Flavourings in baby food

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The German Federal Institute for Risk Assessment (BfR) has addressed the use of flavourings in infant formula and follow-on formula, as well as in formula for special medical purposes intended for infants and young children.

The BfR considers the addition of flavourings as unnecessary to improve the acceptance of these products or to promote the child's sense of taste. If infants were fed on infant formula or a formula for special medical purposes during the first three months of life, problems with acceptance are not typically encountered. If, however, formula feeding starts later—for medical reasons, for example—then acceptance could usually be improved by repeated feeding attempts. Since infant formula is a standardised product, the addition of flavourings cannot provide the variety of flavours offered to infants fed on breast milk. According to the present knowledge, flavoured infant formula is therefore unable to match the ability of breast milk to promote the development of an infant's sense of taste and smell.

Infants are especially vulnerable during their first months of life: the body's detoxification mechanisms such as the liver and kidney functions are not fully developed, nor are other protective mechanisms such as the blood-brain barrier. International expert committees therefore strongly advise against the application of ADI values derived for food additives for infants up to an age of 12 or 16 weeks without obtaining supplementary verification. ADI stands for 'acceptable daily intake' and specifies the quantity of a substance that, expressed in relation to body weight, can be consumed daily over a person's lifetime without adverse health effects being expected.

The BfR is of the opinion that the rationale for assessing the use of food additives in infant formula should also be applied to the use of flavourings in these foods. The BfR, therefore, considers that flavouring substances should generally not be used in infant formula products or formula for special medical purposes intended for consumption by infants in the first four months of life. Should such a use nonetheless be considered necessary in exceptional circumstances, this would require a case-by-case evaluation—in the same way as for food additives.
There is some evidence that sensory experiences during infancy can influence the development of the sense of taste and therefore have an effect on food preferences later in life. However, the available data are not sufficient to enable an assessment of the consequences of using flavourings in infant formula on later eating habits and associated health risks.

1 Subject of the assessment

In an expert opinion submitted to the German Federal Institute for Risk Assessment (BfR), the European Association of Producers of Food for Special Dietary Purposes, Specialised Nutrition Europe (SNE, pre-2013 IDACE), considered that flavourings should be permitted in foods for infants and young children in general, and especially in foods for special medical purposes for infants and young children. Their usage, it was argued, would ensure the acceptance of such foods by infants and young children while promoting the development of the senses of taste and smell in early childhood.

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In accordance with Implementing Regulation (EU) No 872/2012[1] of 1 October 2012, flavouring substances[2] included in the 'Union list'[3] of flavourings and source materials may be used in Member States of the EU unless special restrictions have been specified.

Recital 27 of this Regulation states that the use of flavourings and source materials in dietary foods for infants will be harmonised in the future in the framework of specific rules to be adopted, and that, until this time, Member States can apply national provisions in this matter that are stricter than those named in the list of flavouring substances pursuant to article 2(2) of Regulation (EC) No 2232/96.

Similarly, article 9 of Regulation (EU) 872/2012 states that "*Member States may apply national provisions which are more restrictive than Part A of the Union list as regards the use of flavouring substances in infant formulae, follow-on formulae, processed cereal-based foods and baby foods and dietary foods for special medical purposes intended for infants and young children as referred to in Directive 2009/39/EC. Those national measures must be essential to ensure that consumers are adequately protected and must be proportionate to the attainment of that objective.*"

In the *Codex Alimentarius*, the Standard for infant formula and formulas for special medical purposes intended for infants[4] stipulates that foods in these two product categories may contain only those additives as listed in the standard itself or in the *Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses intended for Infants and Young Children*[5]. Moreover, the Codex standard for processed cereal-based foods for infants and young children[6] (CODEX STAN 074-1981; Rev. 1-2006) permits the use of natural fruit extracts, vanilla extract (in accordance with good manufacturing practice, GMP) and ethyl vanillin in concentrations no greater than 7 mg/100 g of the ready-to-eat product.

