (e.g. 3-MCPD and 3-MCPD-esters, glycidyl esters, trans-fatty acids and erucic acid, residual solvents)

Additionally, for FAs of botanical origin and/or the polysaccharidic nature the assessment addressed also **the microbiological contamination** (*Salmonella* spp. and *Escherichia coli; Cronobacter* (Enterobacter) *sakazakii*; total aerobic microbial count (TAMC) and total combined yeast and mould count (TYMC)).

Other aspects considered were the potential presence of **residual proteins and the characterisation of the microorganisms** used in the production of the food additive (i.e. in the case of xanthan gum (E 415)

CONCLUSIONS

With some exceptions, the FAF Panel **did not identify health concerns for the assessed food additives** used in food for infants below 16 weeks of age

It has to be noted, however, that the **performed assessments were assessing the single FA whereas some infant formulae contain more than one single FA**

The risk assessment for **toxic elements contained in FAs triggered in all cases** a recommendation **to reduce the maximum limits** for toxic elements and/or **to complement** the EU specifications by **adding limits for certain toxic elements**

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