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Protocol for the exposure assessment as part of the safety assessment of phthalates, structurally similar substances and replacement substances potentially used as plasticisers in materials and articles intended to come into contact with food

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Abstract

EFSA was requested by the European Commission to re-evaluate the risks to public health related to the presence of plasticisers such as phthalates, structurally similar substances and replacement substances, as a consequence of migration from food contact materials (FCMs). In the first part of the two-part mandate, EFSA was tasked with establishing a protocol for assessing the exposure of EU consumers to the plasticiser substances. Other tasks in the first part of the mandate include: i) identifying and prioritising those plasticisers used in FCMs that may warrant further data collection and eventual risk assessment, ii) establishing a protocol for the hazard assessment of the prioritised substances, and iii) establishing calls for data and other information on the occurrence of the prioritised substances to support dietary exposure estimates. Work to address those three additional tasks will be reported separately. Close collaboration with the European Chemicals Agency was requested in the mandate for all tasks leading up to the risk assessment stage. This exposure protocol has been developed using the principles and following the recommendations provided in the *Draft framework for protocol development for EFSA's scientific assessments* (EFSA et al., 2020). The protocol describes how the three central questions will be addressed: what is the total dietary exposure, what is the exposure coming from FCMs, and what is the overall exposure (dietary and non-dietary) to the prioritised substances in different population groups and age classes in the EU. The protocol aims to describe as far as possible the approach applied for identifying, extracting, cleaning and selecting data, appraising the relevant evidence, analysing and integrating that evidence and addressing the uncertainties, in order to perform exposure assessments that will be used for the risk assessment of the prioritised substances in the second part of the two-part mandate. This draft protocol has been endorsed by the Panel on Food Contact Materials, Enzymes and Processing Aids for public consultation.

Key words: protocol, phthalates, plasticisers, exposure assessment methodology, food contact materials, dietary exposure, non-dietary exposure

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Background from the mandate letter

EFSA has recently updated the risk assessment of five phthalic acid esters (ortho-phthalates), namely DBP, BBP, DEHP, DINP and DIDP, authorised for use as additives in plastic food contact materials (FCMs), published in December 2019 (EFSA CEP Panel, 2019). Based on this new opinion, DG SANTE is considering whether any changes to the existing EU legislation are necessary.

The previous mandate sent by the Commission was limited to new scientific information which was assessed by the European Chemicals Agency (ECHA) as regards reprotoxicity. This assessment subsequently resulted in several new restrictions under the REACH Regulation (EC) No 1907/2006[1]. The recently adopted EFSA opinion did not identify any risk to human health from current exposure to these five ortho-phthalates from dietary sources. Nevertheless, it highlighted limitations of the work carried out and has set the Tolerable Daily Intakes (TDIs) on a temporary basis. It is therefore appropriate to address these limitations and establish a greater degree of certainty as regards the possible risks from these phthalates in food, from FCMs.

Additionally, the scope of the previous mandate was restricted to the five ortho-phthalates authorised as additives in annex I to Commission Regulation (EU) No 10/2011[2], which are used as plasticisers and technical support agents in plastic FCM. However, information collected by the Commission, including a short EU stakeholder survey[3] as well as results of controls carried out by Member States under Commission Recommendation 2019/794[4], confirms that these five ortho-phthalates are to a large extent being replaced by other plasticisers such as terephthalates, cyclohexanoates and epoxy esters. A list including these substances is provided in annex II to this letter[5]. The information, which we have provided to EFSA, also indicates that other phthalates are used as technical support agents in addition to those specifically authorised for plastic FCM. Of additional importance is the use and occurrence of phthalates and non-phthalate plasticisers in FCM other than plastic, most notably rubber. Whilst it should be stressed that our present findings are not statistically robust enough to draw comprehensive conclusions, it is nevertheless important to take this information into account in the design of the work.

It is understood that ongoing screening and prioritisation work by ECHA on groups of structurally similar substances covers substances that may be relevant as regards their use in FCMs within the scope of this mandate and therefore their possible assessment by EFSA. With reference to the Memorandum of Understanding between ECHA and EFSA[6], the Commission would therefore like to request that the two agencies work together during the first part of this mandate for identification, prioritisation and preparatory tasks in advance of the second part of the mandate concerning the risk assessment work. This pooling of resources and expertise will promote inter-agency cooperation, maximising efficiency and avoiding duplication of work. This will help ensure that the risk from phthalates, structurally similar substances and their replacements are comprehensively assessed and eventually managed.

[1] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L 396, 30.12.2006, p.1–520.

[2] Commission Regulation (EU) 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.

[3] https://ec.europa.eu/food/sites/food/files/safety/docs/cs_fcm_wg_20200224_pres-02.pdf

[4] Commission Recommendation (EU) 2019/794 of 15 May 2019 on a coordinated control plan with a view to establishing the prevalence of certain substances migrating from materials and articles intended to come into contact with food (notified under document C(2019) 3519). OJ L 129, 17.5.2019, p. 37–42.

[5] The mandate letter including Annex II is available at: https://open.efsa.europa.eu/study-inventory/EFSA-Q-2020-00725

[6] https://www.efsa.europa.eu/sites/default/files/assets/mouecha.pdf

Terms of Reference

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002,[7] the European Commission asks EFSA to re-evaluate the risks to public health related to the presence of phthalates, structurally similar substances and replacement substances, as a consequence of migration from food contact materials (FCMs). The following tasks, which constitute the first part of a two-part mandate, should therefore be performed:

1. Prioritise and identify those phthalates, structurally similar substances and replacement substances based on the list in annex II to this mandate letter that warrant further data collection and insofar as they may be relevant for eventual inclusion in an assessment of the risks associated with their presence and migration from food contact materials. Existing relevant information, such as that which may be held by ECHA should also be identified.
2. With a view to ensuring transparency and efficiency during the second part of the mandate, establish a protocol for:

    a) A dietary exposure assessment of the prioritised substances, with the aim of addressing the relative contribution from FCM to dietary exposure considering data on migration from FCM and eventual comparison of these contributions with the overall exposure of EU consumers;

    b) A hazard assessment protocol for the prioritised substances, detailing the criteria for inclusion and appraisal of the toxicological evidence publicly available since 2005 and not yet assessed by EFSA.
3. Establish a call for data on occurrence of the prioritised substances in food to support dietary exposure estimates. Data on migration levels from plastic and rubber FCMs as well as other materials which may be relevant such as printed paper and board should also be collected, where available. This should include articles throughout the whole food chain, including food manufacturing and processing equipment, as well as packaging, kitchenware and tableware. A search and identification of potentially relevant literature on exposure should also be started as part of this task.

1.2. Interpretation of the Terms of Reference

This exposure protocol addresses task 2(a) of the mandate and will be applied to those prioritised substances (task 1) (EFSA CEP Panel, 2021), for which the EC will ask EFSA to perform a risk assessment as the second part of this two-part mandate.

It has been developed with the aim of explaining in as much detail as possible the strategy applied for cleaning and selecting data, appraising the relevant evidence, and analysing and integrating that evidence in order to perform exposure assessments that will be used for the risk assessment of the prioritised substances.

1.3. Scope of the exposure protocol

Materials and articles intended to come into contact with food[8] include those for uses such as films, packaging and containers as well as layers of adhesives, coatings and inks. Packaging and containers include those used for transport, storage and preservation. Kitchen and processing equipment, such as coffee makers or production machinery, as well as cutlery and dishes are also considered to be within the scope. These materials and articles are commonly referred to as FCMs. They can be made

[7] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

[8] In the context of this document, the term 'food' (according to Article 2 of Regulation (EC) No 178/2002) means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans. In this sense 'food' includes drink, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment. It includes water after the point of compliance as defined in Article 6 of Directive 98/83/EC and without prejudice to the requirements of Directives 80/778/EEC and 98/83/EC.

from a variety of materials including plastics, rubber, paper and board. European legislation for food contact materials[9] also covers materials that come into contact with water intended for human consumption, e.g. bottles, but excludes fixed public or private water supply equipment, which is outside the scope of this document.

Plasticisers are lipophilic additives that are used as single substances or mixtures in high amounts, typically at percentage levels and even up to 50% w/w, to change and tailor the physical properties of polymeric materials for their use in non-food and food-contact applications (see for example, Cadogan and Howick, 2020). The classical example is the polymer PVC which is rigid as such. The addition of plasticisers to PVC allows it to be made into flexible films, hoses and sealing gaskets that are used as FCMs. Similarly, although not so obvious, the thin layer of inks, varnishes and adhesives applied to many FCMs are polymeric in nature and may contain plasticisers to help with adhesion and flexibility and hence provide resistance to peeling and cracking. The recovery and recycling of these inked and glued materials, in particular paper or board, can consequently give rise to residues of plasticisers in FCMs made from or containing recycled material. Since plasticisers are normally non-volatile oily liquids and are chemically quite stable, they find use as carrier solvents for the addition of other substances that are used to formulate FCMs. This stability and related persistence means that plasticisers can be also found as incidental ('background') contaminants in a wide variety of materials, including the foods themselves.