According to a consensus paper published by the German network 'Gesund ins Leben – Netzwerk Junge Familie', which represents medical societies, and professional associations and institutions with expertise in the field of infant and young child nutrition, the addition of salt and a strong sweet flavour should be avoided when choosing foods for infants from the age of complementary feeding onwards (Koletzko et al., 2016).

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[1] COMMISSION IMPLEMENTING REGULATION (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC (https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:267:0001:0161:EN:PDF; last accessed 13 October 2020).

[2] Definition of the term 'flavouring substance' (REGULATION (EC) No 1334/2008): defined chemical substance with flavouring properties (https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:354:0034:0050:EN:PDF; last accessed: 13 October 2020).

[3] The Union list is based on the provisions of Regulation (EC) No 2232/96, which envisages a positive list of flavouring substances that have been reported by Member States and which have passed through a special evaluation procedure.

[4] STANDARD FOR INFANT FORMULA AND FORMULAS FOR SPECIAL MEDICAL PURPOSES INTENDED FOR INFANTS (CODEX STAN 72 – 1981, Rev. 2007) (http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXS%2B72-1981%252FCXS_072e.pdf; last accessed: 13 October 2020).

[5] Advisory Lists of Nutrient Compounds for the Use in Foods for Special Dietary Uses intended for Infants and Young Children (CAC/GL 10-1979; Adopted in 1979. Amendment: 1983, 1991, 2009 and 2015; Revision: 2008) (file:///C:/Temp/CXG_010e_2015.pdf; last accessed: 13 October 2020).

[6] CODEX STANDARD FOR PROCESSED CEREAL-BASED FOODS FOR INFANTS AND YOUNG CHILDREN (CODEX STAN 74-1981; Rev. 1-2006) (file:///C:/Temp/cxs_074e%20(1).pdf; last accessed: 13 October 2020).

In light of this, the BfR has considered the use of flavouring substances[7] in infant formula and follow-on formula as well as in formulas for special medical purposes intended for infants and young children from a risk assessment perspective.

2 Results

The BfR sees no benefit in the use of flavouring substances in infant and follow-on formula, neither in terms of improving acceptance of taste nor in promoting the development of the sense of taste.

Unlike breastmilk, whose taste varies according to the nutritional circumstances of the child's mother, industrially produced infant formula is clearly a product with a standardised taste that, even with the addition of specific flavourings, cannot offer the variety of tastes experienced by a breastfeeding infant. The BfR therefore considers it especially important that infants are breastfed in the first months of life and that breastfeeding mothers enjoy a varied diet.

The results from relevant studies indicate that hydrolysed infant formula, which generally taste slightly bitter, are also well accepted by infants if feeding with these food products begins during the first three months of life. However, problems with acceptance can be encountered if indications for the use of an extensively hydrolysed formula are determined only after this age.

There are indications that various sensory qualities of infant formula can influence the development of the child's sense of taste and therefore have an effect on food preferences later in life. However, the data available are not sufficient for estimating the long-term effects of taste experiences in early childhood on eating habits and health (overweight and associated complications).

Infants are especially vulnerable during their first months of life. Accordingly, the FAO/WHO Expert Committee on Food Additives (JECFA) and the former European Commission Scientific Committee on Food (SCF) have stressed that ADI values for food additives should not be considered applicable for infants up to the age of 12 weeks. The European Food Safety Authority (EFSA) considers the first 16 weeks of life as a phase during which health-based guidance values should not be applied unconditionally, and justifies this with specific physiological and developmental/nutritional aspects (EFSA 2017).

The BfR is of the opinion that the arguments presented for food additives should also be applied to flavouring substances. The BfR therefore does not recommend the use of any flavouring substances in infant formula products or formula for special medical purposes intended for consumption by infants in the first 16 weeks of life. If such a use is considered necessary in exceptional circumstances, it should be assessed on a case-by-case basis—in the same way as for additives.

3 Rationale

[7] A 'flavouring substance' as defined by article 3(2) b) of Regulation (EC) No 1334/2008 is a defined chemical substance with flavouring properties (https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:354:0034:0050:EN:PDF; last accessed: 13 October 2020).

