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RISK ASSESSMENT OF NON-LISTED SUBSTANCES (NLS) AND NOT-INTENTIONALLY ADDED SUBSTANCES (NIAS) UNDER ARTICLE 19

INTRODUCTION

This chapter provides an overview of approaches for assessing the risks of non-listed substances as required by Article 19 of the European Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, in this guideline referred to as the Regulation. The Regulation contains in Annex I a list of monomers, starting substances and additives evaluated and authorized for use in food contact plastics (i.e., the Union list).

Under the provisions of the Regulation, a number of substances present in food contact plastics are exempted from the requirement to be included in the Community positive list (Union list) according to the Article 6. The substances exempted of positive listing include: solvents, colorants, Polymer Production Aids (PPA's), Aids to Polymerization (AP's), oligomers and the so-called "Non-Intentionally-Added-Substances (NIAS)". NIAS include substances such as impurities, contaminants, reaction and degradation products. If a substance is not in the Union list but already subject to restriction in a national law, the relevant restrictions shall be met. It should therefore be made clear that this guideline document applies to substances exempted from authorization at the EU level according to the Article 19, unless already listed and subject to restrictions.

The non-listed substances are subject to the provisions of Article 3 of the Framework Regulation (EC) No 1935/2004 that applies to all food contact materials. Article 3 states that exposure to substances from food contact materials should not pose a risk to human health. For non-listed substances this should be demonstrated through a risk assessment and documented in the internal supporting documentation package to the Declaration of Compliance. Article 19 of the Regulation articulates the need for a risk assessment for non-listed substances in accordance with internationally recognized scientific principles on risk assessment. This chapter provides an overview on how to perform a risk assessment according to internationally recognized scientific principles on risk assessment as asked for by the Regulation. Note that extensive literature is available on risk assessment methodology and that slightly different approaches and terminology are used by different organizations. A risk assessment according to internationally recognized scientific principles as asked for by the regulation will be carried out by an expert familiar with the different approaches and their bases. The non-exhaustive list of references at the end of this chapter provides further sources of information on risk assessment (guidance documents on regulatory websites[2,3,4,5], scientific publications, reports, etc…).

The Packaging Materials task force at ILSI-Europe (International Life Science Institute, a non-profit worldwide foundation established to advance the understanding of scientific issues related to nutrition, food safety, toxicology and the environment) has published a range of useful technical reports on risk assessment for food packaging[6]. The website of the US Food and Drug Administration also provides useful guidance on risk assessments[4, 5, 7].

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A risk assessment typically consists of the following three components:

1. Exposure assessment

2. Toxicological assessment

- Hazard identification
- Dose-response assessment (Hazard Characterization)

3. Risk characterization

1. EXPOSURE ASSESSMENT

The exposure assessment aims to define the dose of non-listed substances that individuals receive in exposed populations. This dose is the so-called Estimated Daily Intake (EDI) (mg/person/day).

The EDI's for non-listed substances in food contact materials are estimated in a number of ways depending on the material and the nature of the contact. To assess the dietary exposure to a substance migrating from "repeated-use" applications (e.g. pipes, tubing, food containers, and food processing equipment) conservative models are applied. The assessment of food contact materials that come in contact with foods in non-repeated use applications e.g. food packaging is more complex and often require more refined models and additional data. In both cases, tiered approaches are typically used in exposure assessments. Tiered approaches begin by using simple, conservative, and widely applicable models of exposure. These models require relatively little data but tend to overestimate exposures. If the exposure estimates are found to be too large using the conservative models then the assessor moves on to more refined methods.

All exposure assessments for non-listed substances require the same types of information. These include data on the ability of the substance to migrate from the material into food or ware during contact events (migration data), and data that allow the prediction of the daily dose to exposed individuals (food consumption and food packing data). The findings of migration are a property of the substance, the food contact material, the food, the duration and conditions of the contact. The findings of exposure are determined by how much food and water are consumed by the average consumer and what types and shapes of packaging are used for the food and water.

1.1. Migration data

The migration levels of substances from plastics into the food under the typical conditions of use can be derived from worst case calculations (modeling assuming 100% migration), migration calculation models (diffusion model) or migration studies in food simulants (experimental data). Migration is typically expressed in mg/dm^2 plastic or mg/kg food. For applications where the material or article is intended to come into repeated contact with food stuffs (so-called "repeated-use" applications e.g. pipes, tubing, food containers, food processing equipment) the migration level in the third migration test should be taken as basis for the risk assessment (Annex V chapter 3.3 of the Regulation).

