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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)

Abstract

This Opinion describes recent developments in the safety assessment of chemicals in food and explores their potential impact on EFSA evaluation of food contact materials (FCM). It is not intended to be a guidance document. The draft opinion was subject to a public consultation and this final Opinion takes into account the scientific comments received. The Opinion 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. Four food consumption categories could be set. They are approximately 9, 5, 3 and 1.2 times higher than the current SCF default scenario, i.e. 17 g/kg bw per day, and so using them would afford a higher level of protection, particularly for infants and toddlers. Special exposure scenarios might be used if consumption were lower. The amount of toxicity data needed should be related to the expected human exposure. The tiered approach of the SCF is updated. For substances used in FCM, genotoxicity testing is always required, even if their migration leads to a low exposure. Beyond this, three threshold levels of human exposure, namely 1.5, 30 and 80 µg/kg bw per day, are proposed as triggers for the requirement for additional toxicity data. Regarding the identification and evaluation of migrating substances, experience has shown that more focus is needed on the finished materials and articles. Considering the non-intentionally added substances (NIAS), such as impurities of the substance along with reaction and degradation products including oligomers, 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 have increased importance for the assessment of genotoxicity of NIAS.

Keywords: food contact materials, plastics, substances, safety 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, 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 food contact materials (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 Opinion is an outcome of a self-tasking activity by the CEF Panel. It describes the recent developments in the risk assessment of chemicals in food and explores their potential impact on EFSA evaluation of FCM substances. The draft of this opinion was published for a 3-month public consultation and was then modified in the light of the scientific comments received. EFSA technical report on that consultation process lists the comments received and provides a response to those comments, and it has been published as an accompanying document to this final, adopted Opinion. This Opinion will provide the European Commission (EC) with the scientific basis for a discussion among risk managers on possible implications for risk management. It is intended that, in turn, the EC 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 revisited 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, four 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 (bw) 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 bw per day. For category 3, in which contact with food categories 1 and 2 are excluded but contact is with foods specifically intended for infants and toddlers, the age group with the highest consumption is 'Toddlers', with a value of 50 g/kg bw per day. For category 4, in which the FCM is intended for contact with foods other than those covered by categories 1, 2 and 3, the age group with the highest consumption is 'Toddlers', with a value of 20 g/kg bw per day. The food consumption values for these four categories are approximately 9, 5, 3 and 1.2 times higher than the current SCF default model, i.e. 17 g/kg bw per day (1 kg food consumed by an adult weighting 60 kg bw), and so using them would afford a higher level of protection, especially for infants and toddlers. 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 non-intentionally added substances (NIAS) 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. This change towards the finished FCM and its use calls for an adjustment of the present system of listing substances in order to render transparent what has been evaluated.

In the case of testing for migration using food simulants, new rules are provided in Regulation (EU) No 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 loss in the safety assessment. In this Opinion, 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 FCM, but it is, in principle, also applicable to those used in non-plastic FCM and those substances that are not specifically regulated but are assessed by the users.

For the safety assessment of substances used in FCM, genotoxicity testing is always required, even if exposure is low. Beyond this, three threshold levels of human exposure, namely 1.5, 30 and 80 µg/kg bw per day, are proposed as triggers for the requirement of additional toxicity data. The first level, 1.5 µg/kg bw per day, is intended to be a general threshold for the investigation of potential toxic effects other than genotoxicity. In case a substance can be classified in Cramer class I (the less toxic class, i.e. the substance has a simple chemical structure and can be anticipated to be metabolised to innocuous products, suggesting low oral toxicity), a second level of 30 µg/kg bw per day could be set instead of 1.5 µg/kg bw per day as the threshold for the investigation of repeated-dose toxicity. A third exposure threshold is proposed as a trigger for additional toxicity studies beyond the core set of general toxicity data. This threshold is defined as 80 µg/kg bw per day, consistent with previous SCF guidelines. The Panel considers that exposure above this level would approach that observed for food additives and that it would, therefore, be appropriate to require a corresponding toxicological data set.

The 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 a 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.

Read-across may also be used in the hazard characterisation of all migrating substances. The read-across approach contributes to the reduction in animal testing and resources.

FCM 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 six cases identified may depend on the specific properties of the 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 should be applied for their toxicological assessment, as the same degree of safety should be warranted for all migrating substances. However, non-testing methods could have increased importance for the assessment of genotoxicity of NIAS.

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1 Introduction

1.1 Background and Terms of Reference

Regulation (EC) No 1935/2004[1] on materials and articles intended to come into contact with food describes the authorisation process for substances to be used in food contact materials (FCM). In that regulation it is foreseen that the European Food Safety Authority (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 on Food (SCF). The SCF guidelines date back to 2001 (EC, 2001) and have been used since 2003 by the former Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) of EFSA and by the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) 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 use 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. The SCF used the assumption that a person may consume daily up to 1 kg of food in contact with the relevant FCM. It has to be examined whether this assumption is conservative enough for population groups such as infants and children, and overly conservative for substances that find only minor use in FCM.

EFSA's work is linked to the decisions and regulations of the European Commission (EC). In accordance with Regulation (EC) No 1935/2004, the Commission must obtain from EFSA an evaluation on safety and risks prior to the authorisation of a substance used in plastic FCM. In turn, this EFSA evaluation is reflected in the risk management action taken by the Commission. The Commission regulation covers monomers and additives for plastics. Substances with other technical functions, such as solvents, polymerisation aids, catalysts, etc., may be covered by regulations in Member States.