3.1 Terminology used (as defined by Regulation (EU) No 609/2013[8]):

Infants	Children under the age of 12 months.
Young children	Children aged between 1 and 3 years.
Infant formula	Food intended for use by infants during the first months of life and satisfying by itself the nutritional requirements of such infants until the introduction of appropriate complementary feeding; infant formula is also suitable after the introduction of complementary feeding (from the 5th or 7th month) until the end of the first year of life.
Follow-on formula	Food intended for use by infants when appropriate complementary feeding is introduced and which constitutes the principal liquid element in a progressively diversified diet for such infants.
Food for special medical purposes	Food specially processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision. Such a food is intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients contained therein, or metabolites, or to feed patients with other medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet.
Baby food	Food excluding milk that is intended for the feeding of infants while they are being weaned, and for the feeding of infants and young children during their progressive adaptation to ordinary food.

[8] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32013R0609; last accessed: 13 October 2020).

3.2 Necessity and benefit of the use of flavouring substances in infant formula and follow-on formula, and in formula for special medical purposes for infants and young children

According to an FAO/WHO Meeting Report released in 1971, which formed the basis for a statement from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for the use of additives in infant formula, flavouring substances and flavour enhancers are not necessary in infant formulas (WHO, 1972).

The benefits of using flavouring substances in infant formula, follow-on formula and formula for special medical purposes for infants and young children to improve acceptance is discussed separately in the following section for the respective target groups and product groups, on the basis of the current scientific literature.

For healthy infants who are not (or cannot be) breastfed, infant formula is available that is manufactured on the basis of cow's milk, goat's milk or soy protein. For infants at increased risk of developing allergies, infant formula containing partially hydrolysed protein (hypoallergenic formula, HA formula) are offered.

Follow-on formula, which is suitable for infants only after complementary feeding has started, is also manufactured on the basis of cow's or goat's milk, or soy protein.

Both infant and follow-on formula are covered by the scope of Regulation (EU) No 609/2013[8]. For foods in this category, Article 15 of this Regulation states that any substances added must be included in the 'Union list' in the Annex to this Regulation. Specific compositional requirements for infant formula and follow-on formula are set out in the Commission Delegated Regulation (EU) 2016/127.

The BfR responds as follows to the statement from the European Association of Producers of Food for Special Dietary Uses that flavourings are necessary for the acceptance of infant formula and follow-on formula (IDACE, 2010):

Breastmilk has a highly individual and predominantly sweet taste, and contains a wide variety of natural flavourings from the mother's own diet that allows the breastfed infant to experience a broad spectrum of flavours. In contrast, infant formula has a taste that, while specific to its composition and the manufacturing process, is nonetheless unvarying. Accordingly, cow's milk based formulae taste slightly sweet, sour or 'cereal-like', while soy-based formulae feature a combination of sweet, sour and bitter, and hydrolysed formulae both taste and smell sour or bitter (Cook and Sarett, 1982 cited in: Mennella and Ventura, 2011).

When using standard infant formula or follow-on formula, the BfR does not see any reason to assume that there would be problems with acceptance of the infant being fed. The BfR has seen no data in support of this argument.

One might imagine that infants who have been breastfed since birth would react with distaste to a sudden (necessary) change to or supplement of industrially produced infant formula. However, since it is not normally necessary for breastfed infants to receive infant formula as a supplementary food, or to change the infant's diet from breastmilk to formula at a certain point in time, acceptance problems can be most easily avoided by breastfeeding exclusively for the first four months of life and continuing to breastfeed while complementary feeding is introduced.

If atypical circumstances should require additional or exclusive feeding with industrially produced infant formula, acceptance could be improved if necessary by repeated attempts at feeding with formula or by mixing the formula with breastmilk.

3.2.1 Use of flavouring substances in foods for special medical purposes for infants

Special types of formula based on extensively hydrolysed proteins (whey protein, casein or a mixture of the two) or amino acid mixtures are required for the nourishment of infants with diseases or disorders, including those with a confirmed cow's milk protein allergy, a severe malabsorption syndrome or congenital metabolic disorders such as phenylketonuria (PKU). These formulae are categorised as foods for special medical purposes and must also conform to Regulation (EU) No 609/2013[8]. Specific requirements for the composition of these foods are set out in the Commission Delegated Regulation (EU) 2016/128 on foods for special medical purposes.

