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Draft Scientific Opinion on

Recent developments in the risk assessment of chemicals in food and their potential impact on the safety assessment of substances used in food contact materials

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)

DRAFT for public consultation

Abstract

This document explains recent developments in the safety assessment of chemicals in food and their potential impact on the EFSA evaluation of FCM. It is not intended to be a guidance document. Together with a public consultation, it will provide the European Commission with the scientific basis for a discussion among risk managers on possible implications for risk management. One major area to revisit is the estimation of consumer exposure. Three food consumption categories could be set. They are approximately 9, 5 and 1.2 times higher than the current SCF default scenario, i.e. 17 g/kg b.w. per day, and so using them would afford a higher level of protection. Special exposure scenarios might be used if consumption were lower. The amount of toxicity data needed should be related to the expected human exposure. In this document, the tiered approach recommended by the SCF is updated. For the safety assessment of substances used in FCM, genotoxicity testing is always required, even if their migration lead to a low exposure. Beyond this, two threshold levels of human exposure, namely 1.5 and 80 µg/kg b.w. per day, are proposed as triggers for the requirement for additional toxicity data. Regarding the identification and evaluation of migrating substances, experience gained over the years has shown that more focus is needed on the finished materials and articles. Considering the NIAS, such as impurities of the substance and reaction and degradation products, of which the oligomers can be the dominant class, the same approach as is used for authorised substances could, in principle, be applied for their toxicological assessment, as the same degree of safety should be warranted for all migrating substances. However non-testing methods could be taken into account on a case-by-case basis, for priority setting and for a toxicological assessment of NIAS.

Keywords: food contact materials, plastics, substances, safety risk assessment, migration, exposure, toxicological evaluation

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Summary

In accordance with Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food (FCM), the European Food Safety Authority (EFSA) Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) evaluates the safety of certain substances prior to their authorisation for use in FCM plastics. The current guidelines on this risk assessment process and the corresponding data requirements from applicants date back to the Scientific Committee on Food (SCF) guidelines from 2001. In the light of new developments in science and regulation, along with the experience gained since 2001 from the safety evaluation of hundreds of substances, it is appropriate to revisit the scientific underpinnings of the SCF guidelines published back in 2001 with a view to possibly updating them.

This document is an outcome of a self-tasking activity by the CEF Panel. It explains the recent developments in the risk assessment of chemicals in food and their potential impact on the EFSA evaluation of FCM substances. Together with a public consultation, this document will provide the European Commission with the scientific basis for a discussion among risk managers on possible implications for risk management. It is intended that, in turn, the European Commission will provide feedback for EFSA to prepare updated guidelines for data requirements for the safety assessment of a substance to be used in FCM.

One major area to revisit is the estimation of consumer exposure. For most substances used in FCM, human exposure data were not readily available in the past. For this reason, the SCF used the assumption that a person may consume daily up to 1 kg of food in contact with 6 dm^2 of the relevant FCM. Now that EFSA's Comprehensive European Food Consumption Database is available, based on the 95th percentile value for the highest European Union (EU) country and using the default water consumption figures set by the World Health Organization (WHO) for infants, three food group categories could be set. For Category 1, FCM intended for contact with water and foodstuffs such as reconstituted infant milk formula, the age group with the highest consumption is 'Infants', with a consumption figure of 150 g/kg body weight (b.w.) per day. For Category 2, in which contact with Category 1 is excluded, but contact with milk, milk products and other non-alcoholic drinks is intended, then the age group with the highest consumption is 'Toddlers', with a value of 80 g/kg b.w. per day. For Category 3, in which the FCM is intended for contact with foods other than those covered by Categories 1 and 2, the age group with the highest consumption is 'Toddlers', with a value of 20 g/kg b.w. per day. The food consumption values for these three categories are approximately 9, 5 and 1.2 times higher than the current SCF default model, i.e. 17 g/kg b.w. per day (1 kg food consumed by an adult weighting 60 kg b.w.), and so using them would afford a higher level of protection. Under certain conditions, special exposure scenarios might be used if consumption were lower.

Regarding the identification and evaluation of all substances that migrate, experience gained over the years has shown that more focus is needed on the finished materials and articles, including the manufacturing process used. Substances used in the manufacture of plastic materials or articles may contain impurities originating from their manufacturing. Moreover, during manufacturing and use, reaction and degradation products can be formed, of which oligomers can be the dominant class. These substances have become known as NIAS (non-intentionally added substances) and are referred to as such in Commission regulations. Whether their presence is intentional or not, it is necessary to evaluate the safety of all migrating substances, and not just of the starting substances—for example the monomers or additives alone—and the guidelines should be updated to account more fully for this more comprehensive approach. In the case of testing for migration using food simulants, new rules are provided in Regulation (EU) 10/2011. Similarly, the use of mathematical migration models has developed significantly in recent years, including proper validation for some of the most common types of plastics.

The amount of toxicity data needed should be related to the expected human exposure level, in accordance with the principle that the higher the exposure, the greater the amount of data required. Considering human exposure to determine the data needed may allow more efficient use of resources and contribute to reducing the use of experimental animals, without any loss in the safety assessment. In this document, the tiered approach recommended by the SCF in 2001 is updated

based on scientific progress. It focuses on the evaluation of substances used for the manufacture of plastic FCMs, but it is, in principle, also applicable to those used in other, non-plastic, FCMs.

For the safety assessment of substances used in FCMs, genotoxicity testing is always required for substances migrating from FCMs, even if exposure is low. Beyond this, two threshold levels of human exposure, namely 1.5 and 80 µg/kg b.w. per day, are proposed as triggers for the requirement of additional toxicity data. The first level, 1.5 µg/kg b.w. per day, is intended to be a general threshold for the investigation of potential toxic effects other than genotoxicity. A second exposure threshold is proposed as a trigger for additional toxicity studies beyond the core set of general toxicity data. This threshold is pragmatically defined as 80 µg/kg b.w. per day, in line with previous SCF guidelines. The Panel considers that exposure above this level would approach that observed for food additives and that, in this case, it would therefore be appropriate to require a more extensive data package.

The new EFSA Scientific Committee recommendations on genotoxicity testing strategies call for two tests: (i) a bacterial reverse mutation assay; and (ii) an *in vitro* mammalian cell micronucleus test. This combination of tests fulfils the basic requirements to cover the three genetic endpoints with the minimum number of tests: the bacterial reverse mutation assay covers gene mutations and the *in vitro* micronucleus test covers both structural and numerical chromosome aberrations. The following tests *in vivo* would be suitable to follow-up for substances positive in the *in vitro* base set: (i) the *in vivo* micronucleus test; (ii) the *in vivo* comet assay; and (iii) the transgenic rodent gene mutation assay.

Studies of subchronic toxicity generally provide sufficient information to establish the main toxicological profile of the substance, providing information on the target organs and tissues affected, on the nature and severity of the effects induced, and on the dose–response relationships. Chronic toxicity and carcinogenicity studies may reveal effects not evident in subchronic studies, or may confirm effects observed in subchronic studies, at the same or perhaps lower doses. Subchronic and chronic toxicity studies should allow the determination of the point of departure for safety assessment.