1.1.1 Worst-case migration calculation (general)

The following two formulae can be used to calculate the worst case concentration levels in the food assuming 100% migration.

$$C_{Food}\,(mg/kg) = \frac{C_{Polymer}\,(mg/kg) * d_{Polymer}\,(g/cm^3) * S_{Packaging}\,(cm^2) * e_{Packaging}(cm)}{M_{Food}(g)}$$

$$C_{Food}\,(mg/kg) = \frac{C_{Polymer}\,(mg/kg) * d_{Polymer}\,(g/cm^3) * S_{Packaging}\,(cm^2) * e_{Packaging}\,(cm)}{d_{Food}\,(g/cm^3) * V_{Food}\,(cm^3)}$$

With
$C_{Polymer}$: concentration of the substance in the polymer
C_{Food}: concentration of the substance into the food
$d_{Polymer}$: density of the polymer
d_{Food}: density of the food
$e_{Packaging}$: thickness of the packaging material
$S_{Packaging}$: contact area of the packaging material
V_{Food}: volume of the food in contact with the material
M_{Food}: weight of the food in contact with the material

By convention and as documented in the EFSA Note for Guidance[3(p 91)], it is assumed that for most plastics, migration under typical conditions of use primarily takes place from the first 250 microns of the plastic layer in contact with the food with the exception of plasticized polymers and of the migration of components with low diffusion coefficients (volatile components).

The rate of migration is a function of the substance, the plastic, the food, the contact time and temperature of the food. Data on migration rates are generated based on empirical studies of specific plastics. Such studies typically investigate different types of foods. Ideally, data should be developed for the following types of food: aqueous food, alcoholic food, acidic food and fatty food.

1.1.2 Worst-case migration calculation for pipes (repeated use, dynamic state)

The initial Mass concentration C_0 of the substance is assumed to be uniform into the polymer.

The initial mass concentration of the substance in the polymer is:

$$C_{Pol,0}\,(mg/kg) = \frac{M_{Sub}\,(g)}{M_{Pol}\,(g)} = \frac{M_{Sub}\,(g)}{d_{Pol}\,(\mathrm{g/cm3}).V_{Pol}\,(\mathrm{g/cm3})}$$

Geometry of the pipe:

D_{ext} (cm): external diameter of the pipe
D_{int} (cm): internal diameter of the pipe
E (cm): thickness of the pipe
L (cm): length of the pipe
e (cm): wetted thickness of the polymer
V_{Food} (cm^3): volume of the food in the pipe

$d_{Polymer}$ (g/cm^3): density of the polymer
d_{Food} (g/cm^3): density of the food
V_{Pol} (cm^3): volume of the polymer constituting the pipe

$$D_{ext} = D_{int} + 2 * E$$

$$V_{Pol} = V_{ext} - V_{int} = \frac{\pi}{4} LE\left(D_{int} E\right)$$

$$V_{Food} = \frac{\pi}{4} LD_{int}^2$$

Assumption:
100% migration of the substance into the foodstuffs of each cycle.

$$C_{Food}\,(mg/kg) = \frac{C_{Pol}\,(mg/kg) * d_{Pol}\,(g/cm^3) * V_{Pol}\,(cm^3)}{M_{Food}\,(g)} = \frac{C_{Pol}\,(mg/kg) * d_{Pol}\,(g/cm^3) * V_{Pol}\,(cm^3)}{d_{Food}\,(g/cm^3) * V_{Food}\,(cm^3)}$$

$$C_{Food}\,(mg/kg) = 4C_{Pol}\,(mg/kg)\frac{d_{Pol}\,(g/cm^3)}{d_{Food}\,(g/cm^3)}\frac{E(cm)\left(D_{int}\,(cm) + E(cm)\right)}{D_{int}{}^2\,(cm^2)}$$

The concentration of a substance migrating from a pipe is independent of the length of the pipe. Only the fraction of the substance contained in the “wetted” thickness e of the low diffusivity polymer could migrate. Consequently in the above equation the thickness E of the pipe can be replaced by the “Wetted” thickness e (for drinking water the wetted substance is equal to 100 µm according to the French circular DGS-VS4 n°99-217 published the 12 April 1999. For foodstuffs the wetted thickness is 250 µm according to the EFSA note of Guidance-page 55).
After a first migration, the new concentration of the substance is considered as homogeneous in the entire polymer. So the concentration is:

$C_{Pol,1} = C_{Pol,0} - C_{Food,0}$

After n cycles of migration, the concentration of the substance in the polymer is:

$$C_{Pol,n} = C_{Pol,0} - \sum_{1}^{n} C_{Food,p}$$

After n cycles of use, the amount of food in contact with the polymer is:

$$M_{Food}\,(g) = d_{Food} * V_{Food} = n * d_{Food} * \frac{\pi}{4} LD_{int}^2$$

The average concentration of the substance in the food can be calculated assuming 100% of migration into the total amount of food in contact with the polymer during the lifetime of the pipe.

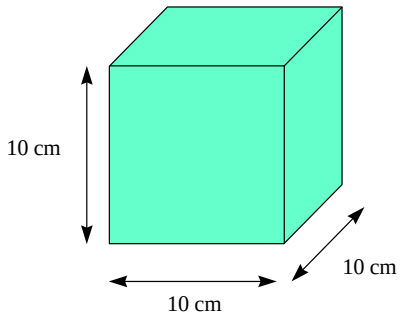
This is the total amount of the substance distributed throughout the total amount of food transported during lifetime of the pipe.

$$\overline{C}_{Food}\,(mg/kg) = \frac{C_{Pol,0} V_{Pol} d_{pol}}{\mathrm{n}\, \mathrm{d}_{\mathrm{Food}} \mathrm{LD}_{\mathrm{int}}{}^{2} \frac{\pi}{4}}$$

1.2. **<u>Food consumption and packaging use data</u>**:

The default (worst-case) assumption in Europe is that every day an adult person consumes 1 kg of food packaged in a 1 dm^3 cube with a surface area of 6 dm^2. It is assumed that the cube is covered by a single type of the same food contact material and the food is the most aggressive extractor of the substance. The individual has the same exposure every day throughout his life. This assumption is the basis for a default food contact rate for the material of 6 dm^2/person/day.