Due to the lipophilic character of most of the prioritised substances, the concentrations of the prioritised substances in water are expected to be low. However, in the list of prioritised substances, it is likely that there will also be substances with other properties. Therefore, all food items (including beverages and water) may contain the prioritised substances and should therefore be considered.

2. Problem formulation

2.1. Objectives of the exposure assessment

The objective is to assess the dietary exposure to the prioritised substances, to address the relative contribution from FCMs to the dietary exposure considering data on migration from FCMs, and the eventual comparison of these contributions with the overall (dietary and non-dietary) exposure of EU consumers.

2.2. Identification of the risk assessment questions and sub-questions

The objectives were translated into three assessment questions and their sub-questions (Table 1). The evidence needs, the methodology for answering the questions and sub-questions and the uncertainty analyses are described in Sections 3, 4 and 5.

Table 1: Questions and sub-questions to be answered for the exposure assessment

Q1		What is the overall chronic and/or acute dietary exposure to the prioritised substances in different population groups and age classes in the EU?
	SQ1.1	What are the concentrations of the prioritised substances in food in the EU?
	SQ1.2	What are the consumption levels of food among the different population groups and age classes in the EU?
Q2		How much of the chronic and/or acute dietary exposure to the prioritised substances originates from FCMs in the different population groups and age classes in the EU?
	SQ2.1	In which FCMs do the prioritised substances under study occur, and in what concentrations and at what frequency of use (market share)?

[9] 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 and repealing Directives 80/590/EEC and 89/109/EEC. OJ L 338, 13.11.2004, p. 4–17.

	SQ2.2	In which step(s) of the food chain is the FCM used? How often and under what conditions of use is the FCM used in the food chain?
	SQ2.3	What is the concentration of the prioritised substances that migrated into food from each identified FCM (SQ2.1), during the relevant step(s) of the food chain (SQ2.2)?
	SQ2.4	What is the reliability and representativeness of the results obtained from testing for composition and migration?
	SQ2.5	What are the consumption levels of relevant food (in which the migration/concentration due to FCMs was assessed under SQ2.3) in different population groups and age classes in the EU?
Q3		How does dietary exposure due to FCMs compare with the overall (dietary and non-dietary) exposure of EU consumers?
	SQ3.1	What are all the actual uses of the prioritised substances and the possible sources and routes of non-dietary exposure?
	SQ3.2	What is the non-dietary exposure to the prioritised substances from the individual uses identified under SQ3.1?
	SQ3.3	What is the overall (dietary and non-dietary) exposure to the prioritised substances measured through human biomonitoring (HBM)?

Q: question; SQ: sub-question

3. Question 1 (Q1): What is the overall chronic and/or acute dietary exposure to the prioritised substances in different population groups and age classes in the EU?

This question concerns overall dietary exposure to each of the prioritised substances that might originate from FCMs or other sources, including environmental contamination. It primarily includes chronic exposure, but might also include acute exposure, depending on the toxicology of the substances that will end up on the list of prioritised substances.

It has to be noted that Q1 does not address migration from FCMs into food during home cooking. This aspect will be covered by Q2.

To answer Q1, three sub-questions and the method for integrating the evidence across the sub-questions were formulated.

Uncertainties identified for each sub-question are discussed in Section 3.4.

3.1. Sub-question 1.1 (SQ1.1): What are the concentrations of the prioritised substances in food in the EU?

Evidence needs

Concentrations of the prioritised substances in food. The concentrations should be representative for the prioritised substances in foods, including drinking water, as consumed in the EU.

Methods for answering the SQ

To address SQ1.1 on the concentrations of the prioritised substances in food in European countries, a structured approach will be followed to collect and evaluate the evidence. Occurrence data on prioritised substances will be collected through the continuous call for chemical data collection. National food authorities, research institutions, academia, food business operators and other stakeholders will be invited to submit occurrence data. Data generated in migration testing (either with food or food simulants) will not be collected in the continuous call for chemical data and will not be used to answer SQ1.1; however, there will be an ad hoc call for data to gather data on

concentration in and migration from FCMs, and the input provided to that ad hoc call for data will be used to address SQ2.3.

The data submission to EFSA will follow the requirements of the EFSA Guidance on *Standard sample description for food and feed* (EFSA, 2010a).

Before being used to estimate dietary exposure, the quality of the initial dataset of occurrence data will be evaluated. This will be achieved by applying several data cleaning and validation steps, in line with the EFSA standard operating procedures[10] on *Analysis of data from the S-DWH for the assessment of dietary exposure* and *Data collection and validation* and the *Technical report on handling of occurrence data for dietary exposure assessment* (Arcella et al., in preparation). Among others, different parameters will be carefully checked, including 'Sampling strategy', 'Sampling year', 'Sampling country', 'Analytical methods', 'Reporting unit', 'Limit of detection' and the sample classification under FoodEx2 (EFSA, 2015).

For instance, for data held in the EFSA data warehouse, data gathered via previous calls for data (before 2022) will be considered case by case, taking into account, e.g., the year of sampling. Obsolete data could be excluded taking into consideration issues such as: whether the time period to be considered is specified in the terms of reference, whether there is a time trend which could cause some data to be outdated, whether a new regulation introduces new restrictions on the given chemical and so provides a cut-off date, or there is an earlier exposure assessment published by EFSA. In the latter case, data collected since that time could be considered, thus the results could show whether there was any significant decrease or increase in the occurrence levels or the exposure.

The available details on sample preparation and analytical methods will be carefully evaluated according to the *Technical report on handling of occurrence data for dietary exposure assessment* (Arcella et al., in preparation). An evaluation of the method performance (specificity, sensitivity, accuracy, precision, recovery, etc.) will be carried out. Furthermore, specific analytical challenges related to the measurement of a given substance and the suitability of the analytical methods reported will be evaluated and decisions on possible data exclusion taken accordingly. In general, methods have to be fit for purpose; in this case for dietary exposure assessment. Occurrence data provided to EFSA are often generated under official monitoring programmes used for checking compliance with regulations and may be affected by a large proportion of left-censored data. High limits of quantification (LOQs) can affect the usefulness of the data for exposure assessment purposes, especially when a large proportion of left-censored values are reported in certain food categories. Left-censored data will be handled according to quality criteria detailed in the '*Technical report on use of cut-off values on the limits of quantification reported in datasets used to estimate dietary exposure to chemical contaminants* (EFSA et al., 2018).

In addition to the occurrence data collected during the call for data, a systematic literature search will be conducted (including research activities and published surveys such as total diet studies (TDSs)). Considering all available data (data received in the call for data along with information from the literature) it will be decided case by case whether the literature information will be used or not for the dietary exposure assessment. If the occurrence data received in the calls are sufficiently complete and comprehensive to calculate dietary exposure, it may not be necessary to use the literature information. Further details on the systematic literature review are provided in Section 6.

All available data will be assessed, based on the criteria listed above and data from the various sources will be combined, as appropriate. Appropriate descriptive statistics by food category and substance will be presented in the exposure assessment.

3.2. Sub-question 1.2 (SQ1.2): What are the consumption levels of food among the different population groups and age classes in the EU?

Evidence needs

Consumption levels of foods for the different population groups and age classes in the EU.

[10] https://www.efsa.europa.eu/en/corporate/pub/sops

Methods for answering the SQ

The EFSA Comprehensive European Food Consumption Database (EFSA Food Consumption Database) will be the primary source of the food consumption information. The food consumption data gathered by EFSA in the EFSA Food Consumption Database are the most complete and detailed data currently available at EU level and provide a compilation of existing national information on food consumption at individual level. The EFSA Food Consumption Database was first built in 2010 (EFSA, 2011; Huybrechts et al., 2011; Merten et al., 2011) and is updated regularly. Details on how the EFSA Food Consumption Database is used are published in the EFSA Guidance (EFSA, 2011). The latest version of the EFSA Food Consumption Database available at the moment of occurrence data extraction will be used (including surveys on specific population groups, e.g. pregnant women, vegetarians) for the age classes from infants to adults aged 75 years or older as described by EFSA (2011).

Individual consumption data were collected using single or repeated 24 or 48 h dietary recalls, and dietary records covering 3–7 days per subject. Owing to the differences in the methods used for data collection, direct country-to-country comparisons can be misleading. Detailed information on the different dietary surveys available in the EFSA Food Consumption Database can be found on the dedicated page of EFSA's website.[11]

As indicated by the EFSA Working Group on Food Consumption and Exposure (EFSA, 2011), dietary surveys with only one day per subject will only be considered for acute exposure as they are not adequate to assess repeated exposure. Similarly, subjects who participated for only one day in the dietary studies, when the protocol prescribed more reporting days per individual, will also be excluded for the chronic exposure assessment. When, for one particular country and age class, two different dietary surveys are available, only the most recent one will be used.