New testing strategies were recently developed to enhance the toxicological information from short-term and reproductive toxicity studies on potential effects on the endocrine, nervous and immune systems. Consequently, these improved study designs should be incorporated into the recommended toxicological test methods and study protocols.

Other updated test protocols are also described and discussed with respect to their applicability in any updating of the FCM guidelines, specifically protocols to test subchronic toxicity, prenatal developmental toxicity, chronic toxicity, toxicokinetics, endocrine disruption, neurotoxic potential, developmental effects on behaviour and neurotoxicity, and, finally, immunotoxic and immunomodulatory effects.

FCMs are one sector for potential use of nanotechnology and nanomaterials. The specific properties of nanomaterials may affect their toxicokinetic and toxicology profiles. The Panel recognised that the availability of data to cope with some of the listed cases may depend on the specific properties of nanomaterials and on the likely impact of the matrix in which they are dispersed.

Considering the NIAS, the same approach as that used for authorised substances could in principle be applied for their toxicological assessment, as the same degree of safety should be warranted for all migrating substances. However non-testing methods could be taken into account on a case-by-case basis, for priority setting and for a toxicological assessment of NIAS. The methods applicable to NIAS could include grouping and "read-across", computational methods (structure–activity relationships, quantitative structure–activity relationships), the Threshold of Toxicological Concern (TTC) and the Margin of Exposure (MoE).

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1. Introduction

9.1. Background and Terms of Reference

Regulation (EC) No 1935/2004[1] on materials and articles intended to come into contact (FCM) with food describes the authorisation process for substances to be used in FCM. In that regulation it is foreseen that the EFSA will publish guidelines on its risk assessment process and the corresponding data requirements from applicants, but that pending the publication of such EFSA guidelines applicants may consult the guidelines of the Scientific Committee of Food (SCF). The SCF guidelines date back to 2001 (EC, 2001)[2] and have been used since 2003 by the former AFC Panel of EFSA and by the CEF Panel which succeeded the AFC.

In the light of new developments in science and regulation, the experience gained since 2001 from the safety evaluations of hundreds of substances and trends in the use of FCM, it is appropriate to revisit the scientific underpinnings of the SCF guidelines published back in 2001.

One major area to revisit is the estimation of consumer exposure. Over the last decades, the usage of FCM has increased, with a trend towards smaller packs with larger contact surface per content, more processed foods with long storage times and products heated in the packaging. For most substances used in food contact materials, human exposure data were not readily available in the past. For this reason the SCF used the assumption that a person may consume daily up to 1 kg of food in contact with the relevant food contact material. It has to be examined whether this assumption is conservative enough for population groups such as infants and children, and if it may be too conservative for substances that find only minor use in FCMs.

Regulation (EU) 10/2011 gives the Union list of authorised substances used to make plastics, but this list does not include what have been termed the NIAS - the Non-Intentionally Added Substances. The regulation states that NIAS should be considered in the risk assessment of plastic food contact materials and included, if necessary, in the specifications and/or restrictions of a substance. Since often the oligomers, other reaction products and impurities can constitute the main part of the migrate, a more detailed consideration of the oligomers and other-NIAS including more consideration of the manufacturing and use conditions of the substances and the plastic made from it, could be necessary.

Similarly, there have been several methodologies recently adopted by EFSA that could have a bearing on the risk assessment of FCM substances. These include the concept of Threshold of Toxicological Concern (TTC) (EFSA Scientific Committee, 2012a), evaluation of nanoscience and nanotechnologies (EFSA Scientific Committee, 2011a) and approaches for testing for genotoxicity (EFSA Scientific Committee, 2011b).

This document is organised with the same structure as the current guidelines and the reader is recommended to become familiar with them (EC, 2001). The focus here is on those sections and scientific areas that could benefit from updating.

This document should not be interpreted as the new guidance on data requirements for the presentation of an application for safety evaluation of a substance intended to be used in food contact materials within the context of the authorisation process. Rather than simply to publish directly updated guidance on data requirement for the presentation of an application, the European Commission and EFSA agreed at the end of 2014 on a two-step approach. First, EFSA will publish an opinion, this opinion, explaining the recent developments in the risk assessment of chemicals in food and their potential impact on the EFSA evaluation of substances used in food contact materials. So this opinion has the character of a discussion document. Once adopted, this opinion will provide to the European Commission the scientific basis for a discussion amongst risk managers on possible implications on risk management. When those discussions have been concluded, the European Commission will in turn provide the necessary feedback to EFSA to prepare the updated guidance on

[1] Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food. OJ L 338, 13.11.2004, p. 4–17.

[2] Regulation No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1–89.

data requirement for the presentation of an application for safety assessment of a substance to be used in food contact materials.

2. Identity of the substance including any impurities

While information about the identity and characteristics of the substance as used is clearly important, experience gained over the years has shown that more focus on the finished materials and articles is needed. For instance, substances used to manufacture FCM may largely disappear and it may be mainly reaction products that turn up in the migrates. In addition, impurities of the substance are of interest only if they persist as residues in the finished FCM and migrate into food.

3. Physical and chemical properties of migrating substances

It is necessary to evaluate the safety of all migrating substances, and not just the starting substance—for example the monomer—or additives. Thus, information is needed on the physical and chemical properties of the substance itself, along with impurities and thermal degradation or other reaction products formed when the substance is used to make the FCM or when the FCM comes in contact with foods. The necessary information includes the thermal and chemical stability of substances used to make the FCM and their impurities during processing of the FCM; the solubility of migrating substances in solvents of different polarity and in food and food simulants; their stability in food simulants and food and/or their hydrolysis in the gastrointestinal tract (using standard digestive fluid simulant for saliva, gastric juice and intestinal fluid); and their possible chemical interactions with the packed food, leading to the formation of reaction products with, or from, the food.

4. Intended application of the substance and the food contact materials

Whereas information on the level of use, the function and the conditions of the manufacturing process allow substantiation of the quantities, types and nature of potentially migrating substances present in the final FCM, information on usage is also needed to allow estimates to be made of the consumer exposure to migrating chemicals. Depending on the degree of detail of information available, such as the nature of the plastics manufactured using the substance and the types of foods the plastic is intended to contact, a more or less refined exposure estimate may be derived. If contact with broad categories of food is foreseen, default assumptions on food consumption and migration levels can be used to estimate the exposure. If limited use of the substance or the FCM is intended, then being as precise as possible on those aspects could help to derive refined estimates of exposure.

5. Data on migration

In accordance with usual practice, migration data can be gathered starting with calculation of total mass transfer.

The use of mathematical migration models has developed significantly in recent years, including proper validation for some of the most common types of plastics and use of multilayers. For guidance on migration modelling, the documents from the Commission services (EUR 24514 EN 2010) should be consulted.[3]

On testing with food simulants, new rules are provided in Regulation (EU) 10/2011 and will be further explained in the European Commission guidelines on migration testing, which are currently being prepared by the Joint Research Centre (JRC). Food simulants are largely designed for testing FCM for compliance with migration limits. This means that, as with migration modelling, the use of food simulants and the associated time and temperature test conditions is designed to overestimate the migration expected into foods. Regulation (EU) 10/2011 states that the results of specific migration testing obtained in food shall prevail over the results obtained in food simulants. This means that, for risk assessment purposes, the applicability of simulation must be considered on a case-by-case basis, and verified if necessary.

