

Safety assessment of additives and ingredients for infants and young children

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Abstract At the request of the European Commission (EC), the European Food Safety Authority (EFSA) will re-evaluate all food additives currently approved for infants and young children. EFSA has subsequently published guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age, which details exposure assessment principles and a decision tree approach to risk assessment. A key consideration for the toxicological risk assessment is systemic availability, which for many additives and ingredients may result in expensive and lengthy reproductive and developmental toxicity studies being requested. Exposure assessment becomes more complex for young children (compared with infants) due to an increasingly varied diet, who can have particularly high intakes of specific foods. Experienced scientific judgement is crucial to ensure all aspects of this safety assessment are considered for new and existing food additives and ingredients.

INTRODUCTION

Food ingredients and additives for infants (up to 1 year) and young children (1 to 3 years) require special considerations for their safety assessment. Because risk = hazard x exposure, both must be assessed in this context. Recently the European Food Safety Authority (EFSA) has been mandated by the European Commission (EC) to re-evaluate the safety of specific food additives which are currently, or had been previously, permitted in foods intended for this age group, which will be reviewed in this article.

This review will cover five key areas. First, we will look at the mandates given by the EC to EFSA in relation to the specific re-evaluation of food additives (as well as contact materials, pesticides and contaminants) in foods for these age groups. Second, we will provide an overview of the first stage of the EFSA process – the publication of guidelines for assessing safety for infants less than 16 weeks of age. Third, we will briefly discuss how this new approach may be extrapolated to nutritional/physiological ingredients being developed and requiring approval (such as novel food ingredients). Following this, other considerations in relation to the risk assessment of ingredients for older infants and young children, mainly related to exposure assessment, will be reviewed. Finally, we will summarise the potential implications for the food industry as EFSA progresses through its re-evaluation program for food additives.

EUROPEAN COMMISSION MANDATES TO EFSA

In November 2014, as a potential result of a new Commission and concerns of the EU member states related to additives to be used in supplements intended for infants and young

children, the EC mandated EFSA to re-evaluate those additives currently approved in infant formula, follow-on formula and baby foods. In addition, EFSA was requested to evaluate those additives that had previously been approved in food supplements for these age groups (1).

In its response, EFSA stated that the process would proceed in two stages (2):

1. To re-evaluate the scientific principles of the age threshold and what additional data should be required when assessing safety for this age group – which would be completed by the Scientific Committee of EFSA, its top-level "umbrella" committee. [EFSA had been discussing the threshold for when the normal Acceptable Daily Intake (ADI) applies, which had previously been established at 12 weeks of age by EFSA's predecessor, the Scientific Committee on Food (SCF), and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)]; and
2. The re-assessment of additives currently permitted in the foods intended for infants and young children, followed by those proposed for use in supplements – which would be conducted by EFSA's Scientific Panel on Food Additives and Nutrient Sources Added to Food (ANS).

The EFSA response indicated that the process would be completed by the end of 2019.

In 2016, the original mandate was widened to include pesticide residues, contaminants and food contact material migration. At this stage, the previous age threshold (of 12 weeks) was changed to 16 weeks. EFSA agreed to combine and expand the remit of the request, at least the first stage – the establishment of safety assessment guidance for infants less than 16 weeks (3).

EFSA SCIENTIFIC COMMITTEE GUIDELINES FOR INFANTS UP TO 16 WEEKS OF AGE

Following public consultation, the EFSA Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age was published in the EFSA journal on 31 May 2017 (4). The structure of the guidance broadly covers (a) exposure assessment principles, (b) consideration of the developmental status of the organ systems and (c) the existing toxicity profile of the substances, and suitable animal models that may be more representative for safety studies.

With regard to the exposure assessment component of this guidance, the EFSA Scientific Committee identified a high consumption level of 260 mL/kg body weight/day (from available literature on consumption patterns of breast milk and/or infant formula by young infants). Consequently, when assessing the safety of a substance to be used in foods intended for infants below 16 weeks of age, exposure is determined by multiplying this value by the maximum approved or proposed concentration.