3.3. Method for integrating evidence across the sub-questions

To estimate the human dietary exposure (Q1), both occurrence and consumption data are required. These are addressed in SQ1.1 and 1.2, respectively, and the numerical integration of these two types of evidence is the main focus here. Both occurrence and consumption data are codified and classified according to the FoodEx2 classification system (EFSA, 2015). After a quality check and cleaning (SQ1.1), the occurrence data will be prepared for exposure assessment and their associated limitations will inform the uncertainty analysis. For the consumption data, this will be based on the 'basic FoodEx2 code', aggregated into food groups and broader food categories in a hierarchical parent–child relationship (up to seven levels). In addition, a catalogue of 28 'facets' is available in order to describe further characteristics of the foods, such as physical state (e.g. powder, liquid) or processing technology (e.g. grinding, milling, crushing). The correct application of the FoodEx2 classification to the data will be verified before dietary exposure is estimated.

Considering the relevant levels of plasticisers that emerge from the occurrence data in different foods (call for data and literature), the best match between occurrence data and consumption data will be performed at the most relevant FoodEx2 level. If there are data gaps for relevant food items or categories, extrapolation from one food matrix to another can be considered where there are similarities in characteristics (e.g. fat content) and supply chain (including FCM use). All assumptions and extrapolations will be reported in the assessment and their possible effect on the estimates of exposure will be assessed in the uncertainty analysis.

The left-censored occurrence data (results below the limit of detection (LOD) or LOQ) will be treated by the substitution method as recommended in *Principles and Methods for the Risk Assessment of Chemicals in Food* (WHO/IPCS, 2009) and in the EFSA scientific report *Management of left-censored data in dietary exposure assessment of chemical substances* (EFSA, 2010b). The guidance suggests that the LB (lower bound) and UB (upper bound) approach should be used for chemicals likely to be present in the food (e.g. naturally occurring contaminants and nutrients). The LB is obtained by assigning a value of zero (minimum possible value) to all samples reported as lower than the LOD (<LOD) or LOQ (<LOQ). The UB is obtained by assigning the numerical value of LOD to values reported as <LOD and LOQ to values reported as <LOQ (maximum possible value), depending on

[11] https://www.efsa.europa.eu/en/data-report/food-consumption-data#the-efsa-comprehensive-european-food-consumption-database

whether the LOD or LOQ was reported by the data provider. The outcome of this approach will generate two exposure assessments under the LB and the UB scenarios.

Other specific scenarios may be developed, such as for seasonal foods, for specific eating habits, for brand-loyal consumers, etc.

To calculate the chronic dietary exposure, food consumption and body weight data at the individual level will be accessed in the EFSA Food Consumption Database. Occurrence data and consumption data will be linked at the relevant FoodEx2 level. Typically, for each individual of the selected surveys, the mean or median occurrence values (LB and UB) of the different food samples collected (pooled European occurrence data) are combined with the average daily consumption of the corresponding food items, and the resulting exposures per food are summed up in order to obtain the total chronic exposure at individual level (standardised by using the individual body weight). The mean and the 95th percentile of the individual LB and UB exposures are subsequently calculated for each dietary survey and each age class separately.

If the toxicological evidence indicates that two or more plasticisers should be grouped into a common assessment group, the dataset will be examined for the occurrence of each plasticiser individually in each food sample/food type and then the co-occurrence of the group members will be calculated for each sample/type, taking into account potency adjustment factors if appropriate (EFSA Scientific Committee, 2019). Summary statistics for exposure to the individual plasticisers will not be simply summed.

The acute exposure is calculated on a per day basis. In the probabilistic approach, acute exposure is assessed for each reporting day by multiplying the total daily consumption amount of food by one occurrence level randomly drawn among the individual results available. Respective exposures from the different foods consumed that day (by the considered subject) are normally summed up and divided by the individual's body weight. This process is usually iterated *n* (e.g. 100) times for each reporting day for each survey. The mean and the 95th percentile of the individual LB and UB exposures are subsequently calculated across all dietary surveys and age classes separately.

Analyses will be run using the SAS Statistical Software.

3.4. Uncertainties related to Q1

The evaluation of the uncertainties in the risk assessment on the prioritised substances will be performed based on the guidance on uncertainty analysis of the EFSA Scientific Committee (EFSA Scientific Committee, 2018) and the guidance on communication of uncertainty in scientific assessments (EFSA, 2019). The sources of uncertainty will be summarised in each assessment in tabular form and the possible ways in which they may influence the final outcomes and conclusions will be explained. It will be attempted to predict their effect on the final estimates (e.g. lead to over- or underestimation) and their possible influence on the assessment conclusions.

Uncertainties relate to the occurrence of the prioritised substance and to the food consumption data used in the exposure assessment calculations.

The main sources of uncertainty related to occurrence data belong to the following categories:

- Sampling strategy (e.g. random sampling vs suspect sampling).
- Representativeness of the occurrence data (e.g. representativity for the whole of the EU when data have been collected in one specific country and/or under particular circumstances; representativity for the food category; inclusion of outdated occurrence data; extrapolation from one food matrix to another when data are lacking for certain food items).
- Data reporting (lacking information on food processing; possible reduction/increase due to household/industrial processing).
- Analytical measurement uncertainty.
- Use of analytical methods with low sensitivity may lead to a high percentage of left-censored data that may contribute to large differences between the LB and UB exposure estimates.

Uncertainties and limitations arising from the use of the EFSA Food Consumption Database have been described in detail elsewhere (EFSA, 2011), and relate to the following methodological aspects:

- Sampling strategy and response rate: using sampling strategies which are convenient (e.g. use of household as sampling unit rather than individuals) and low response rates may lead to survey samples which are not representative of the general population at national level. This could lead to over- or underestimation of the intakes in the general population at national level.
- Representativeness over different weekdays and seasons: surveys not covering weekdays and weekend days, or conducted in one season only, may not capture usual intakes, mostly for foods which are consumed in one season only or on special occasions (e.g. weekends). However, most surveys in the EFSA Food Consumption Database, especially those conducted more recently, cover a whole year with an appropriate proportion of weekdays and weekend days.
- Methodology used to assess dietary intakes: dietary recall vs food records. Each of the two methods has its strengths and limitations as described in EFSA (2011).
- Use of standard portion sizes: this can lead to over- or underestimation of the actual quantity consumed.
- Inclusion of consumption surveys covering only a few days: this leads to an overestimation of high percentiles of chronic intake, whereas it is expected to minimally affect mean intakes of food widely distributed in the diet. For foods not consumed daily, intakes could be over- or underestimated depending on whether consumption days are captured in the survey. This also has an impact on the number (and percentage) of consumers of non-core food groups identified in the surveys.
- Other systematic errors: underreporting has been shown to be associated with sex, age, educational level and body mass index (e.g. obese subjects and male subjects underreport more frequently than lean subjects and females; EFSA, 2009).

Other sources of uncertainty, e.g. due to the building of scenarios, that contribute to the exposure assessment will also be considered.

4. Question 2 (Q2): How much of the chronic and/or acute dietary exposure to the prioritised substances originates from FCMs in the different population groups and age classes in the EU?

This question concerns dietary exposure (primarily chronic, but might also include acute, depending on the toxicology of the substances that will end up on the list of prioritised substances) that originates specifically from FCMs. This covers all food that comes into contact with FCMs along the food chain. This question relates to different materials such as plastic, rubber (all elastomeric materials), paper and board, inks, varnishes and adhesives (e.g. from labels) and covers packaging materials (industrial, retail and home-use), food manufacturing and processing equipment, as well as kitchenware and tableware.

Uncertainties identified for the different SQs are discussed in Section 4.7.

4.1. Sub-question 2.1 (SQ2.1): In which FCMs do the prioritised substances under study occur, and in what concentrations and at what frequency of use (market share)?

Evidence needs

In which FCMs the prioritised substances are intentionally used or may be present unintentionally, the concentration of the prioritised substances in FCMs and information on market share.

Focus will be laid on use of the substances as plasticisers (including plasticiser mixtures) due to the high migration potential and the fact that actual or potential use as a plasticiser was the criterion used for the selection of substances. Nonetheless, because these plasticiser substances may find other technical uses, e.g. as a carrier solvent, these uses will also be taken into account when relevant.

Methods for answering the SQ

Data on the occurrence of the prioritised substances in FCMs will be extracted from the database on migration data available to EFSA when performing the assessment. Such occurrence data will be collected through an ad hoc call for data that is under development at the time of drafting this protocol. National food authorities, research institutions, academia, food business operators and other stakeholders will be invited to submit occurrence data. The outcome of SQ2.4 will be used in the evaluation to decide whether the reported data are representative and reliable to be used to answer SQ2.1.

Other sources of relevant information and data will be accessed to identify FCMs where the prioritised substances may occur and at what concentration ranges and frequency of use. The objective is not to perform a systematic review, screening all possible available articles, studies and databases, but rather to consider the ones that provide an overview of the occurrence of prioritised substances in FCMs and recent trends on their use, or to focus on specific aspects to address gaps and missing data relevant when making the estimate of exposure from FCMs.

Other sources include:

a) articles from the scientific literature available through a narrative review (see Section 6);
b) reports from market surveys and surveillance studies;
c) information from international institutions, such as ECHA and OECD, and industry (plasticiser associations and all FCM sectors such as plastics, paper and board, inks and adhesives);
d) applicable European (harmonised FCMs), as well as national legislations. Any restrictions to the use at national level and maximum use levels of prioritised substances will be considered. The impact of specific national legislations on an EU level will be addressed.