[3] The document is being updated and the latest version should be considered.

Analytical methods have developed since the SCF guidelines were published. At that time food analysis was difficult, and this was one reason for using food simulants, but nowadays food analysis for chemicals at mg/kg or µg/kg concentrations is rather routine. If specific migration is tested using foods, the products selected should ensure that they represent all foods or categories of foods intended for the FCM application with respect to properties determining migration, such as the solubility and mobility of the migrant and the eventual conditions of time and temperature used to process packaged foods. A sufficient number of foods should be used to allow exposure to be estimated.

6. Exposure of the consumer

Since the early days of the SCF Working Group a simple model has been applied to estimate exposure from chemicals migrating from FCM to food and, in turn ,the nature and extent of toxicity data needed for the safety assessment. Given the lack of detailed information on actual consumption of foods in contact with various materials, a default figure of 1 kg of food per person per day was chosen as an assumed maximum intake of total food (solid or liquid; fatty, acidic, aqueous or alcoholic; together or singly) in contact with material releasing the given substance at the legal limit. The exposure scenario set in the SCF guidelines (EC, 2001) is also based on the convention that individuals with a default body weight of 60 kg consume over their lifetime 2 kg of food and drink per day, of which 1 kg is packaged in a material with a contact surface of 6 dm^2. It is assumed that foods are consumed at the end of their shelf life.

The current exposure model contains several elements that may individually and collectively be either conservative or not, depending on the substance, the FCM, the packaging size and the (sub)population under consideration. Better information is now available both on the food consumption patterns of European consumers and on the use of food packaging materials, meaning that exposure can be re-considered. Recent food consumption surveys carried out for different age groups have assessed the daily intake of packaged food and examined the ratio of surface area to food mass in these foods. They were reviewed by the Norwegian Scientific Committee for Food Safety (VKM, 2009), which concluded that the default exposure scenario could be improved with regard to (i) FCM for infants and young children; (ii) FCM for liquid foods; (iii) the proportion of packaged foods; and (iv) the FCM surface area to food mass ratio.

An exposure model can be considered conservative if it provides values that are systematically equal to or higher than the dietary exposure observed in high consumers. The European Food Safety Authority (EFSA) Scientific Committee, in its opinion on uncertainties in exposure assessment, stressed the need to harmonise risk assessment methodologies in the fields falling within its mission and pointed out that standard screening procedures are intended to produce conservative estimates of exposure (EFSA, 2006). As affirmed by EFSA (EFSA, 2011a) and the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO, 2009), international dietary exposure assessments should provide exposure estimates that are equal to or greater than the best available estimates carried out at the national level. Models aiming to assess dietary exposure to FCM should, therefore, take into account the highest level of consumption of packaged food observed in European Union (EU) countries.

Chronic exposure of an individual should, theoretically, be an estimate of the average exposure of the individual over his or her lifetime. However, as pointed out by FAO/WHO (2009), exposure assessments should cover the general population, as well as critical groups that are vulnerable or are expected to have exposure higher than the general population (e.g. infants, children). For this reason, repeated high levels of exposure estimated for infants and children are treated as chronic exposure in the safety assessment of substances used in FCM performed by EFSA. Although these levels of exposure do not hold for the whole life and are higher than those observed in adults, they are used to cover critical groups as well as the general population.

Based on the above considerations and the fact that potential exposure to substances and to their related NIAS depends on the types of applications of materials and articles in which they are used, the CEF Panel has assessed the new information on (i) the quantity of food/beverage that may be in contact with the materials/articles in the population group with the highest potential consumption expressed in g/kg body weight (b.w.); and (ii) the surface to mass ratio to be considered for such applications.

6.1 Levels of consumption of packaged foodstuffs

Food consumption data are a key element of risk assessment, forming the basis of dietary exposure assessment. The level of water consumption by infants was described by WHO in 2003 (WHO, 2003). The Comprehensive European Food Consumption Database (Comprehensive Database) released in 2011 by EFSA (EFSA, 2011b) contains detailed information on foodstuffs consumed by the European population.[4]

The Comprehensive Database gathers together detailed consumption data from 34 national food consumption surveys representing 66 492 individuals from 22 EU Member States. For its development, the usual intake distributions of 589 food items representing the total diet were estimated for 36 clusters, each one composed of subjects of the same age class (children, adolescents or adults) and gender and having a similar diet. Season, body weight and whether or not the food was consumed at the weekend were used to predict likely consumption. Owing to different survey methodologies used, national survey data cannot be combined to generate average European estimates of dietary exposure. The EU Menu project[5] has the aim of collecting harmonised food consumption data at EU level, but these data will not be available before 2018. Until then, the highest consumption among Member States should be used in order to ensure the safety of the whole EU population.

Based on the Comprehensive Database and the consumption of water by infants set by WHO, three food group categories could be set, for which the conservative default food consumption is triggered by the critical population group, this being the group with the highest consumption of one or more of the foods in the category (Table 1). The rationale for the consumption level set for each category is described in detail in the corresponding sections below.

Table 1: Food consumption figures based on the categorisation of application(s) of the food contact material(s) containing the substance under evaluation

Category	Food categories for which the FCM containing the substances under evaluation are intended to be used	Population driving the consumption[6]	Food consumption to be considered for the estimation of exposure (g/kg b.w. per day)
1	Water and baby bottle contents such as reconstituted milk formula	Infants[7]	150
2	Milk, milk products, other non-alcoholic drinks (e.g. fruit and vegetable juices)	Toddlers[8]	80
3	Foodstuffs not covered by Categories 1 and 2	Toddlers	20

6.1.1. FCM intended to be used to pack water and other liquids such as milk formula consumed by babies and infants up to 12 months old

If substances are intended for use in any possible application, their use for baby bottles or for the packaging of water needs to be considered in the exposure assessment in order to ensure the safety of the material/article for both infants and the rest of the population. The high potential water/infant formula consumption per kilogram body weight expected for infants also covers the rest of the population. Although in some EU countries tap water is used to reconstitute infant formula, in some

[4] The EFSA Comprehensive database was recently updated and published in April 2015 (http://www.efsa.europa.eu/en/press/news/150428.htm). Notably, new surveys were added making use of an upgraded version of EFSA's food classification and description system, FoodEx2. This is not expected to have a significant impact on default food consumption, which will be updated, if needed, in the final version of this document after public consultation.

[5] The EU Menu project: http://www.efsa.europa.eu/en/datexfoodcdb/datexeumenu.htm.

[6] This means that the critical population (infants or toddlers) consuming the foods grouped in a category (1, 2 or 3) has the highest consumption of one or more of the consumed foods; this does not mean that the critical population consumes all food types falling into that category.

[7] Infants are young children aged up to 12 months.