Depending on the degree of hydrolysis, hydrolysed infant formula contain oligopeptides and/or amino acids, and have a pronounced bitter and/or sour taste plus an unappealing odour for persons previously unacquainted with these foods (Cook and Sarett, 1982, cited in: Mennella and Ventura, 2011). For infants with medical indications that require them to be fed on hydrolysed infant formula, good acceptance of these foods is absolutely vital.

Evidence has been presented that ascribes a genetic component to the perception of bitter flavours (e.g. El-Sohemy et al., 2007; Kim and Drayna, 2004). In infants, however, the sensory system is not yet fully developed. Therefore, infants differ from adults in their perception of taste (as they also do in the case of other kinds of sensory input) (Mennella, 1999; Mennella et al., 2005a). Schwartz et al. (2009) report that infants aged 3, 6 and 12 months displayed signs of distaste when they encountered a bitter flavour (in the form of urea dissolved in mineral water). At the age of 3 and 12 months, however, this did not lead to a reduced volume of fluid intake in comparison with plain water. When presented with a sour flavour (citric acid dissolved in mineral water) the infants participating in that study responded with a reduced volume of fluid intake only at the age of 3 months, although the overall response in all age groups did indicate a rejection of the sour taste.

In light of the multitude of chemical compounds with a bitter flavour that are perceived by roughly 30 bitter taste receptors (Meyerhof, 2005b), conclusions about the acceptance or rejection of one specific bitter substance cannot be drawn for other substances without further data. Nor can conclusions about the acceptance of a complete food be drawn based on the reaction to an individual substance. Differences between individuals (Schwartz et al., 2009) as well as a potential modification of the taste response by repeated stimulation must also be taken into account (Birch, 1998b; Scaglioni et al., 2008; Mennella and Beauchamp, 1996b; Myers and Sclafani, 2006).

In epidemiological studies that investigated extensively hydrolysed infant formula products, good levels of acceptance by infants were observed in cases where feeding began in the first three months of life (e.g. Mennella and Beauchamp, 1996a; Liem and Mennella, 2002; Mennella et al., 2004; Mennella et al., 2003; Mennella et al., 2011). In one study, Mennella and Beauchamp (2005b) compared the acceptance of two differently hydrolysed formulae in infants aged between 5 and 11 months. The authors found that infants who had previously been fed exclusively with infant formula based on cow's milk rejected the hydrolysed formula, while those infants who had already been fed with hydrolysed formula in the past did not exhibit any problems with acceptance. In the latter group, it was also observed that the hydrolysate formula the infants had received previously was the preferred product, since they had

become accustomed to it. This indicates that a specific taste preference develops in dependence on a taste profile that has been experienced previously. Mennella et al. (2011) also observed that hydrolysed infant formula was initially less well-accepted by infants aged 1.5 and 3.5 months if these infants had no prior experience of this product. Once feeding with the formula commenced, however, infants in both groups were observed to become accustomed to the taste within one month. This acceptance was more pronounced and long-lasting in the younger age group. While infants first confronted with hydrolysed formula at 3,5 months of age did become accustomed to the taste, this group subsequently exhibited lower levels of acceptance at 7.5 months than infants who had first been exposed to the formula when aged 1.5 months. The authors also observed that the best acceptance for hydrolysed formula at 7.5 months was seen in those infants who had received the formula during their first 7 months of life (Mennella et al., 2003; Mennella et al., 2011).

A subsequent study by Owada et al. (2000), conducted in a group of 88 children whose ages ranged from under 18 months to 17 years and with roughly half the group (54.5%) having phenylketonuria (PKU), investigated the acceptance of a formula based on a conventional amino acid mixture compared with a better-tasting new product for phenylketonuria (PKU) patients. In children aged under 18 months, 91 percent of children with PKU and 67 percent of healthy children showed no clear dislike or preference for either product. In children aged between 18 months and 11 years, 67 percent of children with PKU and only 5 percent of healthy children exhibited a preference for one of the two foods, with 29 percent of children with PKU in fact preferring the conventional amino acid mixture to the new product. In the 11 to 17 years age group, 85 percent of PKU patients preferred the new product, with only 15 percent preferring the amino acid formula. These results provide further evidence that suggests taste preferences in infanthood are less developed than in later life.