To gather this information an open call may be considered.

The information retrieved from the data sources listed above will be used to address the evidence needs specified above. The information will be summarised qualitatively (in which FCMs each of the prioritised substances occurs) and quantitatively (provision of descriptive statistics, including numerical summaries of concentrations and frequency of use) per FCM for each prioritised substance.

4.2. Sub-question 2.2 (SQ2.2): In which step(s) of the food chain is the FCM used? How often and under what conditions of use is the FCM used in the food chain?

Evidence needs

The step(s) in the food chain in which the FCM (as identified in SQ2.1) is in contact with food under a given time/temperature, surface-to-volume (s/v) ratio and single vs repeated-use conditions, and where migration might occur. The step(s) will cover the different applications of an FCM (e.g. during processing on an industrial scale and at home, as packaging material used on an industrial scale, in retail and at home, as well as possible migration during storage until the food is consumed). Furthermore, home preparation may result in additional dietary exposure which is not covered when using the concentration of the prioritised substance in food products on the market.

Methods for answering the SQ

To address SQ2.2 a characterisation of the intended use and applications of the FCM will be performed, combining information gathered from various sources. This information will be further developed to determine the step(s) in the food chain where the migration mostly occurs by applying the principles governing the migration mechanism, and considering the impact of the contact conditions, type of food and respective processing and handling conditions along the food chain, on the rate and level of migration.

Sources of information are:

a) articles from the scientific literature available through a narrative review (see Section 6);
b) reports from market surveys and surveillance studies;

c) information from international institutions, such as ECHA and OECD, and food industry using the materials and articles;
d) applicable European (harmonised FCMs), as well as national legislations. Any restrictions to the use at national level, including maximum allowable migration levels of prioritised substances, will be considered. The impact of specific national legislations on an EU level will be addressed.

To gather this information an open call may be considered.

Based on the information retrieved from the data sources listed above, the relevant step(s) in the food chain in which the FCM is in contact with foods and where migration might occur will be identified and characterised.

4.3. Sub-question 2.3 (SQ2.3): What is the concentration of the prioritised substances that migrated into food from each identified FCM (SQ2.1), during the relevant step(s) of the food chain (SQ2.2)?

Evidence needs

For each identified FCM and for each relevant step, the concentrations of the prioritised substances in food that migrated from the FCM.

If such information is not available for each identified FCM and relevant step(s), concentrations of the prioritised substances in food simulants in contact with FCM can be used, as well as data from migration modelling. The uncertainties related to the use of such information will be addressed in the uncertainty analysis.

The concentrations should be representative of the prioritised substances migrated into food as consumed in the EU.

In addition, information on the material of the FCM (e.g. rubber, plastic) as well as the type of article in contact with food will be collected.

Methods for answering the SQ

To address SQ2.3 regarding the concentrations of the prioritised substances migrated into food in European countries, a structured approach will be followed to collect and evaluate the evidence. An ad hoc call for concentration data in FCMs and migration data in food and in food simulants will be launched by EFSA. National food authorities, research institutions, academia, food business operators and other stakeholders will be invited to submit data.

When concentrations from migration testing with food simulants are used, the relevant foods into which the prioritised substances may migrate will be assigned for each FCM identified. The nature of the migration test that has been conducted will give useful information to help this process. The description of the material or article tested, the food simulant(s) used, the time and the temperature of the test applied, and the nature of the contact (single-sided, total immersion, article filling, repeated-use) should all be reported to accompany the test result(s) itself and this information will help to indicate the intended use of that material or article for contact with a particular food item or food category. The information gathered for SQ2.2 will assist this process. For articles with a clearly defined purpose (bottle, gasket, tubing, carton, etc.) it is anticipated that this assignment will be relatively straightforward although still not unambiguous. For materials that are not yet fabricated into their final form (mainly sheets and films), the assignment of the migration test results to specific foods or food categories along with their contact conditions, will inevitably involve a degree of uncertainty. In those situations, conservative assumptions on choices or judgements will be made. The sources and effects of such uncertainties will be addressed in the uncertainty analysis.

To guarantee an appropriate quality of the occurrence data used in the exposure assessment, the initial dataset will be evaluated before being used to estimate dietary exposure. The outcome of SQ2.4 will be used in this evaluation to decide whether the reported concentrations are representative and reliable enough to be used in the dietary exposure assessment.

Prediction of migration from plastic FCMs into foods and food simulants can be achieved based on scientifically recognised migration modelling carried out according to validated procedures. Such models describe the mass transport of a substance from a plastic FCM using known or estimated diffusion coefficients in the FCM and known or estimated partition coefficients between the plastic and the food (simulant). Detailed information about the application of and guidance to a recognised European model can be found in the Joint Research Centre's Technical report *Practical guidelines on the application of migration modelling for the estimation of specific migration* (Brandsch et al., 2015). In chapter 3.2.5.2 of that report, particular attention is given to plasticised polymers. As plasticisers are used at high concentrations, the diffusion coefficient depends on the use level of the plasticiser in the polymer. In general, however, plasticised FCMs are characterised by high diffusion in the polymer so that the extent of migration is predominantly controlled by the partition coefficient, i.e. triggered by the log Po/w of the given substance (see above, introduction to Q2). Such migration modelling also provides a useful tool for checking the plausibility of experimental migration data and estimation of the related uncertainties. This requires appropriate information about the type, nature and structural specifications of the FCM and initial concentration range of the given substance in FCM before the start of migration (which is typically the use level) as well as the applied migration test conditions (time, temperature, type of food or food simulant). These details will be retrieved from the infilled data templates and can, if missing, be completed with reasonable assumptions. It should be noted that migration modelling is intended to be conservative and to deliver the UB rather than realistic concentrations in the food or simulant.

Another option to estimate migration for a prioritised substance is a read-across approach. This approach is of particular interest when the objective is to replace certain plasticisers with alternatives and where reliable use levels in the FCM and migration data exist for the plasticiser to be substituted. The alternative plasticiser (the data recipient) should have similar physico-chemical properties to the original (the data donor), i.e. molecular weight and polarity (log Po/w) as this will give similar quantitative migration behaviour and so allow 're-use' of the existing migration data. Varying use levels of the alternate compared with the original can be corrected by the assumption that the alternate migrates *pro rata* to the use level. Variations in molecular weight and/or polarity can be corrected by migration modelling tools (see above). Contrary to migration modelling where the intention is to provide concentrations conservatively, read-across has strong potential to provide more realistic data as long as the starting reference dataset is on a solid realistic basis.

Other data sources:

a) articles from the scientific body of literature available through a narrative review (see Section 6).

b) other databases (e.g. the Information Platform for Chemical Monitoring database);

c) applicable European (harmonised FCMs) and national legislations. The restrictions on the use at national level, including maximum allowable migration levels of prioritised substances, will be considered. The impact of specific national legislations on an EU level will be addressed.

The information collected from all possible sources listed above will be assessed using the described criteria. It will be summarised quantitatively to obtain estimates of the concentration of the prioritised substances in food that migrated from each identified (by SQ2.1) FCM during the relevant step(s) of the food chain. Possible data gaps will be attempted to be filled by read-across approaches.

4.4. Sub-question 2.4 (SQ2.4): What is the reliability and representativeness of the results obtained from testing for composition and migration?

The test methods have to be appropriate to generate reliable and representative concentrations for use in quantitative dietary exposure assessments.

For a migration test, two aspects are relevant. The first is the migration protocol used to take a sample of the material or article and place it into contact with the food or simulant using defined and well-controlled conditions of s/v ratio, time and temperature. The second is the test method (analytical method) used to measure the concentration of the plasticiser in the exposed food or

simulant. Likewise, to determine the composition of the FCM, an extraction protocol followed by an analytical method is needed.

Evidence needs

For each concentration from SQ2.1 and SQ2.3:

- A full description of the FCM (e.g. nature of the material, chemical composition, type of article, thickness, number and order of layers if it is a multilayer).
- The test conditions: the s/v ratio, the choice of the food simulant and time and temperature conditions.
- The test method used and the LOD/LOQ.

Methods for answering the SQ

The required information on the migration protocol and test method (when available) will be extracted from the EFSA database or from the scientific papers.

The suitability of the test method to generate reliable and representative concentrations for use in quantitative dietary exposure assessment will be evaluated.

The dataset may contain a large amount of left-censored data and the presence of relatively high LODs/LOQs may have a significant influence on the LB and UB scenarios. In order to reduce this impact, a careful evaluation of LODs/LOQs should be performed. Relevant actions will be undertaken in order to avoid bias (such as the application of LOD/LOQ cut-offs (EFSA et al., 2018)).

The evaluation of the extraction/migration protocol and test method for each dataset considered in SQ2.1 or SQ2.3 will serve as an inclusion/exclusion criterion for the study. If they are not appropriate to generate reliable and representative data, the respective dataset will not be considered further.

4.5. Sub-question 2.5 (SQ2.5): What are the consumption levels of relevant food (in which the migration/concentration due to FCM was assessed under SQ2.3) in different population groups and age classes in the EU?

Evidence needs

Individual consumption data for the foods for which concentration data were obtained under SQ2.3 in different population groups and age classes in the EU.