[8] Toddlers are young children aged from 12 months up to and including 36 months.

other EU countries there is a systematic use of bottled water. An infant formula-fed baby would be fed every day with a formula reconstituted either with tap water or with bottled water. The exposure scenario of interest is therefore that of an infant fed with a formula reconstituted with bottled water. According to WHO, the level of water consumption in infants is 150 g/kg b.w. per day based on the consumption of 0.75 l of water per day by a 5-kg infant (WHO, 2003).

The scenarios covered are those of (i) water packed in a FCM containing the substance of interest, used to reconstitute the infant formula; and (ii) reconstituted or ready-to-feed infant formula having been in contact with the baby bottle containing the substance of interest before consumption. The scenarios are that of an infant who constantly consumes food in contact with a packaging material containing the substance of interest (e.g. brand loyalty and/or pack type). This level of consumption is far higher than high levels of consumption of water observed in any other age groups, as reported in the Comprehensive Database. The observed 95th percentile of consumption was up to 96 g/kg b.w. per day in toddlers (12–36 months), 78 g/kg b.w. per day in children (3–9 years), 39 g/kg b.w. per day in adolescents (10–17 years), 35 g/kg b.w. per day in adults (18–64 years), 29 g/kg b.w. per day in the elderly (65–74 years) and 28 g/kg b.w. per day in the very elderly (75 years and older).

Therefore, it is assumed that the level of consumption of 150 g/kg b.w. per day is not achieved in other age groups but would cover the whole population. The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF Panel) underlines the fact that this consumption is approximately nine times higher than that used in the current SCF scenario, i.e. 17 g/kg b.w. per day (1 kg food consumed by an adult weighing 60 kg).

6.1.2. FCM intended to be used in contact with beverages such as non-alcoholic beverages, milk or milk products

If substances are not intended to be used in baby bottles or for the packaging of water but may be used for any other application (stated explicitly or by omission), which includes or could include packaging of non-alcoholic beverages, milk or milk products, then the level of consumption observed in toddlers (young children aged from 12 months up to and including 36 months) needs to be considered to ensure the safety of the material for both toddlers and the rest of the population. Toddlers largely consume milk and beverages that are not specifically designed for this specific age group. The scenario is that of a toddler who is a high consumer of milk, milk products, fruit and vegetable juices or other non-alcoholic beverages and who would be loyal to a packaging material containing the substance of interest.

In the Comprehensive Database (EFSA, 2011a), the 95th percentile of beverage consumption of toddlers in the different Member States ranged from 19 to 84 g/kg b.w. for liquid milk, from 14 to 49 g/kg b.w. for fermented milk products, from 19 to 43 g/kg b.w. for fruit and vegetable juices and from 17 to 76 g/kg b.w. for other non-alcoholic beverages. High levels of consumption of single categories of beverages were considered, rather than consumption of total beverages (95th percentile for toddlers ranging from 84 to 112 g/kg b.w. per day in the different Member States), as loyalty to a beverage packaged in material containing a specific substance is unlikely to occcur at the same time as loyalty to another category of beverage also packaged in a material containing the same substance of interest.

Therefore, the level of consumption of 80 g/kg b.w. per day for these scenarios would cover potential high consumption of beverages such as non-alcoholic beverages, milk or milk products. This value is in good agreement with the average consumption of total packaged food of 68 g/kg b.w. (95th percentile of 114 g/kg b.w.) reported for UK children aged 1 to 4 years (Foster et al., 2010). It would therefore also cover the scenario of children with an average level of consumption of packaged foods, assuming that all packaging always contains the substance of interest. The CEF Panel underlines the fact that this consumption is approximately five times higher than the one used in the current scenario, i.e. 17 g/kg b.w. per day.

In the case of a FCM intended for use with only a specific category of beverages for which the 95th percentile level of consumption is lower than 80 g/kg b.w., an estimate of high potential consumption in the population group with the highest consumption per kilogram body weight of the food/beverage(s) of interest might be more appropriate instead. Different food consumption data extracted from the Comprehensive Database are already available on the EFSA website.[9,10]

6.1.3. FCM intended to be used in contact with all other foodstuffs not covered by Categories 1 and 2

Scenario 3 is considered appropriate for food contact applications other than for water, infant formula, milk, milk products and other non-alcoholic beverages.

Once the liquids considered in the two previous scenarios are excluded, then, according to the Comprehensive Database, consumption of all of the remaining foodstuffs combined does not exceed 32 g/kg b.w. per day at the 95th percentile intakes (for consumers only) at any age. This consumption value is triggered by the highest 95th percentile consumption of alcoholic beverages (mostly beer and beer-like beverages) observed in the adult population. The consumption of all of the remaining foodstuffs combined (excluding alcoholic beverages) does not exceed 20 g/kg b.w. per day at the 95th percentile intakes (for consumers only) at any age. The Panel considers, as a practical approach, that alcoholic beverages should be included in this last category. In fact, the high consumption of alcoholic beverages is unlikely to be concomitant with the use of small pack sizes with a high surface area to mass ratio. In addition, levels of migration into this category of low alcohol content beverages (mainly beers, lagers, etc.) tend to be lower than those into high alcohol content beverages or high fat-containing foods. In addition, alcoholic beverages are mostly packaged in glass (Poças et al., 2009) or are served on draft (from barrels), in pubs and bars, although a high consumer may also be loyal to a different type of packaging material, such as a beverage can or a plastic bottle.

Therefore, the level of consumption of 20 g/kg b.w. per day is considered appropriate to cover the consumption by all population groups of all foods other than those covered in Categories 1 and 2. The CEF Panel emphasises that this consumption is very similar to the current scenario, i.e. 17 g/kg b.w. per day.

6.1.4. FCM intended to be used for specific applications

If substances are intended to be used only for specific applications that result in the level of consumption of the affected foodstuffs being significantly lower than 20 g/kg b.w., an estimate of high potential consumption in the population group with the highest consumption per kilogram body weight of the foodstuff(s) of interest could be used, with appropriate evidence to justify this.

If a very specific application is anticipated and has been evaluated, special rules might be needed to render such estimates manageable. For instance, the special conditions may need to be reflected in the conditions authorising the use of that substance.

6.2. Surface of food contact materials/food mass ratio

From recent surveys it is clear that the ratio of surface area to food mass of food packaging materials is in many cases higher than 6 dm^2/kg (VKM*,* 2009). In a study of the diet of a general population, performed in households in Portugal (Poças et al., 2009), the average surface area to food mass ratio was found to be 11.7 dm^2/kg overall, with a value of 7.2 dm^2/kg specifically for cartons containing liquids. A UK survey found that the ratio in infants (less than 12 months old) was, on average, less than 6 dm^2/kg (Foster et al., 2010), but this was said to be due to the large contribution of either breast milk or tap water used to reconstitute infant formula in this age group. In the same study, the average ratio was found to be 8 dm^2/kg for foodstuffs eaten by children aged 1 to 4 years and 10 dm^2/kg for foodstuffs eaten by children aged 4 to 6 years (Foster et al., 2010). The range of values was 0.8 to 11.6, 4.2 to 18.5 and 2.7 to 20.8 dm^2/kg for the three age groups < 1, 1 to 4 and 4 to 6 years, respectively (Foster et al., 2010). As the number of subjects in the three age groups was 96, 99 and 102, respectively, then the top end of each range is effectively the 99th percentile, albeit for relatively small group sizes.