From available data, it can be concluded that a diet based on foods for special medical purposes is generally accepted by infants and also by older children, if these foods were introduced into the diet within the first three months of life. If these foods first become necessary after the age of three months (if indications for the use of these foods are first identified after this age), this can lead to acceptance problems. In such cases, acceptance can be improved by repeated feeding. The BfR is not aware of any studies that have investigated whether adding flavouring substances improves the acceptance of hydrolysed (infant) foods.

3.2.2 Use of flavourings to promote the development of the sense of taste and smell

The BfR responds as follows to the statement from the European Association of Producers of Food for Special Dietary Uses in which it is claimed that flavourings promote the development of the sense of taste and smell (IDACE, 2010):

Taste preferences and food preferences that they lead to do not only have a genetic component, but are also influenced by societal and environmental factors (Drewnowski and Rock, 1995; Negri et al., 2012; Feeney et al., 2011; Lipchock et al., 2011; Ventura and Worobey, 2013). As one example, infants have an innate taste preference for sweetness and umami[9], which can be biologically explained as a preference for foods rich in energy and protein. On the other hand, infants also have an inborn aversion to bitter and sour tastes (e.g.: Lawless, 1985; Bartoshuk and Beauchamp, 1994; De Graaf and Zandstra, 1999; Liem and Mennella, 2002; Meyerhof et al., 2005a; Ventura and Worobey, 2013). This aversion can be influenced by the perception of/familiarisation with flavours from the environment, both intrauterine by

[9] 'Umami' is the term used to describe a taste sensation that is triggered primarily by glutamic acid, an amino acid.

the inhalation and swallowing of amniotic fluid, and following birth by feeding on breastmilk or industrially produced infant formula (Ventura and Worobey, 2013).

When complementary feeding starts, breastfed infants are more accepting of the foods that they are offered (Maier et al., 2005; Mennella and Trabulsi, 2012; Mennella and Castor, 2012; Galloway et al., 2003; Schwartz et al., 2012; Schwartz et al., 2013; Mennella et al., 2005a) than infants fed with industrially produced infant formula. Young children who were breastfed as infants also exhibit a greater readiness to try out and accept new foods than children who have not been breastfed (Hausner et al., 2010; Nicklaus, 2009). These findings could result from the fact that breastfed infants are exposed to a broad range of natural flavours from their mother's diet, while infants who are not breastfed have experienced only infant formula, and the less diverse range of flavours compared to those in breastmilk. Furthermore, however, the timing of the introduction of solid food as well as the frequency with which infants are presented with new foods in their diet also has apparently an influence on the acceptance of these foods and the development of food preferences (Birch et al., 1998a; Mennella and Trabulsi, 2012; Burnier et al., 2011; Nicklaus, 2011; Spill et al., 2019).

A series of investigations has shown that even in the case of infants fed with infant formula, tastes can be experienced that are capable of exerting an influence on taste preferences even many years later, as a result of the specific sensory properties of these products (Schuett et al., 1980; Schuett et al., 1985; Mennella et al., 2004; Beauchamp and Mennella, 2009; Mennella and Ventura, 2011; Mennella and Beauchamp, 2002; Mennella and Beauchamp, 2005). These studies showed that children who received a hydrolysed infant formula in the first months of life were more accepting of more bitter-tasting vegetables at the complementary feeding stage, and exhibited a preference for sourer flavours at the age of 4 to 5 years (Mennella et al., 2009; Mennella and Beauchamp, 2002; Liem and Mennella, 2002; Mennella et al., 2004; Mennella et al.; 2006). Children aged between 4 and 5 or 10 years of age also exhibited no dislike of the flavour of hydrolysed infant formula if they had been fed with this formula during infanthood (Mennella and Beauchamp, 2002; Sausenthaler et al., 2010).