This is a conservative assumption that does not reflect any real consumption pattern. In reality only a certain percentage of the daily consumed food is packaged in any one food contact material and within plastics a certain percentage is used to package aqueous food, acidic food, alcoholic food, and fatty food.



EU food packaging cube

Total volume = 1 dm^3

Total surface = 6 dm^2

1.3 <u>Derivation Estimated Daily Intake number – three steps approach</u>

In order to calculate the estimated exposure, a tiered, three steps approach is suggested starting with a simple worst case calculation up to very accurate estimates using highly sophisticated probabilistic assessment models. Such refinements require additional information and are more complex and resources intensive than the conservative approach.

<u>Step 1: Worst case exposure calculation based on European default assumption</u>

Based on the default assumption in Europe that every day an adult person consumes 1 kg of food packaged in a 1 dm^3 cube, an estimated worst-case daily intake number can be calculated using the following simple formula.

$EDI_{worst\ case}$ (mg/person/day) = 1 kg food/person/day * Migration (mg/kg food)

Step 2: FRF corrected exposure calculation for lipophilic substances in fatty food

To account for the fact that 95% of the population consumes less than 200 g of fat per day, the Regulation allows dividing the migration levels of lipophilic substances into foods containing more than 20% fat, with a Fat Reduction Factor (FRF). The FRF may vary from 1 to 5 (FRF=1 for food with a fat content of 20% and FRF=5 for food with fat content of 100%). The FRF corrected exposure number can be calculated using the following formula.

$$EDI_{FRF\ corrected}\ (mg/person/day) = \frac{1\ kg\ food/person/day * Migration\ (mg/kg\ food)}{FRF_{lipophilic\ substances}}$$

Annex V chapter 4.1 of the Regulation describes the application of the FRF and the specific cases where the FRF cannot be applied (e.g. infant food).The application of the FRF shall not lead to a specific migration exceeding the overall migration limit.
Step 3: Refined exposure calculation using food distribution/consumption factors

A. FDA exposure assessment

The US Food and Drug Administration (FDA) has generated consumption data for packaged food which are used in risk assessments for regulatory purposes. The food consumption data for different packaging materials (Consumption Factors and Food-Type Distribution Factors) are accessible on the FDA website together with detailed guidance on how to calculate consumer exposure to substances migrating from packaging materials[5].

Under FDA approach, the term "Consumption Factor" (CF) is used to describe the fraction of the daily diet expected to contact specific packaging materials. The CF represents the fraction of daily consumed packaged food that is packed in a certain packaging material. FDA assumes that an individual consumes 3 kg of packaged food (1.5 kg solid and 1.5 kg liquid) per day of which about 80% is packaged in plastics. The Food-type distribution factors (f_T) reflect for each packaging material the fractions of all food contacting each material that is aqueous, acidic, alcoholic and fatty. These data (consumption factors and food type distribution factors) are available on the FDA website (see link:

http://www.fda.gov/Food/default.htm (Documents UCM081825 and UCM081818)

The Estimated Daily Intake (EDI) (mg/person/day) of a substance migrating from a plastic packaging material into a specific type of food can be calculated using the following formula (calculated for a 60 kg person and an intake of 3 kg of packaged food per day):

$$EDI_{FDA}\ (mg/person/day) = 3\ kg\ food/person/day * CF * \langle M \rangle\ (mg/kg\ food)$$

EDI: Estimated Daily Intake (mg/person/day)
CF: Consumption Factor for the particular plastic

<M>: Migration level of substance from the plastic into the food (mg/kg food)

In case specific migration levels are available for the different types of food then the formula can be further refined as follows:

$$<M> = f_{\text{aqueous and acidic}} \cdot (M_{\text{10\% ethanol}}) + f_{\text{alcohol}} \cdot (M_{\text{50\% ethanol}}) + f_{\text{fatty}} \cdot (M_{\text{fatty}})$$

f: Food-Type distribution factors for the particular plastic
M: Migration levels of the substance measured in different types of food simulants

The website of US FDA contains a database with cumulative estimated daily intakes (CEDIs) and acceptable daily intakes (ADIs) for a large number of food contact substances[7].