[9] The EFSA Comprehensive Food Consumption Database: food consumption data per country, survey and age class, in g/day or g/kg b.w. per day available here: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm.

[10] The EFSA Comprehensive Food Consumption Database: specific food consumption data according to food additives nomenclature, available here: http://www.efsa.europa.eu/en/datexfooddb/datexfooddbspecificdata.htm.

Taking high percentiles of consumption of food/beverage potentially in contact with the FCM of interest, and combining them with high percentiles of surface area/mass ratios for such applications, would lead to conservative scenarios that have a low probability of occurring in the population. High surface area to food mass ratios are observed for foods that are not generally consumed in large quantities on a daily basis. Even the estimated average surface to mass ratio in the population group of interest may not be appropriate for combining with a high level of consumption, as high consumers of food products are more likely to purchase these products in large pack sizes.

Based on high potential consumption of water, milk, beverages and soup, the standard value of 6 dm^2/kg is appropriate to represent the surface to mass ratio of packaged foodstuffs. In the case of an FCM intended for specific applications only, then a different surface area/mass ratio may be needed. For instance, in the case of foods or beverages typically sold in small packages (e.g. snacks and confectionery) this ratio is likely to be significantly higher than 6 dm^2/kg, whereas for, for example, plastic parts of food-processing equipment, hoses and tubes, etc., it is likely to be significantly lower than 6 dm^2/kg.

7. Nanomaterials

Nanotechnology and nanomaterials are a relatively new technological development and FCM are one sector in which the use of nanomaterials has featured. The specific properties of nanomaterials, which can also be influenced by the matrix in which the nanomaterials are dispersed, may affect their toxicokinetic and toxicology profiles, but limited information is available in relation to these aspects. There are also uncertainties stemming from the difficulty of characterising, detecting and measuring nanomaterials in food and biological matrices and from the availability of toxicity data. For these reasons, nanomaterials should be evaluated "case by case".

Table 2, adapted from the EFSA Scientific Committee Guidance on nanoscience and nanotechnologies (EFSA Scientific Committee, 2011a), indicates the information relevant for nanomaterials used to make FCM. This applies to three relevant aspects: first, the characteristics of the nanomaterial used to make the FCM; second, the characteristics of the material once it is incorporated into the FCM, as these may differ from the original characteristics, being influenced by the FCM matrix and/or the manufacturing conditions used to make the FCM; and, third, and most importantly, the characteristics of any nanomaterial that migrates into the food matrix and is influenced by the food environment.

At present, no generally valid threshold of toxicological concern can be derived for nanoparticles, i.e. nanoparticles must be considered case by case. If relevant migration may occur, toxicity data are needed, in accordance with the EFSA Guidance on nanoscience and nanotechnologies (EFSA Scientific Committee, 2011a). Where evidence is available that there is no migration, there is no exposure to the nanomaterial via food and, therefore, there is no additional toxicological concern related to the nanoparticle characteristics. Substances used for surface treatment of nanoparticles may migrate independently from the particles themselves and thus may need to be assessed separately.

Table 2: Main parameters, according to EFSA Guidance on nanoscience and nanotechnologies (EFSA Scientific Committee, 2011a), for characterisation and identification of nanomaterials used in FCM, present in final articles, and possibly migrating from FCM; additional parameters might be needed on a case-by-case basis

Parameter	Description
Particle size (primary/secondary)	Information on primary particle size, size range and number size distribution (indicating batch-to-batch variation, if any). The same information is needed for secondary particles (e.g. agglomerates and aggregates), if present
Physical form and morphology	Information on the physical form and crystalline phase/shape. The information should indicate whether the material is present in a particle, tube or rod shape, crystal or amorphous form, and whether it is in free particulate form or in an agglomerated/aggregated state, as well as whether the preparation is in the form of a powder, solution, suspension or dispersion
Chemical reactivity/catalytic activity	Information on relevant chemical reactivity or catalytic activity of the material and of any surface coating
Photocatalytic	Information on photocatalytic activity of relevant materials used in food packaging,

Parameter	Description
activity	coatings and printing inks and on internal reactions

8. Possible impacts on the use of more detailed non-toxicity data

EFSA's work is linked to the decisions and regulations of the European Commission. In accordance with Regulation (EC) No 1935/2004, the Commission must obtain an evaluation on safety and risks from EFSA prior to the authorisation of a substance used in plastic FCM. In turn, this EFSA evaluation is reflected, to a greater or lesser degree, as needed, in the risk management action taken by the Commission. Over time, the evaluations of the SCF and EFSA have increasingly taken the conditions of manufacture and use into account, but the listing in Regulation (EU) 10/2011 on plastic remained largely generic. If the substance is used for other types of plastics, under different manufacturing conditions with a different purity, those applications of the substance may or may not be encompassed by the EFSA evaluation and by the EU legislation. If not, then the user of that FCM containing the substance should perform its own safety assessment. There is also the possibility that the same substance could be used in other FCM that are not plastics and are not subject to EU-wide harmonised legislation. These other uses could have an impact on consumer exposure to that substance, and this may be especially relevant for risk management decisions if a refined estimate was used in the EFSA evaluation.

The use of better estimates of exposure—allowing for consumption by infants and children that is much higher than the current default scenario but also that, vice versa, for limited applications of a substance the consumption and therefore the exposure could be much lower—could give rise to lower or higher migration limits, respectively, offering an equal level of protection for all age groups. If refined estimates of exposure were to be used in the future, the possible impact on other aspects of the legislation on plastics should also be evaluated. Although the default consumption scenario is currently 1 kg of food and 6 dm^2 contact area per person per day, as described above, in the legal implementation, this has been reduced. From considerations of food consumption, the fat reduction factor (FRF) was introduced to allow for the fact that there is a physiological limit on the amount of fat (and so fatty foods) that can be eaten daily which, depending on the fat content of the food, is less than 1 kg. Therefore, measured migration concentrations could be reduced by the corresponding FRF to allow for this lower food consumption. Similarly, on the default contact area, for packages containing less than 500 g or ml, as well as sheets and films not yet in food contact, Article 17 of Regulation 10/2011 enables correction on the assumption of 1 kg food/6 dm^2 contact surface. As most foods sold today are in smaller packages and the ratios of content to contact surface are higher, this usually reduces the contact area and therefore the concentration significantly. These two aspects should also be investigated.

9. Toxicity data

9.1. General considerations

In principle, the toxicity of all substances used in the manufacture of FCM should be evaluated in toxicity studies in order to assess whether or not their possible migration into food may pose a risk to consumers. However, it should be considered that not all chemicals used in the manufacture of FCM will migrate into food to the same extent. Many will form a stable part of a polymer, some will migrate only in minute quantities, if at all, and others will disappear during production, while yet others will decompose completely to result in either no or extremely low consumer exposure. Consequently, the amount of toxicity data needed should be related to the expected human exposure level, in accordance with the principle that the higher the exposure, the greater the amount of data required (see Table 3).