The Union list of authorised substances in Regulation (EU) No 10/2011[2] does not include what have been termed the non-intentionally added substances (NIAS): oligomers, reaction products and impurities. The regulation states that NIAS should be considered in the risk assessment of plastic FCM and included, if necessary, in the specifications and/or restrictions of a substance. As the NIAS often constitute the main part of the migrate, a more detailed consideration of these could be necessary, including more consideration of the manufacturing and use conditions of the authorised substances and the plastic(s) made from them. Substances that migrate into foodstuffs require equivalent treatment in risk assessment, irrespective of their source or intended function. For all those substances that are not specifically regulated, if they migrate to food and irrespective if they are used intentionally or are NIAS, the producers and users have to demonstrate safety in their supporting documentation.

Over time, the evaluations of the EFSA have been increasingly taken into account the conditions of manufacture and use described by the applicant, but the listing in Regulation (EU) No 10/2011 remained largely limited to the substance used. If the substance is used for other types of plastics, under different manufacturing conditions and/or with a different purity, those applications may no longer be encompassed by EFSA evaluation and by the European Union (EU) legislation. However, the user of that substance or FCM should know whether they can consider that the NIAS is covered by the evaluation or whether they need to perform their own safety assessment. The present system of listing substances could be adjusted to improve the transparency on what has been evaluated.

There is also the possibility that the same substance is used in FCM that are not plastics and not subject to EU-wide harmonised legislation. These other uses could have an impact on consumer

[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.

exposure and this may be relevant for risk management decisions if a refined estimate of exposure was used in EFSA evaluation.

Several methodologies recently adopted by EFSA could have a bearing on the risk assessment of FCM substances. They include the concept of threshold of toxicological concern (TTC) (EFSA Scientific Committee, 2012), evaluation of nanoscience and nanotechnologies (EFSA Scientific Committee, 2011a), approaches for testing for genotoxicity (EFSA Scientific Committee, 2011b) and a move towards a more systematic and transparent treatment of uncertainties in a risk assessment (EFSA, 2015a).

Uncertainty can often be the reason for adopting conservative scenarios. In this document, uncertainty is considered in the context, e.g. food consumptions statistics, the characterisation and properties of substances in nanoform, using the read-across approach, and the need for more data depending on toxicological findings especially if they are equivocal.

This Opinion is an outcome of a self-tasking activity by the CEF Panel. It is organised with the same structure as the current guidelines (EC, 2001). The focus is on those sections and scientific areas that could benefit from updating. It should not be interpreted as the new guidance on data requirements to apply for safety evaluation of a substance intended to be used within the context of the authorisation process for FCM. Rather than to directly update the guidance, the EC and EFSA agreed at the end of 2014 on a two-step approach. First, EFSA will publish this Opinion which has the character of a discussion document. The draft of this opinion was published for a public consultation (EFSA, 2015b) and was then modified in the light of the scientific comments received. EFSA technical report on that consultation process lists the comments received and provides a response to those comments and it has been published as an accompanying document to this final, adopted, Opinion. This Opinion will now provide to the EC the scientific basis for a discussion among risk managers on possible implications on risk management. When those discussions have been concluded, the EC will in turn provide the feedback to EFSA to prepare the updated guidance.

As the task is defining safety as required by Article 3 of Regulation (EC) No 1935/2004, the same scientific reasoning and risk assessment principles can apply to all other migrating substances from all types of FCM. So this document should also be relevant for the assessments made by National Authorities as well as by industrial producers for not specifically regulated migrating substances.

2 Identity of the substance including any impurities

Although information about the identity of the substance as used and its impurities is necessary, experience gained over the years has shown that more focus on the migration potential from 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. Concerning impurities, their identification is a first step to enable a decision whether further (toxicological) assessment is required on the impurities themselves and/or their reaction products. No further assessment might be needed if they are eliminated during the manufacturing process.

3 Physical and chemical properties of migrating substances

Chemical properties of a substance are the determinants for its potential to persist or react in the final FCM as well as in food. Their physical properties influence their migration. Information is needed for the substance itself, impurities, oligomers (for instance, when a substance is used as a (co)-monomer) 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 relevant information includes: (i) the volatility and thermal/chemical stability of the substances used as well as their impurities; (ii) the octanol–water partition coefficient (log $P_{o/w}$) and the solubility of the migrating substances in solvents of different polarity and in food and food simulants; (iii) their stability in food simulants and food; (iv) hydrolysis in the gastrointestinal tract (e.g. using standard digestive fluid simulant for saliva, gastric juice and intestinal fluid); (v) 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 material

Information on the level of use, the function of the substance and the conditions of the manufacturing process are needed for assessing the quantities, types and nature of potentially migrating substances. Information on the use of the FCM is essential 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, the types of foods the plastic is intended to contact and whether the FCM is intended for single or repeat use applications, a more or less refined exposure estimate may be derived. If a more general contact with broad categories of food is foreseen, or the possibility cannot be excluded, 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.

The chemical synthesis pathway and the purity of the substance as used may have an impact on the type and nature of migration levels from the FCM. Variability in a given manufacturing process or processes applied by different manufacturers may influence the formation of the migration potential from the FCM. Any significant variation in the formation of potential migrants from the FCM will modify the exposure scenario and needs to be taken into account for the safety assessment. Specifications concerning the purity and the manufacturing process are relevant here.

5 Data on migration

Along with food consumption, migration data represent the core information for exposure and safety assessment. Ideally these data should give a realistic account of migration into foodstuffs. There are three main approaches: (i) modelling, (ii) simulation of migration and (iii) direct measurement in foods.