In terms of toxicity testing, the guidance "leads-off" existing guidance established by EFSA in 2012 for the assessment of food additives for the general population (5), which describes a tiered approach (3 Tier system; see Figure 1). The basic battery of toxicology tests required at Tier 1 comprises an *in vitro* assessment of the absorption, distribution, metabolism and excretion (ADME) properties to ascertain whether the compound and/or its metabolites are absorbed from the GI tract and thus "systemically available". Additionally, 3 studies are required at this tier:

- *in vitro* genotoxicity assessment
 - the bacterial reverse mutation test (OECD 471) (6) covering gene mutations; and
 - the *in vitro* mammalian cell micronucleus test (OECD 487) (7) covering chromosome aberrations;
- subchronic toxicity assessment [a 90-day toxicity study performed in rodents (OECD 408) (8), modified to include assessment of endocrine-related parameters].

If the additive is *not* systemically available, is non-genotoxic and shows no evidence of subchronic toxicity in rodents, testing can stop at Tier 1 (with close scrutiny of local effects on the gastrointestinal system in the 90-day study). Progression to subsequent tiers is dependent on specific effects seen in the first tier (see Figure 1).

The new guidance assumes that Tier 1 studies have already been conducted and looks specifically at the immature gut of infants below 16 weeks of age to determine what additional considerations are required. The decision tree is presented in Figure 2.

Essentially, it specifies that if a substance is systemically available (absorbable), an Extended One-Generational Reproductive Toxicity Study (EOGRTS) (OECD 443) (9) is required. This is an expensive and lengthy undertaking. If the additive is demonstrated to be non-absorbable, only a subchronic toxicity study performed in neonatal (young infant) animals is required. Piglet models are mentioned in the guidance as potential models, due to the similarities shared with humans (especially in the gastrointestinal tract).

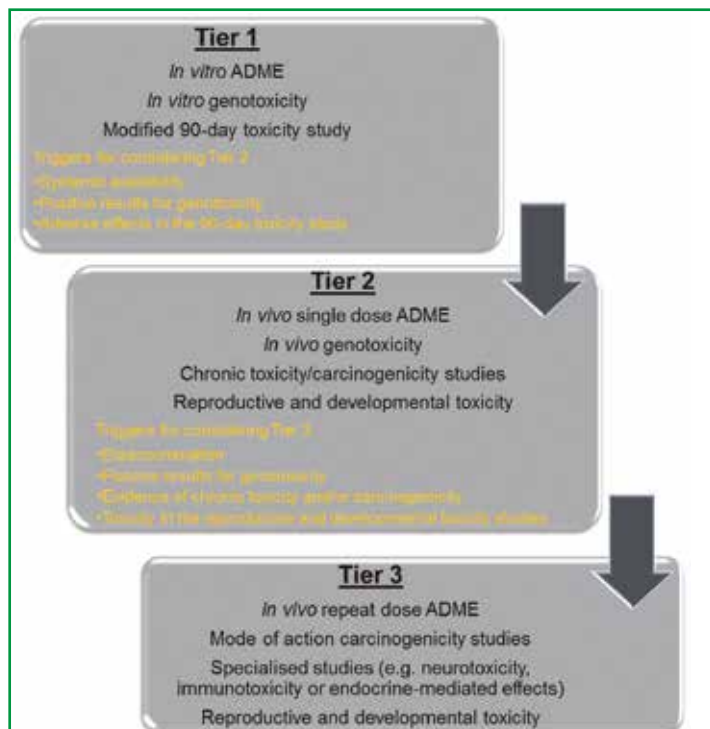


Figure 1. The tiered approach for food additive safety assessment for the general population - Adapted from EFSA (5).

However, there are limitations with using large animals rather than rodents (such as smaller group sizes and less background data); therefore, species selection should be carefully considered on a case-by-case basis.

Recent EFSA Scientific Opinions provide an insight into potential implications for industry. In a recent Scientific Opinion for mixed tocopherols (E 306 to E 309), it was concluded that the re-evaluation was not applicable to infants under 12 weeks of age and that there were insufficient data to address reproductive and developmental toxicity endpoints (10). As a systemically available group of additives, there is the potential for an EOGRTS study to be requested in order to assess their safety for use in foods intended for infants under 16 weeks of age. However, in this case, given their structural similarities with vitamin E (which is widely approved for all age groups), it may be possible to prepare a scientific argument based on safe history of consumption.