Consideration of human exposure for the selection of data needed may allow a more efficient use of resources and contribute to reducing the use of experimental animals, without any loss in the safety assessment. Exposure-based progressive, or tiered, approaches are currently applied in several food and non-food areas such as the regulation of industrial chemicals in the EU (ECHA, 2008).

In this document the tiered approach recommended by the SCF (EC, 2001) is updated based on scientific progress. It focuses on the evaluation of substances used for the manufacture of plastic FCMs, but it is, in principle, also applicable to other non-plastic FCM.

9.2. The tiered approach to toxicity testing of substances migrating from food contact materials

A possible tiered approach to toxicity testing based on two exposure levels is summarised in Table 3.

For the safety assessment of substances used in FCM, genotoxicity testing is always required for substances migrating from FCM, even if exposure is low. Beyond this, two threshold levels of human exposure, namely 1.5 and 80 µg/kg b.w. per day, are identified as triggers for the requirement of toxicity data in addition to genotoxicity.

The first level of 1.5 µg/kg b.w. per day is intended to be a general threshold for the investigation of potential toxic effects other than genotoxicity. This figure is the threshold proposed by Munro et al. (1996) for non-cancer endpoints elicited by substances belonging to Cramer Class III, the most toxic. It should be noted that such a threshold, which provided a large margin of safety (> 100) when compared with a NOAEL (No Observed Adverse Effect Level) for 95 % of the analysed substances, was derived by Munro and co-workers from a database which included the highly toxic organophosphates and carbamates. However, the threshold of 1.5 µg/kg b.w. per day is considered not applicable to substances with structural alerts for specific toxic effects, including neurotoxicity, such as organophosphates and carbamates. Thus, it is conceivable that the threshold of 1.5 µg/kg b.w. per day will provide an even larger margin of safety when applied to FCM. Indeed, a recent examination of 232 authorised FCM for which a NOAEL was established confirmed the conservatism of this threshold (Pinalli et al., 2011).

A second exposure threshold is proposed as a trigger for additional toxicity studies beyond the core set of general toxicity data (see Section 9.4). This threshold is pragmatically defined as 80 µg/kg b.w. per day, in line with previous SCF guidelines (Barlow, 1994).

For all three exposure levels considered, exceptions are anticipated as a result of the presence in the migrating substances of structural alerts for toxicity (see "Comments" below in Table 3) or depending on the outcomes of the minimum toxicity data set (see Section 9.3).

Table 3: The tiered approach to toxicity testing based on exposure levels

Tier number and specifications	Toxicity data required	Comments
Tier 1: Human exposure up to 1.5 µg/kg b.w. per day	Genotoxicity studies (see Section 9.3)	In general, no other toxicity studies are required below this threshold. However, other studies/information may be deemed necessary based on structural alerts regarding other toxicological endpoints, including endocrine effects, as recommended by the OECD guidance document for evaluating endocrine disruption and/or for substances with a high potential to accumulate in humans. Similarly, additional data may be required for nanomaterials, even if the bulk material has been evaluated and approved for FCM (EFSA 2011b)

Tier number and specifications	Toxicity data required	Comments
Tier 2: **Human exposure from 1.5 to 80 µg/kg b.w. per day**	Genotoxicity studies (see Section 9.3) Extended 90-day oral toxicity study in rodents (see Section 9.4)	A study on ADME (absorption, distribution, metabolism and excretion) should be made available to assess the potential for accumulation in humans of substances for which such a potential could be anticipated, e.g. based on a log $P_{o/w}$ above 3 or on known persistence of structurally similar substances, and for nanomaterials if there is any migration of the substance Based on the results of the 90-day study, additional studies, e.g. on endocrine endpoints, as suggested by the OECD conceptual framework for testing and assessment of endocrine disrupters, as well as on neurotoxicity and immunotoxicity, may be required
Tier 3: **Human exposure higher than 80 µg/kg b.w. per day**	Genotoxicity studies (see Section 9.3) Extended 90-day oral toxicity study in rodents (see Section 9.4) Study on ADME (see Section 9.4) Studies on reproduction and developmental toxicity (see Section 9.4) Studies on long-term toxicity/carcinogenicity (see Section 9.4)	Additional studies on specific endpoints may be required when deemed necessary. Moreover, EFSA may request additional data, if the data submitted are equivocal or warrant further investigation

9.3. Genotoxicity

As mentioned above, the genotoxic potential of any substance intentionally used in the manufacture of FCM should be assessed, even at low exposure. The EFSA Scientific Committee reviewed the current state of the science on genotoxicity testing and provided a commentary and recommendations on genotoxicity testing strategies (EFSA Scientific Committee, 2011b). As there is no reason why evaluation of the genotoxic potential of migrating chemicals should be different from that of other chemicals, in line with the new EFSA Scientific Committee's recommendations on genotoxicity testing strategies, two tests are called for:

- a bacterial reverse mutation assay (OECD Test Guideline (TG) 471); and
- an *in vitro* mammalian cell micronucleus test (OECD TG 487).

This combination of tests fulfils the basic requirements to cover the three genetic endpoints with the minimum number of tests: the bacterial reverse mutation assay covers gene mutations and the *in vitro* micronucleus test covers both structural and numerical chromosome aberrations.

In line with the recommendation of the Scientific Committee, the following *in vivo* tests would be suitable for following up substances that test positive in the *in vitro* base set:

- the *in vivo* micronucleus test (OECD TG 474);
- the *in vivo* comet assay (OECD 489);
- the transgenic rodent gene mutation assay (OECD TG 488).

The *in vivo* micronucleus test covers the endpoints of structural and numerical chromosomal aberrations and is an appropriate follow-up for *in vitro* clastogens and aneugens. The *in vivo* comet assay is an indicator test, sensitive to substances that cause gene mutations and/or structural chromosomal aberrations *in vitro*, and can be performed with many tissues. Transgenic rodent assays can detect point mutations and small deletions and are without tissue restrictions. The combination of tests assessing different endpoints in different tissues in the same animal, or the incorporation of such testing within other repeated-dose toxicity studies that will be conducted anyway, should be considered.

More detailed information on *in vitro* test methods, and on strategies for the *in vivo* follow-up of *in vitro* positives, is provided in the Scientific Committee's opinion on genotoxicity testing strategies (EFSA Scientific Committee, 2011b).

9.4. General toxicity

Studies on subchronic toxicity generally provide sufficient information to establish the main toxicological profile of the substance, providing information on the target organs and tissues affected, on the nature and severity of the effects induced, and on the dose-response relationships. The subchronic toxicity study is also useful for estimating the appropriate dose levels for subsequent chronic toxicity studies, and it may provide indications for the need for additional studies on particular effects, such as neurotoxic, endocrine or immunological effects.