5.1 Modelling

Total mass transfer calculations can be understood as a very severe form of modelling. Migration data can be gathered starting with calculation of total mass transfer from the FCM, assuming that migration occurs from a limited thickness. A value of 250 µm was commonly used and leads in many cases to a large overestimation of migration. But in other cases, for high-diffusivity plastics, e.g. for polyolefins, migration may be underestimated especially for plastics articles that are thicker than 250 µm. In that case, a higher thickness should be considered.

The use of mathematical migration models has developed significantly in recent years, including validation for some of the most common types of plastics and multilayers. For guidance on migration modelling, the documents from the Commission services (EUR 24514 EN 2010) should be consulted.[3] As the migration model described there was designed to be conservative for compliance evaluation, it may give large overestimates in the case of migration from low diffusivity polymers, such as polyethylene terephthalate (PET). If different migration models or modelling parameters were to be used, they should be validated to ensure that real migration is not underestimated.

5.2 Simulation

New rules on testing with food simulants are provided in Regulation (EU) No 10/2011 and will be further explained in the EC guidelines on migration testing that are under development. Simulants as well as the time and temperature test conditions to be used were designed to result in migration data at least equal to those in foods, but this is not always the case. Regulation (EU) No 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 checked.

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

5.3 Direct measurement in foods

Analyses in food are needed when simulation is impossible or not reliable. They yield the most realistic data, but there are still limitations when it comes to identification and quantification of substance-related compounds, such as the NIAS. The foods must be selected to ensure that they represent all foods or categories of foods intended for the FCM application with respect to the properties determining migration, such as solubility and mobility of the migrant, and the conditions of time and temperature used to process and store the packed foods.

6 Exposure of the consumer

Since the early days of the SCF Working Group, a simple model has been applied to estimate exposure to chemicals migrating from FCM to food. The nature and extent of toxicity data needed for the safety assessment were derived from it by using a tiered approach. Given the lack of information on actual consumption of foods in contact with the material(s) containing the given substance, 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 beverages per day, of which 1 kg is packaged in a material with a contact surface of 6 dm^2. It is assumed that the packed foods are consumed at the end of their shelf life, when any migration will be maximal.

In the legal implementation, however, the 1 kg assumption has been reduced for many cases by two ways of correction, both correcting for lower consumption. Regulation (EU) No 10/2011 foresees that 'to check the compliance, the specific migration values shall be expressed in mg/kg applying the real surface to volume ratio in actual or foreseen use'. However, for packages containing less than 500 g or ml food as well as sheets and films not yet in food contact 'the value of migration shall be expressed in mg/kg applying a surface to volume ratio of 6 dm^2 per kg of food'. As most foods sold today are in smaller packages and the ratios of contact surface to content are often much higher, this allows a higher migration into the foods, sometimes many fold. The correction is based on the assumption that less food is consumed for small packs. Regulation (EU) No 10/2011 also foresees the application of a fat (consumption) reduction factor (FRF) for lipophilic substances to allow for the fact that no more than 200 g fat can regularly be eaten daily. As with above, this allows for a higher migration concentration into the foods because consumption is less than the 1 kg. Neither correction is applicable to materials nor to articles for foods intended for infants and young children (Regulation (EU) No 10/2011). EFSA has deviated on occasions from the default 6 dm^2 per kg of food, if justified, based on information provided by applicants. Applicants have not used the FRF concept in their dossiers and EFSA has not used it in their safety assessments for proposing restrictions, e.g. specific migration limits.

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 reconsidered. 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 those 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; (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 EFSA Scientific Committee, in its opinion on uncertainties in exposure assessment, stressed the need to harmonise risk assessment methodologies in the fields falling within EFSAs mission and pointed out that standard screening procedures are intended to produce conservative estimates of exposure (EFSA, 2006). As affirmed by EFSA (2011b) 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 EU countries.

According to recommendation 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 FCM for the population group with the highest potential food consumption expressed in g/kg body weight (bw); and (ii) the contact surface to food 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 (2003). The Comprehensive European Food Consumption Database (Comprehensive Database) released in 2011 by EFSA (2011a) contains detailed information on foodstuffs consumed by the European population.[4]

The EFSA 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. At that time, the databases should be re-examined to ensure that the different food categories/exposure scenarios described below, remain soundly based. 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 EFSA Comprehensive Database and the consumption of water by infants set by WHO, four 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 following corresponding sections.

[4] The EFSA Comprehensive database was 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. The figures reported in this opinion are based on the upgraded database.

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

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 substance under evaluation are intended to be used	Population driving the consumption[a]	Food consumption to be considered for the estimation of exposure (g/kg bw per day)
1	Water and baby bottle contents such as reconstituted milk formula	Infants[b]	150
2	Milk, milk products and other non-alcoholic drinks (e.g. fruit and vegetable juices)	Toddlers[c]	80
3	Solid foods specifically intended for infant and toddlers	Toddlers	50
4	Foodstuffs not covered by categories 1, 2 and 3	Toddlers	20

(a): This means that the critical population (infants or toddlers) consuming the foods grouped in a category has the highest consumption of one or more of the foods in that category; this does not mean that the critical population consumes all food types falling into that category.

(b): Infants are young children aged up to 12 months.

(c): Toddlers are young children aged from 12 months up to and including 36 months.

The Panel noted that the food consumption for these four food categories obtained from the WHO and the EFSA Comprehensive Database are in the same range as the current model (1 kg/person per day) when this one kg is expressed by kg bw using the body weight of the population driving the consumption, i.e. 200 g/kg bw for infants (5 kg bw) and 83 g/kg bw for toddlers (12 kg bw).