Information from other specific surveys (e.g. on consumption of packaged food/takeaways) carried out among relevant EU population groups and published in the literature.

Methods for answering the SQ

The EFSA Food Consumption Database will be the source of food consumption information using FoodEx2 and the relevant facets when available. See SQ1.2 for further information.

Apart from the details already given for SQ1.2 on the composition and use of the EFSA Food Consumption Database, specific FoodEx 2 facets could be used to look for products that are packaged or intended to be in contact with FCMs. When available, reported information via use of ad hoc facets for food packaging/processing will be explored. However, the completeness of reporting such information might vary from survey to survey and from one food category to another. Specific use of facets will be evaluated in each assessment, also taking into account the uncertainty. Pragmatic solutions and assumptions might be used and an ad hoc evaluation will be performed case by case. For instance, if consumption data at the level of the individual for cheese packed in plasticised film is not available, an assumption might be made that the consumption is the same as of cheese packaged in any type of plastic or even the same as their total cheese consumption if the type of packaging is not reported at all. In general, the higher FoodEx2 category within the exposure hierarchy will be used to match the occurrence data, unless there are indications from other sources (e.g. Global New Products Database (GNPD), industry information, etc.) that could facilitate a more selective match to a specific lower FoodEx2 category. All such assumptions will be reported in the linkage table (see Section 4.6) and taken into consideration in the uncertainty analysis.

It should be noted that the information on packaging in the EFSA Food Consumption Database is limited and this limitation will be considered as a source of uncertainty.

When information from other specific surveys (e.g. on packaged food) carried out among relevant EU population groups is present in the literature, it might be used to check consumption values or to complement considerations on the uncertainty of the used values. Therefore, a narrative literature search will be conducted to identify papers that provide information on the consumption of packaged food (see Section 6).

Consumption data from all sources will be considered in order to obtain estimates of consumption for the foods for which concentrations of prioritised substances due to FCMs were assessed under SQ2.3.

4.6. Method for integrating evidence across the sub-questions

To estimate the human dietary exposure from FCMs (Q2), representative scenarios will be given reflecting the exposure that may occur for the identified FCMs and relevant step(s) of the food chain. The concentration levels of prioritised substances in relevant food categories due to migration will be used for exposure assessment.

Initially, the answer to Q2.1 will clarify in which FCMs each of the prioritised substances occurs, in what concentrations and at what frequency. The assessment of SQ2.2 will show the relevant step(s) in the food chain where the FCM is in contact with foods and when migration might occur. The work done to address SQ2.3 will provide information on the concentration of the prioritised substances in food that migrated from each identified FCM (under SQ2.1) for the step(s) identified under SQ2.2. The assessment of SQ2.5 will provide the consumption levels of the foods that were considered under SQ2.3. The information collected and assessed for SQ2.4 will serve as inclusion or exclusion criteria for the dataset to be used to answer SQ2.1 and SQ2.3.

Question 2 will be answered by mathematically combining the estimates from SQ2.3 and SQ2.5. Hence, a linkage table will be created to match the food or simulant with the relevant FoodEx2 categories to enable the integration of the food consumption data. The first level of match will be based on Table 2 of Annex III of Regulation (EU) No 10/2011. Then the best match with individual consumption data will be performed selecting the most suitable Foodex2 level on a case-by-case basis. The use of facets (e.g. those related to packaging or processing when available and relevant) to refine the match will be considered when data are available. Unless there are indications from other sources (e.g. GNPD, industry information, market share, etc.) that can facilitate the selective match to a specific FoodEx2 category, the higher level food category will be used in the assessment. In view of the available migration data and of the identified factors driving the occurrence of the prioritised substance in the relevant food categories, pragmatic assumptions and solutions will be made. All the assumptions will be documented in the assessment and taken into consideration in the uncertainty analysis.

Finally, the relative contribution of exposure to the prioritised substance from FCMs (Q2) to the total dietary exposure (Q1) will be calculated, making it possible to estimate how much of the total dietary exposure to the prioritised substances originates from FCMs. The proportion of the total dietary exposure due to FCMs will be estimated separately for the different population groups and age classes in the EU.

4.7. Uncertainties related to Q2

Uncertainties that result from addressing Q2 fall into four main categories. These concern the uses of the substance in FCMs, the migration data available, the related food consumption information used and the methods used to combine this information to derive estimates of exposure.

Uses in FCM

- Uncertainties here relate to incomplete information and possibly inaccurate information (over- or underreporting) regarding the range of FCMs in which the substance is used, the respective use levels (concentrations) of the substance in those FCMs, and the likelihood (or frequency) that those materials find actual use (e.g. consumer preference for home uses, market shares for packaging retail foods and for FCMs used by the industry).

Migration data

- For data on migration into foods, the sources of uncertainty were described in Section 3.4 in relation to occurrence data in foods when addressing Q1.
- For data on migration into food simulants, there will be uncertainty over the extent to which the real concentration of plasticisers in food will tend to be overestimated using results from migration experiments. Migration tests simulate the situation at the end of the shelf-life, whereas data collected on occurrence in food (Q1) will represent an earlier time point. Similarly, the nature of the food simulant along with the time and temperature test conditions used are intentionally conservative and designed to elicit higher migration than expected in real use with foods. If migration levels are overestimated and not corrected for, this would feed into overestimates of exposure.
- For repeated-use FCMs such as conveyor belts, tubing and plasticised gloves, there will be uncertainty inherent in extrapolating the results of migration tests using simulants to migration levels into food expected during the service life of the FCMs, taking into account divergent s/v ratios, the effect of ageing, cleaning procedures, etc.
- For migration levels estimated using migration modelling, the main sources of uncertainty are the same as when using data from food simulants, since most migration models and the modelling parameters aim to estimate migration into simulants and not into foods.

Consumption

- When using data on migration into foods, the sources of uncertainty relating to food consumption were described in Section 3.4 when addressing Q1.

Method for integrating the evidence

- When using data on migration into food simulants and from migration modelling, the main uncertainty will be in linking the migration results (which will pertain to only very broad food characteristics such as fatty/oily, acidic, aqueous, alcoholic) to the food categories described at the various levels of the FoodEx2 classification system used for the EFSA Food Consumption Database.
- The final output from addressing Q2 is how much of the overall dietary exposure to the prioritised substances originates from FCMs. Comparing the conclusions from Q2 (exposure from FCMs) with Q1 (total dietary exposure) could entail large uncertainties. The estimates to be compared will be obtained using different methodologies, will be distributions not fixed values, and will come with their own attendant uncertainties.

5. Question 3 (Q3): How does dietary exposure due to FCMs compare with the overall (dietary and non-dietary) exposure of EU consumers?

This question concerns the overall (dietary and non-dietary) exposure of EU consumers to prioritised substances and how it compares with dietary exposure due to FCMs (Q2). Depending on the availability and quality of the data, the following two approaches may be used (either individually or in combination) in order to gain information on the overall exposure of consumers.

- Overall exposure based on aggregation of non-dietary exposure from uses of the substance in consumer products (articles and chemical products) (SQ3.1 and SQ3.2) and dietary exposure from FCMs and other sources, including environmental contamination (Q1).
- Overall exposure based on human biomonitoring (HBM) data (SQ3.3).

Occupational exposure is not within the scope of Q3.

Uncertainties identified for the different sub-questions are discussed in Section 5.5.

5.1. Sub-question 3.1 (SQ3.1): What are all the actual uses of the prioritised substances and the possible sources and routes of non-dietary exposure?

Examples of sources could be consumer exposure to articles (e.g. plastic flooring or furniture, toys) and chemical products (e.g. cleaning products) as well as exposure via dust/inhalation.

Evidence needs

There is a need to collect information on uses of the prioritised substances with a focus on the use of articles and chemical products by consumers. Primarily, there is a need to identify product categories and article categories[12] correlated to the prioritised substances (this will help to categorise uses and also determine default conditions of use, see SQ3.2); secondly, other information can be collected at this stage to help to understand how the substance is used and the potential route of exposure, for example: a) the tonnage band to understand, in correlation to uses, whether we are addressing a niche or widespread use; b) the technical function of the substance to appreciate, for example, the potential release when embedded into a solid matrix; c) some basic substance properties to better qualify the route of exposure (e.g. low volatility can be an indication of low exposure via inhalation of vapour).

While REACH requires registrants to cover all uses in their registration dossiers, for some specific uses there may be a more detailed assessment done under other pieces of legislation. Furthermore, uses in cosmetics are exempted from the authorisation requirement and REACH restrictions for hazards and risks to human health. Authorisation requirements do not cover the risks to human health arising from the uses in medical devices either. Consequently, ECHA has not developed methods and tools to assess human health exposure (SQ3.2) associated with these products and articles.

Methods for answering the SQ

The methods proposed for identifying uses and routes of exposure to chemical products and articles used by consumers are listed below.