Only a few studies are available that have investigated the effects of consuming flavoured infant formula on drinking and feeding behaviour of infants. Mennella and Beauchamp (1996b) investigated the response of infants to vanilla flavour in breastmilk (from the mother's consumption of vanilla flavouring), and observed significant differences both in suckling time and milk volume intake compared with a control group. When infants were offered an industrially produced infant formula flavoured with vanilla at intervals of 60 seconds, alternating with the provision of non-flavoured formula, infants drank the flavoured formula both more forcefully and rhythmically, and also in greater volumes (Mennella and Beauchamp, 1996b). Another study administered flavoured infant formula as the sole source of food to a group of infants over a period of two days; a further group served as the control group. A significant difference in suckling duration was observed in comparison with the control group in the case of the first bottle offered (infants in the flavoured formula group drank more slowly); no difference was observed in the volume consumed, however. From the second bottle onwards, no differences were observed compared with the control group either in terms of suckling duration or the volume consumed. This would indicate familiarisation with the new flavour after a relatively short period of time (Mennella and Beauchamp, 1996b).

Only a single study has been identified that has investigated the potential long-term effects of consuming infant formula flavoured with vanilla on taste preferences in adult life (Haller et al., 1999). In this study, 133 unsystematically recruited test subjects between the ages of 12 and 59 were asked to taste two ketchup varieties (with and without vanilla) and express a prefer-

ence. Two-thirds of those test subjects who had self-reported as not being breastfed as infants exhibited a stronger preference for ketchup with vanilla, while 30 percent of those who had self-reported as not being breastfed exhibited no particular preference. For the group of non-breastfed test subjects, it was assumed that these individuals had probably been fed with a product containing vanilla flavouring, based on the availability of flavoured infant formula at the time. These findings could indicate that taste sensations experienced in early childhood can sometimes be retained even in later adult life. Additional studies—especially prospective studies—would be needed here in order to be able to draw reliable conclusions.

The BfR is aware of no other studies that have investigated the medium- or long-term effects of the consumption of flavoured infant formula. The BfR is also unaware of any studies that have investigated the potential effects of flavoured follow-on formula on the taste development.

In the context of the positive effect of flavoured infant formula on the development of taste in children, as has been claimed by SNE, the following points can be made:

- The specific sensory properties provided by flavoured infant formula products cause infants to experience certain flavours in a way that may influence these individuals' taste preferences for many years into the future.

- Unlike breastmilk, infant formula is a food product with a standardised composition that, even with the addition of certain flavourings, is unable to provide the broad taste experience that breastfed infants enjoy from their mother's milk. To suggest that an infant's sense of taste and smell can be fostered by feeding flavoured infant formula in a similar way as for breastfed infants by breast milk is, in the BfR's opinion, an untenable argument.

- On the basis of the available scientific data, it is not currently possible to assess the long-term effects of exposure to flavouring substances in early childhood on food and taste preferences in later life.

3.3 Risk assessment from the perspective of nutritional physiology

When assessing the risks that are posed by the use of flavouring substances in infant formula and follow-on formula, the decisive role played by innate and acquired taste preferences in determining dietary behaviour must be properly accounted for. Furthermore, there are indications that taste preferences established in early infancy can have an influence on the dietary behaviour in later life (Mennella, 2006; Beauchamp and Mennella, 2009). It is also well-known that nutrition and growth in infancy (e.g. overweight and obesity as well as the risk of associated complications) can affect later health (Koletzko et al., 2012; Forestell, 2017).

However, there is a lack of well-controlled longitudinal studies aimed at improving our understanding of the development of the taste preferences in infants and their influence on later eating habits (Nicklaus, 2017).

Therefore, on the basis of the data currently available, the long-term effects of the use of flavouring substances in infant formula on dietary behaviour and the health of the general population cannot be reliably assessed.