Chronic toxicity and carcinogenicity studies may reveal effects not evident in subchronic studies, or may confirm effects observed in subchronic studies, at the same or perhaps lower doses. Chronic toxicity may be evaluated in a stand-alone study. Alternatively, the use of a combined protocol to study chronic toxicity and carcinogenicity in the same experiment will often be appropriate. The combined test is more efficient in terms of time, animals and cost than conducting two separate studies, without compromising the quality of the data in either the chronic phase or the carcinogenicity phase. Subchronic and chronic toxicity studies should allow the determination of the point of departure for safety assessment, for example the benchmark dose (BMD), i.e. the dose associated with a predetermined level of effect, using mathematical modelling (EFSA, 2009), or the NOAEL, i.e. the highest dose at which no adverse effects are observed. It should be noted that, in the longer term, the Scientific Committee anticipates that the BMD approach will be used as the method of choice for the determination of the reference points for deriving health-based guidance values and margins of exposure (EFSA, 2009). The Scientific Committee is currently reviewing the implementation, experience and acceptability of the BMD approach in EFSA's work.

Reproductive toxicity studies provide information about the effects and potency of a substance on male and female libido and fertility, on the female's ability to carry a pregnancy to term, on maternal lactation and care of the young, on prenatal and postnatal survival, on the growth and functional and behavioural development of the offspring, and on the reproductive capacity of the offspring, and they identify histologically any major target organs for toxicity (including reproductive organs) in the parents and offspring.

Prenatal developmental toxicity studies identify the potential for a substance to cause lethal, teratogenic and other toxic effects on the embryo and fetus, by examining embryonic and fetal resorptions or deaths and fetal weight and sex ratio and external, visceral and skeletal morphology.

Data on the extent or levels of systemic exposure to a substance, as well as an understanding of the major processes involved in its absorption, distribution, metabolism and excretion (ADME), can assist in the interpretation of toxicity studies and the prediction of possible accumulation.

New testing strategies were recently developed to enhance the toxicological information from short-term (OECD TG 407) and reproductive (OECD TG 443) toxicity studies on potential effects on the endocrine, nervous and immune system. Consequently, the improved study designs are incorporated into the recommended toxicological test methods and study protocols:

- The subchronic toxicity study should normally be conducted for a period of at least 90 days (OECD TG 408) in rodents. The new recommendation is to perform the testing with a modification to include the assessment of some additional parameters described in the more recent guideline on repeated-dose 28-day oral toxicity study in rodents (OECD TG 407). The additional parameters place more emphasis on endocrine-related endpoints (e.g. determination of thyroid hormones, gross necropsy and histopathology of tissues that are indicators of endocrine-related effects) and (as an option) assessment of oestrous cycles. The modified 90-day study should also allow the identification of chemicals with the potential to cause neurotoxic, immunological or reproductive organ effects, which may warrant further investigation in specialised studies.

- The prenatal developmental toxicity study (OECD TG 414) in rats or rabbits.
- For reproduction toxicity testing, the recently developed guideline for the Extended One-Generation Reproduction Toxicity Study (EOGRTS) (OECD TG 443) in rodents is recommended. As an alternative to the EOGRTS, the multi-generation study (OECD TG 416) could also be acceptable.
- Studies on chronic toxicity (12 months) and carcinogenicity in rodents, either separate studies (OECD TGs 452 and 451, respectively) or the combined study (OECD TG 453).
- The study on toxicokinetics (OECD TG 417), providing data on absorption, distribution, metabolism and excretion of the substance with consideration of the potential for accumulation in the human body.

Additional studies of endocrine activity, neurotoxicity or immunotoxicity may be required in the event that the substance bears specific structural alerts, or based on the findings of the toxicity studies performed. In this case, the following test methods are recommended:

- to address specific endocrine endpoints, further studies on the basis of the OECD Conceptual Framework for Testing and Assessment of Endocrine Disruptors (OECD, 2012);
- to address a neurotoxic potential, testing in accordance with OECD TG 424;
- to address developmental effects on behaviour and neurotoxicity, testing in accordance with OECD TG 426;
- to characterise immunotoxic and immunomodulatory effects, specific studies in accordance with the WHO Guidance for immunotoxicity risk assessment for chemicals (WHO, 2012).

At present, no validated methods are available that would allow assessment of a substance's potential to cause intolerance and/or allergic reactions in susceptible individuals following oral exposure. Studies on dermal or inhalation sensitisation may give information relevant to possible hazards from occupational exposure and could be helpful in assessing consumer safety, although their relevance to oral exposure remains unclear.

Non-testing methods, which include read-across structure–activity relationships (SARs) and quantitative structure–activity relationships (QSARs), may also be used in the hazard characterisation of the substance. The read-across approach contributes to the reduction of animal testing and resources. In this approach, one chemical (the source chemical) for which toxicological effects have been tested can be used to predict the same toxicological endpoints for an untested chemical (target substance) on the basis of structural similarity and analogous physico-chemical and toxicokinetic properties. It can be used on a case-by-case basis only if adequate justification, documentation and supporting data are available. OECD published a guidance document on grouping of chemicals describing the read-across strategy and describing the nature and content of information required to document and support this strategy.[11] The European Chemicals Agency (ECHA) has also provided background information on read-across, including general considerations and examples illustrating the reasoning and approach taken.[12] It should be emphasised that the use of the read-across approach may be accompanied by additional uncertainties. It should be noted that EFSA is funding a project on the development and application of read-across methodologies for the hazard characterisation of chemicals (EFSA, 2015).

All requested toxicity studies should be carried out in accordance with the principles of Good Laboratory Practice (Council Directives 87/18/EEC13 [14] and 88/320/EEC15 [16]), following the most recent version of the relevant OECD or European Commission guidance, as applicable.

[11] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282014%294&doclanguage=en
[12] http://echa.europa.eu/fr/support/grouping-of-substances-and-read-across
[13] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31987L0018:en:NOT
[14] Council Directive 87/18/EEC of 18 December 1986 on the harmonization of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances. OJ L 15, 17.1.1987, p. 29–30. http://eur-lex.europa.eu/LexUriServ/LexUri Serv.do?uri=CELEX: 31987L0018:en:NOT
[15] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31988L0320:en:NOT

9.5. Toxicological assessment of oligomers

Oligomers formed during the manufacture of plastics may migrate into food and should also be considered for safety assessment. Given that oligomers can be the dominant class of NIAS, using the same approach for their toxicological assessment as used for authorised substances could be justified. Oligomers are also an important part of polymeric additives. Oligomers with a molecular weight above 1 000 Da are unlikely to be absorbed by the gastrointestinal tract and so they are not considered to present a toxicological hazard, unless they are hydrolysed or able to induce a local effect on the gastrointestinal tract, such as stomatitis, oesophagitis and/or mucositis. If the occurrence of adverse effects affecting the mucosa lining the upper and lower gastrointestinal tract can be excluded, the cut-off value of 1 000 Da is recommended because it allows for any effect of the shape of molecules, which has an important influence on the likelihood of absorption of substances in the range 600–1 000 Da.[17] Below 600 Da, most substances are absorbed and the rate of absorption is determined by factors other than the size and shape of the molecule. Different cut-off values may be used based on a consideration of the nature of the polymer. For example, a cut-off value of 1 500 Da could be appropriate for poly- and per-fluoro compounds because the molecular volume of C-F is smaller than that of C-H molecules of the same molecular weight.