One of the few (or even only) additives currently approved for infants which is confirmed as non-absorbable is guar gum (E 412). A recent EFSA Opinion on the general food additive re-evaluation of guar gum stated that "for uses of guar gum in foods intended for infants and young children the occurrence of abdominal discomfort should be monitored and if this effect is observed doses should be identified as a basis for further risk assessment" (11). The Panel concluded that in the absence

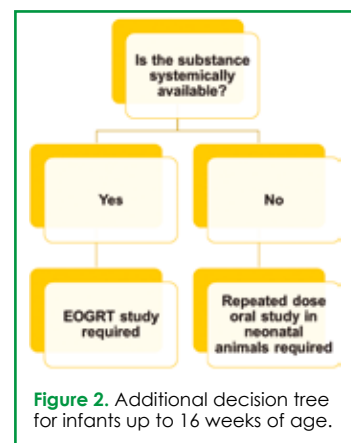


Figure 2. Additional decision tree for infants up to 16 weeks of age.

of adequate specific studies, it was not possible to assess the safety of use of this additive in food categories intended for special medical purposes for infants and young children. The implication here is that EFSA is looking for a tolerability study in neonatal animals to be able to extend its conclusions on safety to infants less than 16 weeks of age.

EXTRAPOLATION OF ADDITIVES GUIDANCE TO NOVEL FOOD INGREDIENTS

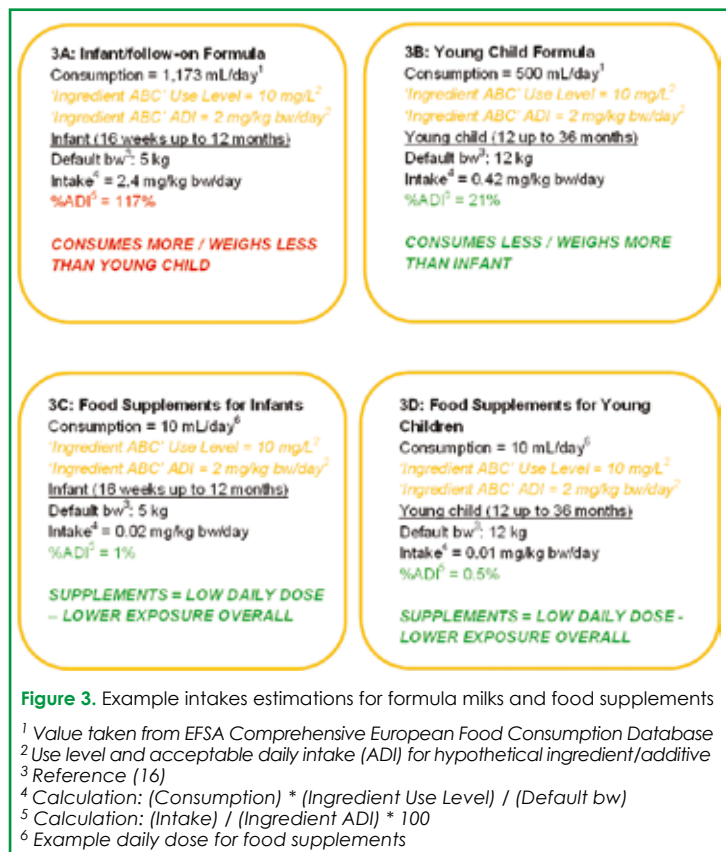
Importantly, within the new guideline, EFSA states that the main principles of the toxicological requirements can be read-across (on a case-by case basis) to all types of ingredients and contaminants in foods for this age group; the guidance does reflect current practice for novel foods for infant formula.

A very recent example of a Scientific Opinion published for an absorbable ingredient is synthetic N-acetyl-D-neuraminic acid (NANA) as a novel food (12), primarily for use in infant formula and follow-on formula. The basis of safety included the following statement "an oral toxicity study in rats with the NF, which consisted of an initial in utero and lactational phase that was followed by a subchronic 90-day oral toxicity study in the first generation offspring". This study is not a replacement for the EOGRTS; however, reproductive and developmental toxicity endpoints were assessed as part of this modified 90-day study. It should be noted that although NANA is systemically absorbed, it is naturally present in human milk (i.e. there is a history of safe consumption) and it is largely excreted unchanged in urine, which may have contributed to the decision that Tier 2 reproductive and developmental toxicity studies were not required. This demonstrates that it is possible to deviate from the guidance, provided there is a robust scientific justification.

An example of a Scientific Opinion published for a non-absorbable ingredient is the EFSA Scientific Opinion on the safety of 2'-O-fucosyllactose (a human milk-identical oligosaccharide) as a novel food ingredient (13). The subchronic 90-day study cited in this Opinion was an adapted OECD 408 study (8) conducted with neonatal rats (rather than the standard OECD 408 approach using weaned rats), which essentially followed EFSA's guidance for infants under 16 weeks of age described above.