B. European consumer exposure assessment tools

B1. Risk Assessment of non-intentionally added substances (NIAS) using the MATRIX method

Only limited food consumption data are publicly available for plastic packaging materials in Europe[6f]. The assessment of NIAS apart from their occurrence also requires exposure data for the specific plastics materials.
The Matrix Project was jointly initiated, financed and supported by Cefic-FCA, European Plastics Converters (EuPC), Flexible Packaging Europe (FPE) and PlasticsEurope[8]. Within the project generic levels of migration into food for resp.packaging plastics materials were derived. Above these levels every migrant should be identified and assessed, however, below which the corresponding exposure is so minor that further assessment could be neglected. This level has been defined “Level Of Interest (LOI)”: it is linked to each packaging material and will be a function of the exposure of consumers to this material. The calculation of the LOI follows similar conditions as applied to non-listed substances used behind a functional barrier as described in the articles of regulation (EU) No 10/2011.
The Matrix Project derived country data sets for Germany, France, Italy, Spain and United Kingdom with the respective packaging surface to which consumers are exposed per plastic material group and per consumed food and the respective calculation of LOIs.
Plastics material groups can be assessed on a country base to define the level where identified migrants need to be further risk assessed or not.
If NIAS assessments are addressed using the Matrix method the data and assessments become part of the supporting documentation of the products investigated at the respective stage in the Plastics value chain.
In general, the same methodology applied here for NIAS can be used for any non-listed substances.

B2. The FACET Project

Within the 7th Framework Research Program, Europe has developed a new tool for exposure of substances migrating from food contact packaging. FACET (Flavours, Additives and food Contact material Exposure Task) is an EU-funded project aimed at estimating exposure to three types of food chemicals: Food additives, Flavorings and Migratable substances from food contact materials. The FACET project which was officially finished in October 2012 developed a software tool that will model exposure to substances migrating from food contact material on a country base for the EU population. The probabilistic exposure results are based on comprehensive pan-European food consumption and food packaging data encrypted into the software (see www.ucd.ie/facet).

2. TOXICOLOGICAL ASSESSMENT

The aim of the toxicological assessment is to identify the adverse toxicological effects that a substance could cause (Hazard Identification) and secondly, to define the critical dose or exposure level of a substance in the daily diet, below which the substance is not expected to pose a risk to human health (Dose response assessment or Hazard Characterization).

Most adverse effects for chemicals occur at a particular dose (Paracelsus: "dose makes the poison"). Toxicological studies or alternative data will be applied to derive the daily dose which can, based on conservative assumptions, be assumed with reasonable certainty to be safe.

This critical dietary exposure level is often referred to as the Tolerable Daily Intake (TDI), generally used for substances appearing in food but not intentionally added or the Acceptable Daily Intake (ADI) for substances intentionally added to food, usually expressed in mg/person/day or mg/kg bodyweight/day.

Based on the TDI and the European default assumption that a 60 kg person consumes a kilogram of food per day a self-derived Specific Migration Limit (SML) for the substance can be calculated using the following formula

Self-derived SML (mg/kg food) = 60 (kg body weight)* TDI (mg/kg body weight/day)/1 kg food/day

However, genotoxic mutagens and carcinogens are an exemption to this basic principle. For their mode of action, it is traditionally assumed that already one interaction event between a substance molecule and a DNA molecule could theoretically lead to an adverse effect, so that a no-threshold-mechanism is assumed[1*]. Generally, the aim is to strictly avoid the presence of genotoxic mutagens and carcinogens in food contact materials. However, this may not always be possible, especially for NIAS. A safety assessment for such cases would follow the internationally accepted scientific principles of linear low dose extrapolation, the Margin Of Exposure[9] approach or Derived Minimal Effect Levels[10] approach. In the case of food contact materials applied in Europe, the MOE approach is preferable, as it has been reviewed and recommended by the EFSA Scientific Committee[11]

Regulatory agencies in the United States, the Food and Drug Administration (FDA) and the European Union (EU) use a tiered approach based on the "dose makes the poison" principle to regulate substances that e.g. migrate from food packaging and processing equipment to food. Toxicological data may not be required when the exposure is extremely low. Under U.S. FDA guidance, substances with an exposure below the Threshold of Regulation of 1.5 µg/person/day and no concern of genotoxicity, don't require specific toxicological data. For Europe, under the provisions of the Regulation, substances that have not been evaluated and authorized and are not classified as Carcinogenic, Mutagenic or Reprotoxic, can be used in plastics layers behind a functional barrier if they don't migrate at a detection limit of 10 µg/kg food. This "no-migration" concept for non-CMR substances has been adopted under the CEPE Code of Practice for non-listed substances in direct food contact coatings.

* There is ongoing scientific debate about this hypothesis and the consensus may change in the near future, but this has to be discussed elsewhere and the current guidance document will build on the traditional hypothesis and risk assessment methods.

The first step of a safety assessment is always the search for toxicity data on the substance. Subsequently, there are basically two approaches to determine the dietary exposure thresholds for substances:

- Based on toxicological studies performed on the substance or a structurally similar substance (read across).
- Based on the Threshold of Toxicological Concern (TTC) concept if no substance-specific data are available.

Substances being suspected or known genotoxins and/or carcinogens require specific risk assessment methodology which shall not be discussed here. For guidance, please refer to the MOE approach[10, 11].