- It is proposed to use the ECHA database of REACH-registered substances as the main source to collect and categorise uses (e.g. using product and article categories) by consumers; it is also possible to collect information on the technical function and volatility of the substance.
- It is also possible to further investigate the presence of some prioritised substances in articles via the 'Substances in articles' list[13] and the 'Substances of concern in articles as such or in complex objects (products)'[14] database (imported articles are also addressed here, possibly not subject to REACH registration). However, the relevance of this information will be very limited, since this database includes only information on substances identified as substances of very high concern under REACH and most of those substances are classified as CMR Cat 1 or identified as 'endocrine disruptor', 'persistent, bioaccumulative and toxic' or 'very persistent, very bioaccumulative' and thus a risk assessment will be conducted only if the substances may nevertheless be used in FCMs following the implementation of risk management measures in accordance with the Chemicals Strategy for Sustainability (EC, 2020).

[12] Lists of relevant product categories and article categories are reported in ECHA's *Guidance on Information Requirements and Chemical Safety Assessment* Chapter R.12: Use description Version 3.0 December 2015, Tables R12-10 and R12-14. Available online: https://echa.europa.eu/documents/10162/17224/information_requirements_r12_en.pdf/ea8fa5a6-6ba1-47f4-9e47-c7216e180197#page=10&zoom=auto,-108,8

[13] Producers and importers have to notify ECHA of the substances listed on the Candidate List that are present in their articles if both the following conditions are met: i) the substance is present in the article above a concentration of 0.1% w/w; ii) the substance is present in the article in quantities totalling over 1 tonne per year. Companies have to notify no later than six months after the inclusion of the substance in the Candidate List. For further details see: https://echa.europa.eu/regulations/reach/candidate-list-substances-in-articles/notification-of-substances-in-articles.

[14] This is a database established under the Waste Framework Directive (Directive 2008/98/EC). In accordance with the Directive, companies supplying articles containing substances on the Candidate List in a concentration above 0.1% w/w on the EU market have to submit information on these articles to ECHA, from 5 January 2021. The information provided is included in the database: https://echa.europa.eu/scip

- A literature search is proposed as an additional means for identifying uses of the prioritised substances (see Section 6).

The collected data via registration and literature review may be complemented with an open call to provide information.

Data on all known uses of the prioritised substances and potential sources and routes of consumer exposure originating from all the sources listed above will be assessed, collated and summarised qualitatively.

5.2. Sub-question 3.2 (SQ3.2): What is the non-dietary exposure to the prioritised substances from the individual uses identified under SQ3.1?

Here we consider the estimation of non-dietary exposure from the uses and routes of exposure identified in SQ3.1 by taking into account e.g. qualitative argumentations, modelling approaches or, in the case of availability of data, measurements performed at European level or in individual European countries.

Evidence needs

To estimate the consumer exposure after the identification of potential uses, an identification of the main physico-chemical properties is in the first instance needed to perform any exposure estimation; molecular weight, solubility, n-octanol partition coefficient and vapour pressure are the main parameters used to run the most common exposure estimation models. Other important factors needed to estimate exposure are the 'conditions of use' (i.e. how the substance is used by consumers), e.g. concentration of the substance in consumer products, frequency and duration of use of the product or article, the body surface exposed, the amount of product used, indoor or outdoor application, etc. If measured data (e.g. indoor air concentrations, migration to saliva, sweat, mucus membranes and skin) are available, contextual information is needed to understand the representativity of the data that can be used to estimate the exposure.

Methods for answering the SQ

The methods that can be proposed to estimate non-dietary consumer exposure are discussed below:

- Qualitative approach: if the substance is not used in consumer products (articles or chemical products) or the tonnage band suggests a very low amount ending up in consumer products, it might be concluded that the consumer exposure is unlikely or minimal.
- Quantitative approach (modelling): tools are available to estimate exposure to chemical products and articles used by consumers[15] via a tiered approach; input parameters (see conditions of use and physico-chemical properties of the substance) are needed to estimate exposure via modelling. If information on condition of uses[16] cannot be found from literature, open-source databases will be consulted. Moreover, default (conservative) parameters are provided in the tools (e.g. via RIVM factsheets[17]) to estimate exposure. Two main models are mentioned in the ECHA R15 guidance on consumer exposure: ECETOC targeted risk assessment consumers (first tier, conservative, covering both chemical products and articles) and ConsExpo[18] (first and second tiers, mainly covering chemical products, can be used in combination with the above-mentioned RIVM factsheets). Modelling has a tendency to overestimate exposure, with the first tier being more conservative and advanced tiers more data-demanding.

[15] See ECHA R15 Guidance at https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

[16] This information might be reported in the Chemical Safety Report by registrants, but they are confidential.

[17] RIVM (Dutch National Institute for Public Health and the Environment) factsheets are available online: https://www.rivm.nl/en/consexpo/fact-sheets

[18] National Institute for Public Health and the Environment (RIVM), Dutch Ministry of Health, Welfare and Sport: https://www.rivm.nl/en/consexpo/consexpoweb

- Measured data related to different exposure routes can also be retrieved from literature searches (see Section 6). For example, several studies have been run to measure the migration of phthalates to sweat, saliva and skin from different types of articles giving dermal and oral exposure. Information on the presence of substances in indoor house dust can also be present, giving exposure by inhalation; although the information available in the literature might be limited to a few substances.
- Read-across from exposure to other (similar) substances. This can be a very valuable source of information in the case of migration from articles to saliva (oral exposure) or skin; e.g. if the substance is used as plasticiser in plastic articles and has similar physico-chemical properties (log Po/w and molecular weight) to a well-known and data-rich substance (e.g. phthalates), then the migration to skin (sweat) and saliva from the data-rich plasticiser can be read across for the substance of concern (in the event that adaptation to concentration in the article and duration of exposure might also be possible). The concept is very similar to the one described in SQ2.3 in relation to read-across of migration from FCMs.

Similar to SQ3.1, the collected data via literature review may be complemented via an open call to provide information.

This sub-question will be addressed quantitively. The approaches described above will be used in combination, depending on data availability, in order to obtain exposure estimates for the relevant uses.

5.3. Sub-question 3.3 (SQ3.3): What is the overall (dietary and non-dietary) exposure to the prioritised substances measured through HBM?

Evidence needs

- Measurement of validated biomarkers of exposure to the prioritised substances in studies covering EU consumers.

- Information to convert biomarker concentrations into exposure.

Methods for answering the SQ

Human biomonitoring (HBM) is the measurement of substances (biomarkers) as parent compounds, their metabolites or their reaction products in human tissues and body fluids. HBM data incorporate exposures from all sources and all routes (oral, dermal and inhalation). The measurements incorporate individual variability in exposure and the kinetics of the substance in the body (absorption, distribution, metabolism and excretion).

To address SQ3.3 a systematic literature review will be carried out to identify all available HBM studies concerning the prioritised substances that have been carried out in the EU. The literature search strategy will be developed according to the substances included in the priority lists. Careful consideration of the study design, biomarker selection, toxicokinetics and populations examined (including biased sampling) are critical when interpreting HBM data. The systematic review will also evaluate the literature concerning toxicokinetic (TK) models and information concerning correlations between exposure to the prioritised substances and the corresponding biomarker(s) that are measured.

The toxicokinetic (TK) data and/or the simple empirical correlations between exposure and biomarker concentration found in the literature will be used to calculate the overall (dietary and non-dietary) exposure of the individuals in the study population to the prioritised substance. It may be the case that the publications identified may already have made such estimations of exposure, in which case the basis for the calculations will be evaluated before the estimations of exposure are accepted.

If TK and empirical correlation data are missing for a prioritised substance, it may be possible to read across from a source substance (for which the information is available) to the target substance. This will only be done if it is established that a prediction of the TK parameters is possible, based on a consideration of the chemical structures of the source and target substances (ECHA, 2017).

5.4. Method for integrating evidence across the sub-questions

The information available at this stage will be combined to answer Q3.

The estimates of dietary exposure due to the use of FCMs will be available from addressing Q2.

The overall exposure (also known as aggregated exposure) comprises total dietary exposure (estimated when addressing Q1) plus total non-dietary exposure (estimated when addressing Q3.2). The algorithm to sum up the two exposure estimates may follow a deterministic or probabilistic approach depending on the quality of the data. If a deterministic approach is followed, scenarios corresponding to different combinations of average and high estimates will be applied for different consumer population groups as it is unlikely that each consumer is exposed to a certain substance at the highest level for both dietary and non-dietary sources.

The overall exposure will also be estimated independently (addressed in SQ3.3) for those substances that have HBM studies available along with TK or empirical relationship data to make it possible to calculate exposure from biomarker concentration data.

The estimates of overall exposure obtained by aggregation of dietary and non-dietary exposures will be compared with the estimates of exposure obtained through HBM, if these are available. This quantitative comparison will take due regard of the uncertainties present in the two ways of estimation, especially the degree of coherence between the different population groups that might be covered, and in the nature and magnitude of any conservative assumptions that have been made. If, taking these considerations into account, the HBM estimates significantly exceed the exposure estimates calculated by aggregation (dietary plus non-dietary) then this might suggest that important sources of exposure may have been missed or underestimated. In that case the data and the underlying assumptions to answer the Qs/SQs will be revisited. If, on the other hand, the estimates from HBM are significantly lower that the estimates from aggregation, this would suggest that some assumptions made are overly conservative and should be revisited to see if some refinement is justified.