6.1.1 FCM 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 (young children up to 12 months) 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 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 bw per day based on the consumption of 0.75 l of water/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 (RTFF) having been in contact with the baby bottle or the packaging of the RTFF, 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 the high levels of consumption of water observed in any other age groups, as reported in the EFSA Comprehensive Database. The observed 95th percentile of consumption was up to 96 g/kg bw per day in toddlers (12–36 months), 78 g/kg bw per day in children (3–9 years), 39 g/kg bw per day in adolescents (10–17 years), 35 g/kg bw per day in adults (18–64 years), 29 g/kg bw per day in the elderly (65–74 years) and 28 g/kg bw per day in the very elderly (75 years and older).

Therefore, the level of consumption of 150 g/kg bw per day would cover the whole population. The 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 bw per day (1 kg food consumed by an adult weighing 60 kg).

6.1.2 FCM used in contact with beverages such as non-alcoholic beverages, milk or other liquid milk-based 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, which includes or could include packaging of non-alcoholic beverages, milk or other liquid milk-based 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 EFSA Comprehensive Database (EFSA, 2011a), the 95th percentile of beverage consumption by toddlers in the different Member States ranged from 19 to 86 g/kg bw per day for liquid milk, from 14 to 49 g/kg bw per day for fermented-milk products, from 19 to 43 g/kg bw per day for fruit and vegetable juices and from 17 to 76 g/kg bw per day 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 bw per day in the different Member States), as loyalty to a beverage packaged in material containing a specific substance is unlikely to occur 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 bw 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 (to be clear, all foods including beverages) of 68 g/kg bw (95th percentile of 114 g/kg bw) reported for UK children aged 1 to 4 years (Foster et al., 2010). It would, therefore, also cover the scenario of toddlers 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 figure of 80 g kg bw per day is approximately five times higher than the one used in the current scenario, i.e. 17 g/kg bw 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 bw, 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 EFSA Comprehensive Database are available on the EFSA website.[6]

6.1.3. FCM used in contact with solid foods specifically intended for infants and toddlers

If substances are not intended to be used in food contact applications as described in Sections 6.1.1. and 6.1.2., but may be used in contact with solid foods (i.e. other than beverages) specifically intended for infants and toddlers, then the level of consumption of these groups of population must be considered.

In the EFSA Comprehensive Database, specific foods for infants and toddlers comprise (besides infant and follow-up formulae, juices and tea, which are covered in previous sections) cereal-based foods (pasta, biscuits, simple cereals and cereals with an added high-protein food which are or have to be reconstituted), ready-to-eat meals (based on different ingredients: vegetable, cereal, meat or fish), fruit purée and dairy products (yoghurt, cheese preparations, milk-based dessert and puddings). The highest 95th percentiles of consumption of toddlers in the different Member States were: 12.3 g/kg bw per day for dairy products, 22.5 g/kg bw per day for cereal-based foods and 48.3 g/kg bw per day for ready-to-eat meals. Plastics and non-plastics materials are used as packaging for these foods and brand/packaging loyalty is to be expected. Particularly for the ready-to-eat meals, glass jars with metal lids and plastic sealing gaskets are commonly used. For such packaging materials, the level of consumption of baby food and drinks as a potential source of semicarbazide from the sealing gaskets

[6] The EFSA Comprehensive Food Consumption Database: food consumption data per country, survey and age class, in g/day or g/kg bw per day are available online: http://www.efsa.europa.eu/en/food-consumption/comprehensive-database.

was previously considered (EFSA, 2005). The consumption ranged, on average, from 11.5 to 26.6 g/kg bw per day, and, at the 95th percentile, from 33.1 to 52.7 g/kg bw per day, for infants during the first year of life (EFSA, 2005). The comparison with the values now extracted from the database for toddlers indicates that it can be considered, in these cases, that toddlers' consumption values also cover consumption of younger ages.

Consistent with the approach followed in the other consumption categories of this opinion, the highest 95th percentile value of a single category of food – 48.3 g/kg bw day for ready-to-eat meal – is considered to represent the total amount of food consumed that was packaged in a FCM containing the substance under evaluation. In fact, this value is in good agreement with the value obtained for the highest 95th percentile of the total consumption of specific foods for infants and toddlers, i.e. when all subcategories are considered together in each Member State, which is 49.4 g/kg bw day. These data, as in the previous cases, are subject to uncertainty inherent to the many factors affecting precision and accuracy of data of the present nature. As for example, the highest 95th percentile value reported (48.3 g/kg bw day) originated from a German Survey conducted in 2006–2008, whereas a more recent survey also in Germany reports a 95th percentile value considerably lower at 28 g/kg bw day. The value is plausible, however, as it corresponds, e.g. to a soup (typically 200 g), a menu (220–250 g) and a dessert (140–160 g) marketed in glass jars, not fully eaten up per day.

The level of consumption of 50 g/kg bw per day is considered appropriate to cover the consumption by infants and toddlers of solid foods specifically intended for infants and toddlers. The CEF Panel underlines the fact that this consumption is approximately three times higher than the one used in the current scenario, i.e. 17 g/kg bw per day.

6.1.4. FCM intended to be used in contact with all other foodstuffs not covered by Categories 1, 2 and 3

Scenario 4 is considered appropriate for food contact applications other than for those covered in categories 1–3, i.e. water, infant formula, milk, milk products and other non-alcoholic beverages, and solid foods specifically intended for infant and toddlers.