2.1 Determination Tolerable Daily Intake (TDI) based on specific toxicological studies

Once it has been excluded by data available, SAR (Structure Activity Relationship) or expert judgment, that the substance does not pose any concern with regard to genotoxicity, an appropriate dose descriptor from repeated dose (chronic/subchronic/sub-acute) toxicological studies can be selected. Guidance on dose descriptor selection is for example available by the ECHA guidance on information requirements and chemical safety assessment Chapter R8.2, the ECETOC report TR 85 - Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies[12], ECETOC report TR 99 - Toxicological Modes of Action: Relevance for Human Risk Assessment[13].

The Tolerable Daily Intake number can be derived from e.g. the NOAEL (No-Observed-Adverse-Effect-Level) or a benchmark dose (BMD-L) obtained from repeated dose (chronic/sub chronic/sub-acute) toxicological studies and taking into account certain assessment factors.

TDI (mg/kg body weight/day) = NOAEL (mg/kg body weight/day) / assessment factor

For EU food contact materials, the typical convention is to calculate the TDI by dividing the NOAEL obtained from an oral sub chronic (90 days) study with a default assessment factor of 100. This factor gives an additional margin to take into account the possibility that humans may be more sensitive than animals and that some humans may be more sensitive than others. The factor 100 is constituted of two factors of 10.

One factor of 10 is intended to account for interspecies differences. This factor of 10 is envisaged as converting the findings in animals to equivalent findings in humans.

A second factor of 10 is used to account for differences in typical humans and sensitive sub populations such as children, the elderly or compromised individuals.

These two assessment factors are intended to be conservative and address a wide range of chemicals. Recent guidance provided by the IPCS[14] and ECHA[10] allows for deviation from the values of 10 when the data on the specific substance is sufficient to justify alternative values. In certain instances, smaller values can be justified using data on mechanism of actions or modeling of the pharmacokinetics of the compound.

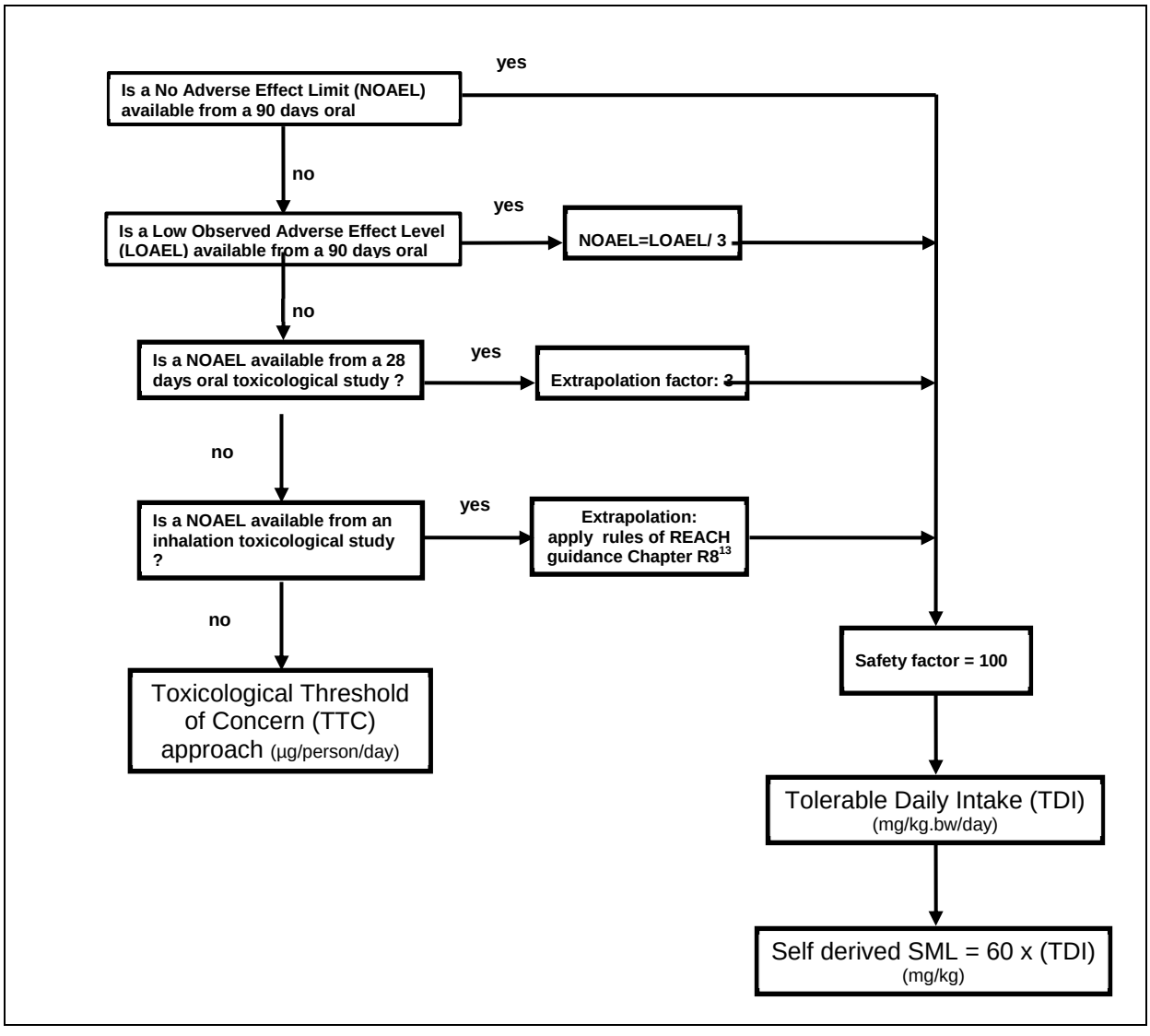
Additional assessment factors might be required in certain cases. Guidance on the need for additional uncertainty factors can be taken from the ECHA guidance for setting DNELs (Derived No-Effect Levels)[10]. Examples where additional factors may be required include the following cases:

- To reflect uncertainties/data gaps in the database (e.g. study not performed to current scientific standards, read-across study);
- Where a LOAEL (Lowest-Observed-Adverse-Effect-Level) is available instead of a NOAEL;
- When sub-acute (28 days) study is available and is used to estimate the NOAEL in a (sub)chronic study.

In case those oral studies are not available, it may be possible to perform a route to route extrapolation[10] to derive an oral NOAEL from a systemic NOAEL obtained from a non-oral exposure route (e.g. inhalation or dermal study).

Figure 1 provides an overview of various options to derive a TDI for a substance and the assessment factors to be applied. The Threshold of Toxicological Concern is discussed in the following section.

Figure 1: Overview different pathways to derive TDI from toxicological studies



If no data on the substance to be assessed exist but data are available on a substance being structurally very similar, and based on a scientific rationale[15] it can be shown with reasonable certainty that the toxicological properties of both substances are comparable, a NOAEL from the surrogate substance may be used to define the TDI of a substance. This process is referred to as a “read across”.

An additional source of toxicity data on substances or potential surrogates is the U.S. FDA webpage. This web page includes a database of Cumulative Estimated Daily Intakes (CEDIs) and Acceptable Daily Intakes (ADIs) for a large number of food contact substances[7]. While the information can be useful, it has to be evaluated against the most recent toxicology studies on the substance of interest.

2.2 Determination Threshold of Toxicological Concern (TTC)

The TTC is a risk assessment tool that, establishes human exposure levels for chemicals below which there is no appreciable risk to human health. It is a useful tool for assessing substances of unknown toxicity present at low levels in the diet where the structure of the compound is known [16,17,18,19], but no substance specific toxicity data or data on a similar substance exist.

The TTC approach is used by EFSA for the safety assessment of flavoring substances and metabolites, degradation and reaction products of pesticides; further applications are risk assessments for cosmetic ingredients, household products and impurities in therapeutic drugs. EFSA has established a TTC Working Group to study the applicability of the TTC approach for safety assessments for other applications including food contact materials[20]. A task force at ILSI[21] is working on further developing the science of the TTC concept. This approach was used first by FDA to establish the Threshold of Regulation for substances that migrate at 0.5 μg/kg or less into food wherein such substances are exempt from food additive regulations and procedures.

The TTC methodology is based on a decision tree approach (figure 2) that uses information on the molecular structure of a substance to assign the substance to one of a number of classes. Certain substance classes are exempt from the TTC concept, either because they were not part of the toxicological database used to derive the thresholds, or because they are of high toxicological concern and warrant a safety assessment based on substance specific data. The lowest thresholds for substances to which the concept can be applied are applied to a class of substances with functional groups that are structural alerts for genotoxicity. Substances without these alerts are assigned into one of several classes that are based on data from non-cancer endpoints in toxicological studies. These non-cancer classifications include the class of organophosphates and three broad classes of chemicals referred to as Cramer classes I, II, and III.

For illustration, table 4 lists the TTC thresholds as described by Kroes at al. 2004. The reader is directed to the original references of Kroes et al. 2004[16] and Cramer and Ford 1978[18] for additional information on using the concept. IT tools, e.g. ToxTree[22] are available to facilitate the determination of the Cramer Class of a chemical.