Although it is anticipated that few of the prioritised substances will have adequate HBM information available that would allow such a cross-check, it is possible that such an exercise may help to identify any data gaps, methodological shortcomings, and insufficiently or overly conservative assumptions made, which could be systematic in the evaluation approach used. In that case, it would be appropriate to take any general lessons learned and corrections/adjustments made, and also apply them to those substances lacking the independent estimations of overall exposure made via HBM data.

Finally, the best estimates of dietary exposure due to FCMs (coming from Q2) will be compared with the overall aggregated exposure to the prioritised substances for EU consumers (coming from Q1 and SQ3.2), using the HBM information (coming from SQ3.3) to cross-check and possibly adjust the estimates of overall exposure (see Figure 1). Similarly to the situation above, this quantitative comparison will take due regard of the uncertainties present in the two estimations and in the nature and magnitude of any conservative assumptions that have been made.

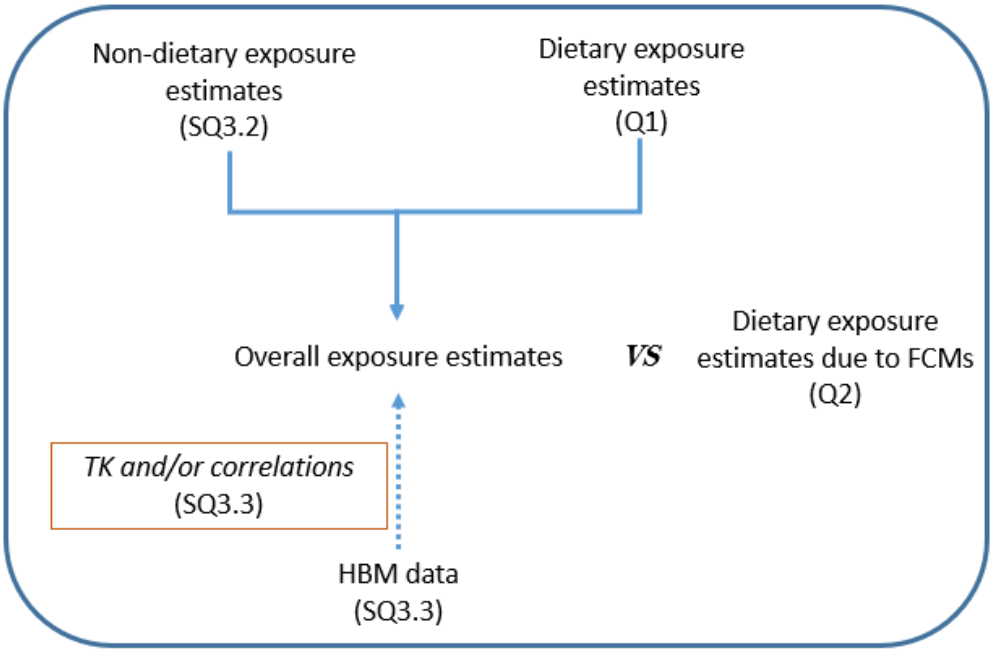

Figure 1: Scheme summarising the framework adopted to answer Q3.

5.5. Uncertainties related to Q3

The main uncertainties related to non-dietary uses and exposure to the prioritised substances are described below.

Uncertainties related to uses

- Quality of the information provided in REACH dossiers. Underreporting and, especially, overreporting of uses have been noticed for several substances. The registration update process promoted by ECHA might bring improvements on use reporting, with the cleaning by the registrants of uses wrongly reported in their registration dossier. However, low-quality reporting might lead to false positive use identifications in several cases.

Uncertainties related to non-dietary exposure

- Lack of available, good-quality data.
  - More realistic exposure values can be estimated using more advanced tools or measured data; however, the former needs more input data that are not easy to obtain and the latter might not be available for many of the prioritised substances.
- Exposure overestimation by first-tier exposure models.
  - First-tier models tend to overestimate exposure which may be acceptable for REACH purposes, but in this context, uncertainties may be too high and unacceptable. This may lead to unreliable conclusions; in particular if (inaccurate, overestimated) non-dietary exposure values are compared with accurate and more realistic dietary exposure figures.

These aspects, in particular the level of possible overestimation of the exposure, need to be taken into account while evaluating the component of non-dietary exposure.

Uncertainties related to human biomonitoring data

- If HBM data are obtained from a non-representative cohort or not necessarily covering all the different population groups and age classes in the EU, assumptions will have to be made on the possibility of generalising the results to the different population groups.

- If TK models or empirical correlations obtained for similar substances are used, the consequences in terms of uncertainty will be considered on a case-by-case basis.

Overall, the possible effects of all the sources of uncertainty identified during the assessment for Questions 1, 2 and 3, on the final outcomes and on the conclusions, will be investigated in the uncertainty analysis. It is expected that the level of uncertainty will be different for the three questions, with the level of accuracy and precision of estimates decreasing from Q1 to Q3. Depending on the assumptions made, the availability and completeness of the information, possible uncertainties linked to representativeness of the sampling, to modelling, to measurements and, in general, to the quality of certain pieces of evidence, it has to be expected that some estimates will be accompanied by considerable uncertainty, which may be very different in magnitude for different types of outcome estimates. The effect of this on the final conclusions cannot be predicted, especially since the final estimates of the assessment will be produced by combining estimates obtained for all three main questions. In extreme cases, the components of these calculations may differ in implausible ways; if, for example, the estimates of dietary exposure due to the use of FCMs obtained from addressing Q2 appear to be higher than the overall estimates of dietary exposure obtained from Q1. For those reasons, uncertainty analyses for each individual question will attempt to produce distributions of plausible values (instead of deterministically calculated point estimates), considering all assumptions and related uncertainties, employing a sensitivity analysis whenever necessary to assess, for example, the effect of different methodological choices and the impact of variability characterising the distribution of certain parameters. Ultimately, it will be attempted to produce probability distributions or statements on the final estimates and appropriate conclusions. However, the uncertainty accompanying those, and therefore their usefulness, will be contingent upon the availability, accuracy and quality of evidence obtained during this exposure assessment and, generally, on the factors mentioned above.

6. Protocol for literature reviews

As previously described, a systematic approach to review the literature will be taken to answer SQ1.1 and SQ3.3. SQ 2.1, SQ2.2, SQ2.5 and SQ3.1 will be addressed narratively. SQ2.3 and SQ3.2 will be initially addressed narratively but a full systematic review of the evidence may be performed at a later stage, depending on the evidence retrieved from other sources (especially evidence on the actual use of the prioritised substances coming from the calls for data and input from interested parties).

The same process will be followed up to the data extraction step for all the SQs independently whether they will be addressed narratively or systematically.

Table 2: Sub-questions and approaches considered to review the literature

Sub-question	Approach
SQ1.1: What are the concentrations of the prioritised substances in food in the EU?	Systematic
SQ2.1: In which FCMs do the prioritised substances under study occur, and in what concentrations and at what frequency of use (market share)?	Narrative
SQ2.2: In which step(s) of the food chain is the FCM used? How often and under what conditions of use is the FCM used in the food chain?	Narrative
SQ2.3: What is the concentration that migrated into food from each identified (SQ2.1) FCM, during relevant step(s) of the food chain (SQ2.2)?	Narrative/conditionally systematic
SQ2.5: What are the consumption levels of relevant food (in which the migration/concentration due to FCM was assessed under SQ2.3) in different population groups and age classes in the EU?	Narrative
SQ3.1: What are all the actual uses of the prioritised substances and the possible sources and routes of non-dietary exposure?	Narrative
SQ3.2: What is the non-dietary exposure to the prioritised substances from the individual uses identified under SQ3.1?	Narrative/conditionally systematic
SQ3.3: What is the overall (dietary and non-dietary) exposure to the prioritised substances measured through HBM?	Systematic

961 Narrative reviews might be also performed to address background information (e.g. possible sources
962 other than FCMs for the presence of the prioritised substance in food, such as use as a food additive,
963 carrier solvent, or environmental contamination).

964 Steps to perform the narrative and systematic reviews are described in the following sections.

965 6.1. Eligibility criteria

966 Tables 3 to 6 describe the eligibility criteria for the selection of studies relevant for SQ1.1 and SQ3.3
967 that will be addressed using a systematic review.

968 The detailed eligibility criteria on study and reporting characteristics for the rest of the questions will
969 be set a later stage. The level of detail in the eligibility criteria might vary depending on the
970 characteristics of each SQ and the availability or evidence retrieved by other methods. Special
971 considerations will be taken in the development of the eligibility criteria for SQ2.3 and SQ3.2 as they
972 might be addressed systematically.

973 **Table 3:** Criteria for selecting studies based on study characteristics for SQ1.1

Study design	**In**	Studies measuring concentrations of the prioritised substances in food (including TDS)
	Out	Studies measuring concentrations from migration testing (either with food or food simulants)
Food samples	**In**	All types of food, including drinking water, sampled in the EU and EFTA countries
	Out	Other sample types
Outcome	**In**	Concentration of the prioritised substances: • Studies reporting concentrations of individual samples • Studies reporting the mean or median concentration, and the number of samples analysed
	Out	Studies not reporting or referencing the analytical method.