Once the previous scenarios are excluded, then, according to the EFSA Comprehensive Database, consumption of remaining foodstuffs (FoodEx group level 2) does not exceed 41 g/kg bw per day at the 95th percentile intakes (for consumers only) for any single food group at any age. This consumption value is triggered by the highest 95th percentile consumption of the food group 'alcoholic beverages' (mostly beer and beer-like beverages) observed in the adult population. The consumption of remaining food groups (excluding alcoholic beverages) does not exceed 22.5 g/kg bw per day at the 95th percentile intakes (for consumers only) for any single food group at any age. The Panel considers, as a practical approach, that alcoholic beverages should be included in this fourth 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.

Overall therefore, the level of consumption of 20 g/kg bw per day is considered appropriate to cover the consumption by all population groups of foods other than those covered in Categories 1, 2 and 3. The CEF Panel underlines the fact that this consumption is very similar to the current scenario, i.e. 17 g/kg bw per day.

6.1.5. FCM intended to be used for specific applications

If substances are intended to be used only for specific applications that result in a level of consumption of the affected foodstuffs being significantly lower than 20 g/kg bw, 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 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 Calculation of the exposure to set the toxicological data requirement

As a general principle, the exposure could determine the toxicological data required according to the tiered approach as presented in Section 8.2. The exposure for a food category (see Table 1) could be estimated by using information on the amount of food consumed that has been in contact with the FCM containing the substance of interest and the concentration levels in the foods.

6.2.1 Combination of food consumption scenarios with migration

Exposure could be estimated from each food category covered by the intended uses of the food contact materials/articles, i.e. category 1, 2, 3, 4 or a combination of all or parts of the four food categories.

The Panel considers that it is conservative enough to use the highest calculated exposure of all categories to determine the toxicological data required instead of summing up highest exposures calculated for each of the categories, for the following reasons:

a. The proposed model, which is expected to cover potential cumulative high consumption of all four food categories, is conservative. Food consumption data for high consumers (i.e. at the 95th percentile level) is combined with a high-level migration whereas an average migration would be, in theory, more appropriate. Indeed, migration is determined using the most severe conditions of time, temperature, polymer type, concentration in the polymer, food/simulant type, etc.
b. The highest migration determined in the category is combined with the corresponding food consumption instead of averaging the migration in all subfood categories (e.g. water and reconstituted milk for category 1).
c. Several recent independent studies, targeting data collection on consumption of packaged food (and not total food consumption) by different age groups, indicate that the average consumption (and the 95th percentile) of total packaged foods are below the levels considered here. Bearing in mind that total packaged foods are not all packed in plastics, and for plastics not even in the same type of polymer, it is a conservative scenario of exposure to not apply a type of packaging use factor[7] (e.g. US Food and Drug Administration (US FDA)) but to assume that all consumed foods are packed in plastics that contain always the same substance. The data reported in these studies support the fact that summing up the exposures estimated for each category would yield a large overestimation of the total exposure. Especially, it is unlikely that loyalty to a beverage packed with material containing a specific substance is concomitant with loyalty to another category of beverage (category 2) or food from another category, packed with the same or another material containing the substance of interest.

The exposure for a food category can be calculated by combining the consumption level of the food category (see Table 1) with the migration levels into the foods covered by the food category.

Deviations from this standard approach might be appropriate. Taking food consumption data for high consumers (i.e. at the 95th percentile level) and combining this with migration data using the most severe conditions of time, temperature, polymer type, concentration in the polymer, food/simulant type, etc., may give rise to a combination of conservative assumptions that is very unlikely to occur in practice. More refined calculations of exposure could be envisaged, using for example typical rather than worst-case values for one or more migration parameters or using packaging use factors, provided that the reliability of the approach taken in providing protection of consumers is demonstrated. Packaging use factors are unlikely to be justified for consumption of categories 1, 2 and 3 for the reason of brand/packaging loyalty.

[7] Packaging use factors aim to describe the proportion of the diet that is packed in different types of FCM and are derived from market share information.

6.2.2 The ratio of food mass to contact area

From recent surveys, it is clear that the ratio of surface area of food packaging materials to food mass 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 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 for 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 from 1 to 4 years and 10 dm^2/kg for foodstuffs eaten by children aged from 4 to 6 years (Foster et al., 2010). The range of values was 0.8–11.6, 4.2–18.5 and 2.7–20.8 dm^2/kg for the three age groups < 1, 1–4 and 4–6 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.

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 ratio is 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 an appropriate conversion factor to represent the surface to mass ratio of packaged foodstuffs when these other considerations are also taken into account. In the case of an FCM intended for specific applications only and if reliable data were available then a different surface area/mass ratio along with packaging use factors and other relevant parameters could be justified. 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.

6.3 Other sources of exposure

Other sources of dietary exposure to the substance of interest need to be considered, in particular known or anticipated human exposure to the proposed substance from other food contact plastic materials, from non-plastic FCM and from other food sources (e.g. natural constituent, food additives, flavourings, from drinking water, substance developed during the normal processing of foods, carry-over originating from their use in animal feed). When non-dietary exposure (e.g. consumer products such as toys, cosmetics, pharmaceuticals, exposure via dermal or inhalation routes) is significant, the possible impact on the safety assessment of the dietary exposure needs also to be considered.