RISK ASSESSMENT OF INGREDIENTS FOR OLDER INFANTS AND YOUNG CHILDREN - EXPOSURE ASSESSMENT

At its most basic level, exposure to a substance of interest is calculated based on the consumption of the foods/beverages containing the substance multiplied by the level of the substance in those foods/beverages. Infants and young children are typically noted to have the highest exposure level of all age groups in a population due to their relatively higher consumption on a body weight basis. Figure 3 shows the calculation of exposure (expressed on a body weight basis and as a percent of the ADI) for a hypothetical ingredient ('Ingredient ABC'), which is intended to be used at a single use level (10 mg/L) in 4 different food types (i.e., infant/follow-on and young child formulae, and food supplements for infants and young children). The calculations demonstrate that exposure is affected by (1) the volume of the 'food' being consumed, and (2) the body weight of the individual. For



example, infants (aged 16 weeks to 12 months) consuming ~1 litre of infant/follow-on formula may be more likely to exceed the toxicological threshold of concern than young children (12 to 36 months) consuming formula due to a lower body weight (5 kg versus 12 kg) and a higher level of consumption (1,173 mL/day versus 500 mL/day), see Figures 3A and 3B. In contrast, ingredients used in food supplements will generally have a much lower level of intake than those used in formula, due to the smaller dose of the supplement consumed (~10 mL/day), see Figures 3C and 3D.

While the EFSA guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age (4), provided a simplistic approach for assessing high exposure in infants up to 16 weeks of age, this is not necessarily appropriate for older infants and young children (i.e. 16 weeks to 3 years), as this age group have typically commenced weaning, and may therefore be exposed to a greater variety of sources of the substance. Furthermore, this is a cohort associated with unique consumption patterns, such as pickiness and food neophobia, which may lead to higher consumption of particular foods and beverages. In light of these considerations, it is necessary to conduct a more comprehensive assessment of intake for older infants and young children, which considers the total diet.

To this end, there are a variety of resources available to industry to determine potential dietary exposure. For example, the EFSA Food Additive and Ingredients Model (FAIM) template (14) and the EFSA Comprehensive European Food Consumption Database (15), as well as default body weights for different age groups (specifically 5 kg for infants and 12 kg for toddlers) (16), are available. These resources are useful as they allow a simplistic, top-line review of potential exposure to be performed.

However, they can result in large overestimations of exposure, which may indicate safety issues where none exist. Depending on the results from these simplistic tools, it is often necessary to use more sophisticated datasets which are based on actual food consumption patterns by individuals, such as the UK Diet and Nutrition Survey of Infants and Young children (UK DNSIYC) and French Individual and National Food Consumption Survey (INCA) survey data. It is important to obtain the most accurate exposure levels to consider potential future use of the ingredient.

In short, from an exposure assessment perspective, the main considerations are (a) the specific uses and use levels of the ingredient/additive and (b) the characteristics (consumption patterns and body weight) of the target population. There are various resources available, the use of which should be considered carefully.

IMPLICATIONS FOR INDUSTRY

Having considered the detailed review above, the implications for the food industry are quite evident. It is necessary to consider the totality of the evidence available for the substances to evaluate whether they meet the requirements of EFSA's guidance. If there are any "gaps", it is essential that these can be filled, or that a robust scientific argument is developed to negate their need. In practical terms, it is quite likely that EFSA will be resistant to deviation from the guidance, which will result in new studies being requested, likely funded by groups of companies and requests to EFSA for interim measures while these tests are conducted, without threatening the integrity and stability of the food products by hasty withdrawals. Beyond toxicology testing, exposure assessments are complex for weaning infants and young children, where the total diet must be considered. Overall, theoretical study protocols, web tools and databases are a valuable starting point; however, experienced scientific judgement is essential to ensure the interests of the company are protected, and most importantly, that the safety of this critical age group is protected.

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About the author

Nigel Baldwin is a recognised scientific and regulatory expert with more than 20 years' experience in the area of food and feed additives, novel foods, food enzymes, functional foods, infant formula, health claims and supplements. He has worked on over 30 successful regulatory approvals. Nigel is the Director of the European office at Intertek, where the team includes Danika Martyn, a recognised international expert in food intakes and toxicologist Kirt Phipps.