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975 **Table 4:** Criteria for selecting studies based on study characteristics for SQ3.3

Study design	**In**	a) Studies measuring concentrations of biomarkers of exposure for the prioritised substances b) Studies establishing the correlation between external dose and biomarker concentration c) TK studies
	Out	
Population	**In**	For (a) human populations (consumers, and control groups from occupations studies) in the EU and EFTA countries For (b) and (c): human populations (consumers and workers)
	Out	
Outcome	**In**	For (a) concentration of biomarkers of exposure for the prioritised substances (individual or summary concentrations) For (b): correlation between external dose and biomarker

		concentration For (c): TK model
	Out	For (a) and (b): studies not reporting or referencing the analytical method

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977 **Table 5:** Criteria for selecting studies related to report characteristics for SQ1.1

Time	**In**	Published from the year of authorisation or implementation of any additional restrictions of the prioritised substance
	Out	Published before the year of authorisation or implementation of any additional restrictions of the prioritised substance
Language	**In**	English EU languages for reports from national/international risk assessment bodies
	Out	Other languages
Publication type	**In**	• Primary studies (i.e. studies generating new data) • Theses • Reports from national/international risk assessment bodies and published reviews will be used to identify relevant references • Reports from national/international monitoring bodies (data from national monitoring bodies should be submitted via the call for data). These reports will be used to identify bodies in the possession of such data and they will be requested to submit the data to EFSA. Care will be taken to ensure that they are not double-counted)
	Out	• Letters to the editor • Expert opinions • Editorials • Conference abstracts or posters

978

979 **Table 6:** Criteria for selecting studies related to report characteristics for SQ3.3

Time	**In**	For (a): published from the year of authorisation or implementation of any additional restrictions of the prioritised substance For (b) and (c): no time restriction
	Out	For (a): published before the year of authorisation or implementation of any additional restrictions of the prioritised substance
Language	**In**	English EU languages for reports from national/international risk assessment bodies

	Out	Other languages
Publication type	**In**	(a), (b) and (c): • Primary studies (i.e. studies generating new data) • Theses • Reports from national/international risk assessment bodies and published reviews will be used to identify relevant references • Reports from national/international research studies and databases
	Out	(a), (b) and (c): • Letters to the editor • Expert opinions • Editorials • Conference abstracts or posters

6.2. Search for studies meeting eligibility criteria

The sources of information to retrieve relevant studies will be identified in line with the scope of the SQs and the publication types of interest set out in the eligibility criteria.

At least three bibliographic databases will be searched for the identification of primary studies (including one database with special focus on chemical information and that allows a search by CAS number). Additional databases might be used for the identification of theses. The websites or repositories of national or international risk assessment/monitoring/research bodies will be searched and/or browsed to identify reports relevant for the review. Additional sources, such as consumer product databases, notification databases of alert systems, chemical product categories and/or substances in products, might be considered for some of the SQs to be addressed narratively (e.g. SQ3.1).

For SQs on the prioritised substances, searches could be structured using only the concept of the prioritised substance or might include additional terms to represent other factors (e.g. population/food samples, outcome of interest). More targeted searches might be considered for some of the narrative reviews.

A wide range of search terms will be used to cover possible language variations (synonyms, related terms, CAS numbers, etc.) of the substances of interest but other terms (e.g. phthalates, plasticisers) could be considered. The same approach will be applied if additional concepts are added to the searches. Several sources will be consulted to select the search terms: PubChem, thesaurus, previous publications on the topic, etc. The terms, syntax and structure of the search will be adapted taking into consideration the characteristics of each source of information.

The output of the searches will be uploaded into Endnote reference management software (Clarivate Analytics) or equivalent. Duplicate references will be removed by a combination of automatic and manual detection of duplicates using reference management software or other tools.

The final search processes and strategies will be documented and reported, i.e. the date of the search, sources of information, search string or method of search for source of information, and the number of records before and after de-duplication.

Snowballing techniques to identify citations of the national/international risk assessment bodies and published reviews identified and/or other relevant documents could be considered for some of the questions according to what is given in their eligibility criteria.

The sources of information and search strategies will be documented and reported.

6.3. Study selection process

The records retrieved via the literature searches will be screened against the eligibility criteria set out above.

The study selection process will be carried out in two steps:

1. Step 1: title and abstract screening, to exclude obviously irrelevant records. All other apparently relevant records or those of unclear relevance will be moved to the following step.
2. Step 2: full-text screening, to select records for inclusion or exclusion.

These steps will be performed by two independent reviewers in parallel to minimise the risk of error using DistillerSR (Evidence Partners, Ottawa, Canada) or alternative tools. The DistillerSR Artificial Intelligence functions or other relevant tool could be used as the second reviewer at title and abstract screening to speed up the selection process. Inter-reviewer conflicts that are not solvable via one-to-one discussions will be evaluated and resolved among all the reviewers.

Screeners will be trained using written documentation on study eligibility. Selection criteria will be piloted on a subset of records, and refined if needed at each step.

The results of the different phases of the record selection process will be reported in a flowchart as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses (Page et al., 2021).

Papers relevant as background information (e.g. sources other than FCMs for the presence of the prioritised substance in food) could be tagged during the screening process.

6.4. Data extraction from included studies

6.4.1. Systematic reviews

Pre-established data extraction forms will be used for collecting the data from the individual studies. The extraction forms will be developed at a later stage, but they will comprise data on the characteristics of the studies (e.g. study design), and their key elements, results, analytical methods, aspects related to the internal and external validity of the studies, etc. The study authors will not be contacted for clarifications or to retrieve missing data.

If a full-text document reports on more than one study, the individual studies will be identified in this step to allow for data extraction at individual study level. If a single study is reported in more than one publication, duplicated use of the data will be avoided.

Clear instructions for extracting data will be developed. The data extraction forms will be implemented in DistillerSR, Excel and/or other tools, and will be pilot-tested on a subset of studies. After piloting, the forms and instructions may be refined. The data extraction will be conducted by one reviewer, and a second reviewer will confirm the data extracted.

6.4.2. Narrative reviews

The level of detail and method on the data extraction might depend on the SQ to be addressed but it should include all the relevant factors needed to reply to the question. A data extraction form for each SQ will be developed to determine which variables to extract. It could include variables such as bibliographic details, objective of the study, design, main results, etc. The data extraction will be performed by one reviewer and a second reviewer will confirm the data extraction.

6.5. Evidence appraisal and synthesis

6.5.1. Systematic reviews

For each SQ the risk of internal and external bias (RoB) of each included study will be assessed separately. For SQ1.1 it may be decided not to use the literature data for the dietary exposure assessment of one or more of the prioritised substances (e.g. when the occurrence data received in the calls for data are sufficient to calculate dietary exposure), in which case the evidence appraisal will not be performed.

Internal validity (internal bias) refers to the degree to which the result of a study is likely to be true and free of bias (systematic errors). Risk of bias relates to the propensity of a study to be affected by systematic errors.

External validity (external bias) affects the extent to which the study results are generalisable to the assessment question, e.g. when the study settings are not representative of the reference population or conditions.

Internal and external validity (or RoB) will be appraised for each individual study using an appropriate critical appraisal tool (CAT). Each study will be appraised by two independent reviewers. Possible discrepancies not solvable via discussion between the two reviewers will be discussed by the whole group. If upon further discussion the group cannot reach an agreement on a rating, the more conservative judgement (the highest RoB) will be selected. The CAT will be pilot-tested by two reviewers. Feedback from this testing phase will be used to further refine this process, starting from adjusting the CAT itself.

For each appraisal question a rating will be provided assessing the probability of RoB. An algorithm to combine the answers to the appraisal questions and allocate studies to tiers of RoB (both internal and external validity) could be written to combine the judgements to the RoB questions into an overall RoB judgement for each individual study (by outcome).

An appropriate methodology of synthesis of the evidence will be used.

6.5.2. Narrative reviews

Appraisal of the studies might be performed in a narrative manner. The evidence will be summarised and discussed in a narrative manner.

7. Plans for updating the protocol

Every amendment to this protocol during the risk assessment will be documented and duly justified. The amended version of the protocol will be published together with the risk assessment to ensure full transparency of the evaluation process.

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1162 # Abbreviations

BBP	benzyl butyl phthalate
CAS	Chemical Abstracts Service
CAT	critical appraisal tool
CEP	Food Contact Materials, Enzymes and Processing Aids [EFSA Panel]
CMR	carcinogenic, mutagenic, or toxic for reproduction
DBP	dibutyl phthalate
DEHP	di-(2-ethylhexyl) phthalate
DIDP	diisodecyl-phthalate
DINP	diisononyl-phthalate
EC	European Commission
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
FCM	food contact material
GNPD	Mintel Global New Products Database
HBM	human biomonitoring
JRC	Joint Research Centre
LB	lower bound
LOD	limit of detection
LOQ	limit of quantitation
OECD	Organisation for Economic Co-operation and Development
TK	toxicokinetic
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVC	polyvinyl chloride
Q	question
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	Dutch National Institute for Public Health and the Environment
RoB	risk of internal and external bias
UB	upper bound

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