7 Nanomaterials

Nanotechnology and nanomaterials are a new technological development and FCM are one sector in which the use of nanomaterials has featured. The specific properties of nanomaterials 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 in biological matrices, and from the limited availability of toxicity data and test methods. 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 likely to be 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. Substances used for surface treatment of nanoparticles may be soluble and so may be

released and migrate independently from the particles themselves. If so, they 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 the FCM and possibly migrating from the FCM

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 activity	Information on photocatalytic activity of relevant materials used in food packaging, coatings and printing inks and on internal reactions.

8 Toxicity data

8.1 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, whereas 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 Opinion, 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 FCM, but it is, in principle, also applicable to other non-plastic FCM, oligomers and other NIAS.

The testing strategy should be based on the available information on the substance(s) in question. This includes an appropriate literature search including the existing information from other databases (e.g. from ECHA), before planning the experimental studies described in Section 8.2). In accordance with rules from the EC, especially Directive 2010/63/EU[8] (Article 4), unnecessary animal studies should be avoided.

8.2 Tiered approach to toxicity testing of substances migrating from food contact materials

A possible tiered approach to toxicity testing based on exposure levels is summarised in Table 3. It applies in principle to all migrating substances, i.e. used and non-intentionally added substances

[8] Directive No (EU) 2010/63 of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

(including oligomers). For NIAS which migrate into foods, further considerations on genotoxicity and toxicity testing are possible and are expressed in Sections 8.7 and 8.8.

For the assessment of genotoxicity potential of substances used in FCM, testing is always required, even if exposure is low.

Beyond this, three threshold levels of human exposure, namely 1.5, 30 and 80 µg/kg bw per day, are identified as triggers for the requirement of toxicity data in addition to genotoxicity. The thresholds of 1.5 and 30 µg/kg bw per day originate from the TTC concept (EFSA Scientific Committee, 2012).

The first level of 1.5 µg/kg bw per day is intended to be a general threshold for the investigation of repeated-dose toxicity. This figure is the threshold proposed by Munro et al. (1996) for non-cancer endpoints elicited by substances belonging to Cramer Class III (Cramer et al., 1978) which represents substances with the highest anticipated toxicity. It should be noted that such a threshold, which provided a large margin of safety (> 100) when compared with a no observed adverse effect level (NOAEL) 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 bw 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 bw per day will provide an even larger margin of safety when applied to FCM. Indeed, a recent examination of 232 authorised FCM substances for which a NOAEL was established confirmed the conservatism of this threshold (Pinalli et al., 2011).

In case a substance can be classified in Cramer class I (Cramer et al., 1978), i.e. it has a simple chemical structure and can be assumed to be metabolised to innocuous products, suggesting low oral toxicity, a second level of 30 µg/kg /bw could be set instead of 1.5 µg/kg bw per day as the threshold for the investigation of repeated-dose toxicity. This figure proposed by Munro et al. (1996) was considered sufficiently conservative by the EFSA Scientific Committee (EFSA Scientific Committee, 2012).

A third exposure threshold, 80 µg/kg bw per day, is proposed as a trigger for additional toxicity studies beyond the core set of general toxicity data (see Section 8.4). This threshold is pragmatically defined in line with previous SCF guidelines (Barlow, 1994).

For all 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.

Table 3: A tiered approach to toxicity testing

Tier number and specifications	Toxicity data required	Additional considerations
Tier 1: **Human exposure up to 1.5 µg/kg bw per day** **or if** **The substance is classified as Cramer class I and exposure is less than 30 µg/kg bw per day**	– Genotoxicity studies (see Section 8.3) – Available information including an appropriate literature search (Section 8.1)	In general, no other toxicity studies are required below this threshold. Exceptions are: (1) if there are existing data indicating the potential to affect endocrine or neural systems; (2) for substances with a high potential to accumulate in humans; (3) for nanomaterials, even if the non-nanoform material has been evaluated and approved for FCM.

Tier number and specifications	Toxicity data required	Additional considerations
Tier 2: Human exposure from 1.5 to 80 µg/kg bw per day	As above, plus: – Extended 90-day oral toxicity study in rodents (see Section 8.4)	A study on absorption, distribution, metabolism and excretion (ADME) should be used to assess the potential for accumulation in humans of substances for which such a potential could be anticipated. If there are existing data indicating endocrine activity suggesting potential effects from prenatal exposure, a 90-day study with a prenatal treatment period or an extended one-generation reproduction toxicity study (EOGRTS) should be considered.
Tier 3: Human exposure higher than 80 µg/kg bw per day	As above[(a)], plus: – Study on ADME (see Section 8.4) – Studies on reproduction and developmental toxicity (see Section 8.4) – Studies on long-term toxicity/carcinogenicity (see Section 8.4)	If there are existing data indicating endocrine activity suggesting potential effects from prenatal exposure, a chronic study with a prenatal treatment period or an EOGRTS should be considered.

(a): The extended 90-day oral toxicity study required in tier 2 might not be necessary as it is covered by the long-term testing.

For all tiers, additional studies on specific endpoints (e.g. on endocrine endpoints, as suggested by the OECD conceptual framework for testing and assessment of endocrine disrupters (OECD, 2012), as well as on neurotoxicity and immunotoxicity), may be needed depending first on the initial testing strategy (see Section 8.1) and secondly, if the studies conducted are equivocal or warrant further investigation.