As only the fraction below the cut-off value is regarded as toxicologically relevant, safety assessment should focus on this low-molecular-weight fraction following the tiered approach, depending on the migration level observed, in accordance with Table 3. Toxicity tests should be conducted on an isolated low-molecular-weight fraction, but in the case of polymeric additives containing a high proportion of this fraction, toxicity tests may be conducted using the whole (unfractionated) additive.

9.6. Toxicological assessment of nanomaterials

In line with the EFSA Guidance on nanoscience and nanotechnologies (EFSA Scientific Committee, 2011a), six cases outline different toxicity testing approaches applicable to engineered nanomaterials (ENM) as follows:

Case 1—No presence/persistence of the ENM in the FCM as marketed; and **Case 2**—no migration of EMN from FCM to food matrix. No exposure, therefore no toxicity data needed.

Case 3—Complete ENM transformation into the non-nanoform takes place in the food matrix before ingestion; and **Case 4**—complete ENM transformation into the non-nanoform takes place in the gastrointestinal tract following ingestion. The safety assessment is fully based on the non-nanoform in accordance with the approach specified in Table 3. However, in Case 4 the possibility of the induction of direct local adverse effects of ENM on the upper and lower gastrointestinal tract has to be considered.

Case 5—Some of the ENM persists in the food matrix and in gastrointestinal fluids. The testing approach recommended is based on a comparison of information on ADME, toxicity and genotoxicity of the non-nanoform with, in the first instance, ADME, a repeated-dose 90-day oral toxicity study in rodents and genotoxicity information on the ENM. The purpose of comparing ADME and toxicity data from the two forms is to identify any major differences between the behaviour of the non-nanoform and that of the ENM.

Case 6—All the ENM persists in the food matrix and in gastrointestinal fluids. The approach to toxicity tests on the ENM should be based, in the first instance, on ADME, a repeated-dose 90-day oral toxicity study in rodents and genotoxicity information on the ENM. The ENM toxicity testing strategy provided for hazard identification and hazard characterisation should take into account the nanoproperties (EFSA Scientific Committee, 2011a).

[16] Council Directive 88/320/EEC Council Directive 88/320/EEC on the inspection and verification of Good Laboratory Practice (GLP). OJ L 145, 11/06/1988, p. 35–37. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31988L0320:EN:HTML.

[17] Regulation No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. OJ L 12, 15.1.2011, p. 1–89.

The Panel recognised that the availability of data to cope with some of the above-listed cases may depend on the specific properties of nanomaterials and on the likely impact of the matrix in which they are dispersed.

6.3. Toxicological assessment of substances non-intentionally added (NIAS) to plastic food contact materials

Substances used in the manufacture of plastic materials or articles may contain impurities originating from their manufacture. Moreover, during manufacture and use, reaction and degradation products can be formed. Impurities and reaction or degradation products migrating from FCM are evaluated by EFSA when related to the substance to be authorised for use, but there is no general authorisation or listing of these, which means that an evaluation in one application cannot necessarily be transferred to another.

Nevertheless, NIAS should be considered in the risk assessment of plastic FCM and included, if necessary, in the specifications and/or restrictions of a substance. The same approach as that used for authorised substances could, in principle, be applied to the toxicological assessment of NIAS, since the same degree of safety should be warranted for all migrating substances. However, NIAS frequently occur as multiple chemical species structurally inter-related and/or related to the parent substance. Non-testing methods could be taken into account on a case-by-case basis, for priority setting and for a preliminary toxicological assessment of NIAS. The methods applicable to NIAS could include grouping and "read-across" (see Section 9.1), computational methods (structure–activity relationships and quantitative structure–activity relationships), the Threshold of Toxicological Concern (TTC) (EFSA Scientific Committee, 2012a) and the Margin of Exposure (MoE) (EFSA, 2005; EFSA Scientific Committee, 2012b).

The TTC approach might be helpful when assessing low-exposure NIAS for which genotoxicity data are unavailable or the substance is only partly identified. The Scientific Committee concluded that a TTC of 0.15 µg/person per day [18] would provide sufficient protection against (genotoxic) carcinogenic and heritable effects (EFSA Scientific Committee, 2012a). [19] So, where human exposure to NIAS in food is below the TTC of 0.15 µg/person per day, genotoxicity data may be not necessary if, on the basis of the available structural information, it can be ruled out that they are part of the exclusion category (EFSA Scientific Committee, 2012a).

In a recent statement, the Scientific Committee has clarified the applicability of the MoE to genotoxic and carcinogenic substances present as impurities in substances added to food/feed (EFSA Scientific Committee, 2012b). Thus, this approach might also be considered for the preliminary assessment of suspected genotoxic and carcinogenic NIAS.

[18] To cover the endpoint of cancer, a human exposure threshold value of 1.5 µg/person/day was derived by the US Food and Drug Administration (FDA) (Rulis, 1986, 1989, 1992) to be applied to substances that do not contain a structural alert for genotoxicity/carcinogenicity. The threshold value was derived by mathematical modelling of risks from animal bioassay data on over 500 known carcinogens, based on their carcinogenic potency. Assuming that only 10 % of untested chemicals were carcinogenic, at this exposure level, 96 % of the chemicals would pose a less than one in a million lifetime risk of cancer (Munro, 1990; Barlow et al., 2001). In 1995, the FDA incorporated this threshold value in its Terms of Reference policy for substances present in FCM (US-FDA, 1995). Kroes et al. (2004) refined the threshold for the endpoint of cancer by deriving a value of 0.15 µg/person per day for substances containing a structural alert for genotoxicity (EFSA, 2012a).

[19] It should be noted that scientific experts from around the world met at the end of 2014 to review the science underlying the TTC concept. The workshop, co-hosted by EFSA and the WHO, was part of a broader EFSA/WHO project that aims to develop a globally harmonised tiered approach to TTC. In a wide-ranging series of discussions, the experts considered topics such as possible revisions of the Cramer classification scheme, modification of the TTC decision tree, and the general criteria that should be considered when deciding whether or not to apply the TTC method. The comments gathered will then be published along with the final workshop report.

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Abbreviations

ADME	absorption, distribution, metabolism, and excretion
AFC	former Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
BMD	benchmark dose
b.w.	body weight
CEF	Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
Da	Dalton
EC	European Commission
ECHA	European Chemicals Agency
EEC	European Economic Community
EFSA	European Food Safety Authority
ENM	engineered nanomaterial
EOGRTS	Extended One-Generation Reproduction Toxicity Study
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FCM	food contact material
FRF	fat reduction factor
JRC	Joint Research Centre (EC)
MoE	Margin of Exposure
NIAS	non intentionally added substance(s)
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
$P_{o/w}$	octanol/water partition coefficient
QSAR	quantitative structure–activity relationship
SAR	structure–activity relationship
SCF	Scientific Committee on Food
TG	Test Guideline
TTC	Threshold of Toxicological Concern
VKM	Norwegian Scientific Committee for Food Safety
WHO	World Health Organization