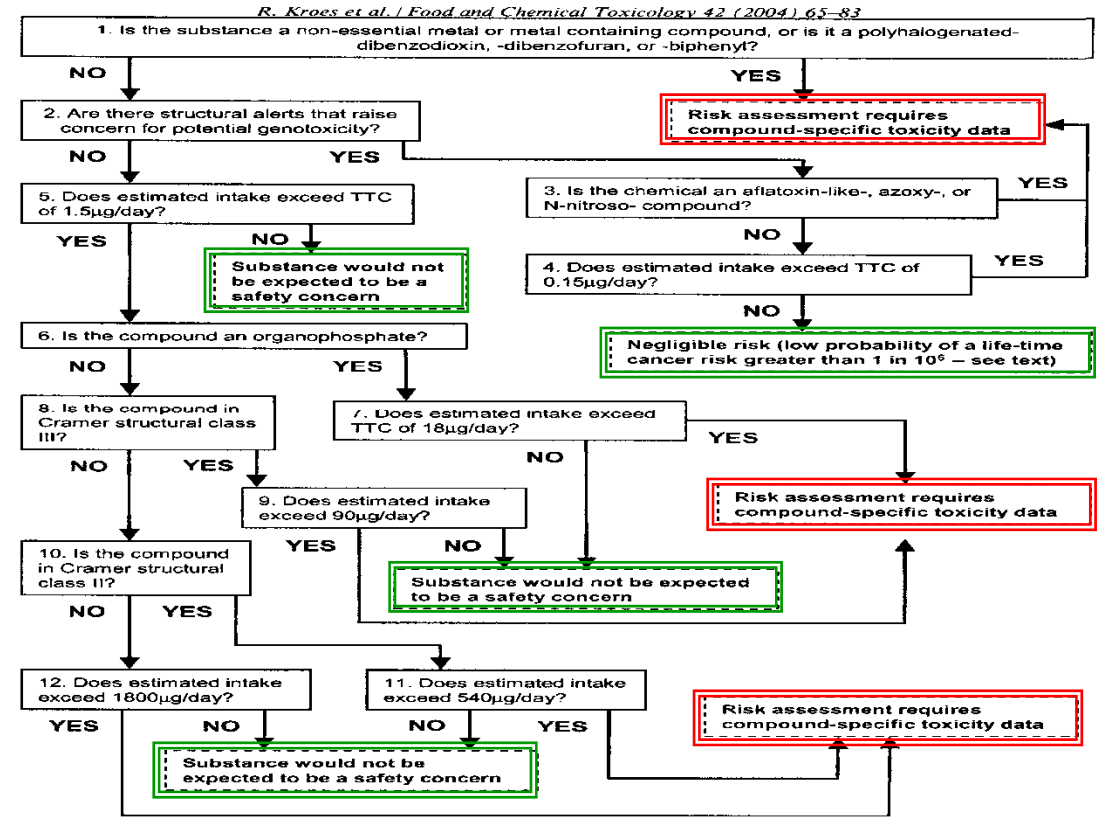
Table 4: TTC exposure thresholds as described by Kroes et al. 2004[16]. Each threshold requires the classes listed below its level, to be excluded.

Structural class	Description	TTC exposure limit (μg/person/day)
Cramer class I (least toxic)	Substances with simple chemical structure and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity.	**1800**
Cramer class II (intermediate)	Substances which possess structures that are less innocuous than class I substances, but do not contain structural features suggestive of toxicity like those substances in class III.	**540**
Cramer class III (most toxic)	Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups.	**90**
Organophosphates	Organophosphate structures which may have neurotoxic properties	**18**
Threshold of regulation	Substances for which there are no structural alerts for genotoxicity	**1.5**

Genotoxicity alerts	Substances for which there are structural alerts for genotoxicity but which are not aflatoxin-like, azoxy- or N-nitroso-compounds	**0.15**

Substances, for which there are no structural alerts for genotoxicity and which do not belong to one of the TTC exempt classes (e.g. non-essential metals), are considered safe if the exposure is below 1.5 μg/person/day. The US FDA regulation has specified this exposure limit in the law (CFR 21 par 170.39) as the so-called "Threshold of Regulation" sometimes also referred to as "Threshold of Regulatory Concern" (TORC). For substances with structural alerts for genotoxicity an even lower exposure threshold of 0.15 μg/person/day has been defined.

Figure 2: Decision tree TTC[16]



A special challenge may occur when several non-intentionally added substances migrate at very low level. First, albeit difficult from analytical perspective, the assessment requires certain knowledge on the substances' structures to be able to search for toxicity data or to apply the TTC concept[1]. With respect to the latter, the assessor would have to have sufficient structural information/knowledge on the origin of the substances to answer the questions of the TTC decision tree.

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3. RISK CHARACTERISATION

In the final risk characterization step, the typical exposure level to the substance in the daily diet (the Estimated Daily Intake) is compared to the maximum tolerable exposure level (the Tolerable Daily Intake). Alternatively the migration level into the food is compared to a self-derived Specific Migration Limit (SML). As long as the Estimated Daily Intake is below the Tolerable Daily Intake or the migration level under the typical condition of use is below the self-derived SML, the use of the substance is considered safe.

EDI < TDI or Specific migration < self-derived SML ⇒ PRODUCT IS SAFE!

In case the product is not considered safe in the application, then either the risk assessment needs to be refined (refine the exposure estimation or generate more toxicological data) or the exposure to the substance (migration level) needs to be reduced.

The risk assessment must be reviewed regularly to take into account the evolution of the knowledge relating to the toxicity of the substance and if the conditions of use are changed or different.