3.4 Risk assessment from a toxicological perspective

In an FAO/WHO Meeting Report released in 1971, which formed the basis for a statement from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for the use of additives in infant formula, the authors noted that the detoxification mechanisms, the physiological barrier function (blood-brain barrier) and other protective mechanisms are not yet fully developed in infants up to the age of 12 weeks. The authors advised that "*It is therefore prudent that foods intended for infants under 12 weeks should contain no additives at all.*", but acknowledged that certain exceptions due to technical requirements may be justified. The report continues by stating that it is likely that some additives would accumulate in infants aged up to 12 weeks, as a result of their immature metabolic systems and the limited kidney function at this stage in the child's life. Before the use of an additive in infant formula could be considered as safe, the authors therefore argued for the completion of additional toxicological studies for the respective substance, which must also include multi-generation studies (WHO, 1972).

Equivalent conclusions were also drawn by participants in a workshop conducted by the International Life Science Institute (ILSI Europe) on 8 and 9 January 1997 (Larsen and Pascal, 1998).

The former Scientific Committee on Food (SCF) of the EU Commission also confirmed JECFA's 1971 statement while also drawing attention to other aspects (SCF, 1998), noting that stomach pH is relatively high in neonates and only becomes acidic when the child is several months old. The degree to which substances are ionised, as well as their potential uptake and distribution in the body, is therefore different compared with older infants. Protein binding levels are lower in neonates and the proportion of substances not bound to proteins is therefore higher than in older infants. The immune system is also relatively immature in infants during their first months of life and chemical substances may interfere with its development. The SCF emphasised that a special evaluation is needed for additives that are intended for use in formula for infants up to 16 weeks of age (infant formula), since this phase of exposure is not covered by standard toxicological studies (SCF, 1998).

These aspects have also been accounted for in the FAO/WHO guidance on the 'Principles and methods for the risk assessment of chemicals in food' (IPCS, 2009): *"Very young infants are a particularly sensitive subgroup because their metabolic capacities are not yet fully developed. It should be noted that health-based guidance values are not considered applicable to infants under the age of 12 weeks who might be at risk at lower levels of exposure. Accordingly, risk characterization of exposure of such infants to chemicals (e.g. in infant formula or occurring as contaminants) has to be considered on a case-by-case basis. This is in accordance with similar advice in EHC 70 (IPCS, 1987), where the scientific rationale for this conclusion was originally set out. EHC 237, which provides a systematic analysis of the scientific principles to be considered in assessing health risks in children from exposures to environmental agents during distinct stages of development, is a useful reference in this regard (IPCS, 2006)."*

In 2012, the European Food Safety Authority (EFSA) confirmed the recommendations made by JECFA and the SCF concerning the use of food additives for infant formula (EFSA 2012). In 2017, EFSA published a Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age, in which 'infants under 16 weeks of age' was defined as a subpopulation for which health-based guidance values such as ADI values should not, when accounting for special physiological aspects as well as aspects of infant

development and nutrition, be considered applicable without further consideration on a case-by-case basis (EFSA, 2017).

The BfR considers that the same rationale based on which JECFA (WHO, 1972), the former SCF (1998) and EFSA (2012 and 2017) have all argued against the general application of ADI values derived for food additives to infants aged below 12 or 16 weeks without further consideration on a case-by-case basis should also be applied to flavouring substances. The BfR, therefore, considers that flavouring substances should generally not be used in infant formula products or formula for special medical purposes intended for consumption by infants in the first four months of life. Should such a use nonetheless be considered necessary in exceptional circumstances, this would require a case-by-case evaluation—in the same way as for food additives.

4 Risk management options/recommendation

The BfR sees no benefit in and therefore no necessity for the use of flavouring substances in infant or follow-on formula, neither in terms of improving acceptance of taste nor in promoting the development of taste. Furthermore, the results of relevant studies indicate that formulae for special medical purposes without added flavouring substances are well accepted by infants, especially if feeding with these food products begins during the first few months of life.

The BfR considers that flavouring substances should generally not be used in infant formula products or formulae for special medical purposes intended for consumption by infants in the first four months of life. Should such a use nonetheless be considered necessary in exceptional circumstances, this would require a case-by-case evaluation—in the same way as for food additives.

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