It should be noted that *in vitro* studies on endocrine effects are useful to identify potential modes of action but do not necessarily reflect the *in vivo* situation, e.g. in case of *in vitro*-effects at inappropriately high concentrations. Consequently, *in vitro* data should be interpreted carefully along with other available information on the applied substance to decide whether or not *in vivo* follow-up studies are needed. Currently, the CEF Panel is following ongoing discussion and developments (EFSA, 2012; EFSA Scientific Committee, 2013). Notably, EFSA is involved in a number of initiatives to develop scientific knowledge in the field of endocrine active substances and also on overlapping issues such as non-monotonic dose–response relationships and biological relevance in risk assessment. These can be consulted from the EFSA website (http://www.efsa.europa.eu/en/topics/topic/eas). The CEF will align with any new EFSA position on these matters when appropriate.

8.3 Genotoxicity

As mentioned above, the genotoxic potential of any substance intentionally used in the manufacture of FCM should always be assessed. 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, consistent 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);
- 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.

Consistent 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 evaluating DNA primary lesions is an indicator test sensitive to substances that cause gene mutations and/or structural chromosomal aberrations *in vitro*. Particularly, it is a useful tool for the assessment of local genotoxicity, especially for organs/cell types which cannot easily be evaluated with other standard tests. 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).

8.4 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, 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. In case the potential for prenatal effects (e.g. endocrine) is identified or suspected, inclusion of prenatal exposure should be considered.
- 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). As for the subchronic toxicity study, in case the potential for prenatal effects (e.g. endocrine) is identified or suspected, inclusion of prenatal exposure should be considered.
- 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.

If there are existing data suggesting a potential for neurotoxicity or immunotoxicity additional studies may be required. In this case, the following test methods are recommended:

- 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.

All toxicity studies should be carried out in accordance with the principles of good laboratory practice (Council Directives 87/18/EEC[9] and 88/320/EEC[10]), following the most recent version of the relevant OECD or EC guidance, as applicable.

8.5 Read-across

Non-testing methods and approaches such as read-across, may also be used in the hazard characterisation of all migrating substances. The read-across approach contributes to the reduction in 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)

[9]Council Directive 87/18/EEC of 18 December 1986 on the harmonisation 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/LexUriServ.do?uri=CELEX:31987L0018:en:NOT

[10]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

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 (OECD, 2014). The European Chemicals Agency (ECHA) has also provided background information on read-across, including general considerations and examples illustrating the reasoning and approach taken (ECHA, 2013a, 2013b, 2015). 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, 2015c).

8.6 Toxicological assessment of nanomaterials

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

Case 1 – No presence/persistence of the NM in the FCM as marketed; and **Case 2 –** no migration of NM from FCM to food matrix. The maxim 'No exposure, therefore no toxicity data needed' could be applied. However, at present, no generally valid threshold of toxicological concern can be derived for nanoparticles. Although migration modelling indicates that very low (if any migration at all) is likely to occur for many polymer/NM combinations (Ntim et al., 2015; Bott et al., 2014a,b,c), the possibility of transfer to the food by the processes of abrasion and swelling/leeching cannot be discounted, especially if the combination of plastic plus NM plus food is not well matched. Analytical methods for testing foods or food simulants for migration of NM have detection limits that are generally higher and inferior to methods for substances in conventional form. This being so, given the lack of a trigger value and the impossibility of demonstrating zero migration, nanoparticles must be considered case-by-case. If relevant migration may occur, toxicity data are needed starting with an assessment of genotoxic potential, in accordance with the EFSA Guidance on nanoscience and nanotechnologies (EFSA Scientific Committee, 2011a).

Case 3 – Complete NM transformation into the non-nanoform takes place in the food matrix before ingestion; and **Case 4 –** complete NM transformation into the non-nanoform takes place in the gastrointestinal tract following ingestion. Similar to the cases 1 and 2, the question of what constitutes 'complete transformation' of the NM arises. It is not possible at this stage of scientific understanding to give concrete guidance as each case of NM must be considered individually. For the transformed (solubilised) form, 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 NM on the upper and lower gastrointestinal tract has to be considered.

Case 5 – Information on non-nanoform available. When information on a non-nanoform of the same substance is available and where some or all of the NM persists in the food matrix and in gastrointestinal fluids, a 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 NM. 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 NM. If the differences observed indicate increased hazard, then more toxicity testing will be required on the NM, beyond ADME, 90-day and genotoxicity tests. If the differences observed indicate less hazard then any request to waive further testing should be scientifically justified.

Case 6 – No information on non-nanoform available. When information on a non-nanoform is not available and where some or all of the NM persists in the food matrix and in gastrointestinal fluids, the approach to toxicity tests on the NM should follow the relevant EFSA guidance for the intended use with the modifications in the present opinion to take into account the nanoproperties. The toxicity testing strategy provided for hazard identification and hazard characterisation should take into account the nanoproperties (EFSA Scientific Committee, 2011a).

As there are no specific data requirement for migrating NM in the FCM area, the CEF Panel considers that, in the first instance, toxicity testing required for NM in case 6 are the same as for NM in case 5. The decision on further testing requirements should be made in the light of the results.

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. The Panel also took note that the safety assessment of NM is likely to be a priority topic of the EFSA Scientific Committee for its current three-year mandate. The CEF Panel will align with any new EFSA position on these matters when appropriate.

8.7 Toxicological assessment of polymeric additives and oligomers

Polymeric additives are specifically made as such whereas oligomers are an unintentional consequence of incomplete polymerisation when making plastics. They both may consist of lined-up monomers either with the free main terminal functionality from the monomer and/or in a cyclic form. They often include or consist of compounds reacted with a chain stopper (intentionally added or impurity) or polymerisation is blocked by internal reactions, such as ring formation, giving the molecules new properties. Hence, polymeric additives and oligomers not necessarily have toxicological properties which can be extrapolated from those of the monomer(s).

The safety assessment of polymeric additives and oligomers should take into consideration the molecular mass. Compounds 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 induce a local effect on the gastrointestinal tract, such as stomatitis, oesophagitis and/or mucositis. If the latter can be excluded, a cut-off value for the molecular mass at 1,000 Da is recommended, as it covers any shape of molecules influencing the likelihood of absorption.[11] Most substances below 600 Da are absorbed and the rate of absorption is determined by factors other than size and shape of the molecule. For poly- and per-fluoro compounds, a cut-off value of 1,500 Da could be appropriate, because the molecular volume of C-F is smaller than that of C-H molecules of the same molecular mass.

Safety assessment should focus on the low-molecular mass fraction and follow the tiered approach in accordance with Table 3. In the case of polymeric additives containing a high proportion of constituents below the cut-off of molecular mass, toxicity tests may be conducted using the whole (unfractionated) additive. For oligomers, tests should be conducted on an isolated low-molecular-weight fraction or a mixture of oligomers similar to that migrating from the plastic FCM.

For the assessment of genotoxicity potential, experimental testing referred to in Section 8.3 may not be necessary. For instance, testing is not necessary if the absence of genotoxicity has been demonstrated for the monomers and the oligomers have the same functionality as the monomer. If not evaluated yet, genotoxicity potential of the monomer(s) should be evaluated according to Section 8.3. In the case of polymeric additives or oligomers derived from evaluated and authorised monomers with genotoxic properties, genotoxicity data on the fraction below 1,000 Da fraction are needed, unless scientific arguments are provided to rule out genotoxicity concern, such as that the reactive functional group of the monomer is eliminated (e.g. the double bond of vinyl chloride in polyvinyl chloride (PVC)).

Relevant scientific arguments may also be considered, such as metabolism (e.g. hydrolysis to the monomers), structure–activity relationships and read-across from similar substances. If partial or complete hydrolysis of a polymeric additive or oligomers occurs in the food following migration or *in vivo* following consumption, then the amount of the monomer thus liberated should be added to the amount of monomer migrating *per se* when estimating the exposure level and the consequent toxicity data requirements.

[11] 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.

8.8 Toxicological assessment of impurities, reaction and degradation products (other than oligomers)

Substances used in the manufacture of plastics may contain impurities originating from their manufacture and may form reaction and degradation products during production or treatment of the FCM. Safety evaluation of impurities and reaction and degradation products (NIAS) is often demanding and requires a careful selection of the tools used. Some approaches have been proposed in the literature and/or are under further development (Rennen et al., 2011; Koster et al., 2014; ILSI, 2015).

There is no general authorisation or listing of NIAS, which means that the listing of a substance may or may not cover them. EFSA considers reaction and degradation products and impurities in the risk assessment of substances for plastic FCM and, if necessary, these are included in the specifications and/or restrictions of a substance (Regulation (EU) No 10/2011). However, the evaluation is restricted to the use described by the applicant. Basically the same approach as that used for authorised substances is applied, as the same degree of safety should be warranted for all migrating substances.

Reaction and degradation products and impurities frequently occur as structurally inter-related multiple chemical species and are often related to the parent substance. Non-testing methods may be taken into account on a case-by-case basis, for priority setting and for a preliminary toxicological assessment. Applicable methods include grouping and 'read-across' (see Section 8.5), computational methods (structure–activity relationships (SAR) and quantitative structure–activity relationships (QSAR)) and the TTC (EFSA Scientific Committee, 2012). The CEF Panel noted that the EFSA Scientific Committee had special considerations with regards to applying the TTC to substances with endocrine activity.

The TTC approach may be applicable with regard to genotoxicity. The EFSA Scientific Committee concluded that a threshold of 0.15 µg/person per day[12] would provide sufficient protection against (genotoxic) carcinogenic and heritable effects when it can be ruled out that the compounds are part of the exclusion category (EFSA Scientific Committee, 2012).[13] Therefore, no genotoxicity data are needed for NIAS if exposure is below 0.15 µg/person per day.

Testing on mixtures of reaction products and impurities might be a tool to address genotoxic potential. As this enables to apply Tier 1 (Table 3), it could be useful where the identification and evaluation of a large number of reaction products and impurities is not feasible. Testing on mixtures presupposes, however, sufficient sensitivity for detecting genotoxic substances constituting minor proportions of the mixture. This may require fractionation of the mixture and prior removal of bulk components which are then evaluated separately. These mixtures would have to be representative for migration from the particular FCM application.

[12] To cover the endpoint of cancer, a human exposure threshold value of 1.5 µg/person per day was derived by the US Food and Drug Administration (US 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 US 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 Scientific Committee, 2012).

[13] 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
bw	body weight
CEF	Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
Da	dalton
DNA	deoxyribonucleic acid
EC	European Commission
ECHA	European Chemicals Agency
EEC	European Economic Community
EOGRTS	extended one-generation reproduction toxicity study
FAO	Food and Agriculture Organization of the United Nations
FCM	food contact material/s (and/or article/s)
FRF	fat reduction factor
NIAS	non-intentionally added substance(s)
NM	nanomaterial
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PET	polyethylene terephthalate
$P_{o/w}$	octanol–water partition coefficient
PVC	polyvinyl chloride
QSAR	quantitative structure–activity relationship
SAR	structure–activity relationship
SCF	Scientific Committee on Food
SML	specific migration limit
TG	Test Guideline
TTC	threshold of toxicological concern
US FDA	United States Food and Drug Administration
WHO	World Health Organization