4. REPORTING OF RISK ASSESSMENT IN SUPPORTING DOCUMENTS TO DOC

The risk assessments on non-listed substances should be reported in the Supporting Documentation to the Declaration of Compliance (DOC) according to Article 16 of the Regulation. The format and content of the Supporting Documentation should be defined on a case-by-case basis. Below are some suggestions about information to be included as applicable:

- Identity and the address of the company
- Date of the risk assessment
- Authors
- Identity of the substance:
    - Trade name
    - Chemical name
    - CAS number
    - Chemical structure
    - Molecular weight
    - Purity criteria and the main impurities
- Physical and chemical properties available (especially partition coefficient or solubility, boiling point...)
- Thermal stability and/or decomposition products (for example for organic peroxide) if available and appropriate
- Conditions of use in the polymer:
    - Description of the conditions of use
    - Function of the substance in the manufacturing process and in the final polymer
    - Maximum concentration in the final material
    - Specific steps used to minimize the residual amount of the substance in the final polymer...
- Toxicological data:
    - Cramer class and TTC exposure limit if TTC approach is used
    - Read across if appropriate and arguments used to do this read across
    - Toxicological data if available:
        - Genotoxicity and mutagenicity

- NOAEL
- TDI derived
- SML calculated based on toxicological data

- Evaluation for the Exposure:
  - Method used to determine the migration level:
    - Worst-case calculation
    - Migration modeling
    - Migration tests: conditions used (time, temperature, nature of the simulants)
- Conclusions
- List of references (if appropriate)

ANNEX (examples)

Note: Solely for the purpose of illustration, the examples provided below are assessed both via substance specific data and the TTC approach. While this demonstrates the conservatism inherent to the TTC approach, it must be clearly stated that substance-specific data are always the first choice.

Example 1:

Risk assessment on the use of a solvent as processing aid in a plastic food contact material

Liquid paraffin solvents, known also under the designation of linear or branched aliphatic hydrocarbons or alkanes, could be used as desensitizing agent and/or carrier of organic peroxides in the manufacturing process of several polymers like polyolefins, PVC, ethylene copolymers, rubbers etc., intended for food contact applications. The use of desensitizing agents is essential to comply with the transportation regulation relating to dangerous substances and for safety reasons. The boiling point of the aliphatic hydrocarbons used is often above 150° C following the requirements of the transportation regulation of dangerous chemicals. Due to the high boiling point of these aliphatic hydrocarbons, they could be present in the final plastic materials intended for food contact applications. Alkanes don't provide physical or chemical properties to the final materials and could be considered as Aids to Polymerization exempted from positive listing under Regulation (EU) 10/2011. These solvents present as impurity in the manufacturing process, have to be risk assessed according to the Article 19 of the Regulation to guarantee the safety of the final material.

The Cramer Class of liquid alkanes is I. Consequently the exposure threshold for aliphatic hydrocarbons is 1800 µg/person/day or 1.8 mg/person/day. So, for a European eating 1 kg food per day, the SML based on TTC approach will be:

$$\mathbf{SML_{TTC} = 1.8\ mg/kg\ food}$$

For one of the aliphatic hydrocarbons currently used in Food Contact Materials, a NOAEL value has been determined of 330 mg/kg bw/day, based on a 90 days sub chronic oral toxicity study on rats. Following the pathway given by the Figure 1, the Tolerable Daily Intake can be derived by dividing the NOAEL by the Safety Factor 100.

$$TDI = NOAEL / 100 = 3.3\ mg/kg\ bw/day$$

The self-derived SML, for a 60 kg weight European eating 1 kg of food per day will be:

Self-derived SML = TDI * 60 = 198 mg/kg food

The comparison of these two SML's shows that the TTC approach is conservative compared to real toxicological data. The SML calculated, on the base of toxicological data, is higher than the overall migration limit of 60 mg/kg food set by the Regulation.

The maximum concentration in the plastic of aliphatic hydrocarbons coming from organic peroxides used during the different manufacturing processes is less than 3500 mg/kg. But the synthesis is often followed by a finishing step inducing a reduction of the residual concentration of aliphatic hydrocarbons at a level below 1000 mg/kg .

Assuming 100 % migration from a 6 dm^2 packaging having 100 µm thickness and a density between 1 g/cm^3 to 1.4 g/cm^3, the migration level according to the formula in section 1.1.1 will be **between 6 and 8.4 mg/kg food**. This worst-case migration is a factor 23 to 33 below the SML of 198 mg/kg food as derived from toxicological data and above the SML_{TTC} of 1.8 mg/kg food given by the TTC approach.

As the TTC approach is very conservative compared to the real toxicological data measured on the substance, the conclusion of the risk assessment is that final materials containing the assessed aliphatic hydrocarbons are safe for the consumer in the intended use.

Example 2:

Risk assessment on a surfactant used in the manufacturing of a polymeric additive used in a plastic food contact material

Impact modifiers used as a polymeric additive in different Food Contact Materials are often manufactured using an emulsion, suspension or micro suspension polymerization process. Surfactants or generally surfactant systems are used to disperse the monomers into the water. According to the Regulation, the surfactants can be considered Polymer Production Aids in these manufacturing processes. Certain surfactants are used as additives in food contact plastics and are listed in Annex I of the Regulation. Others are not listed and require a risk assessment according to Article 19 of the Regulation.

Impact Modifiers are often acrylic and methacrylic copolymers with styrene, butadiene and other specific monomers such as cross-linking agents. Depending on the manufacturing process, the concentration of the surfactants system may vary between 1 to 10 % of the total active ingredients of the recipe excluding water that is eliminated during the finishing and drying steps.

For this example, based on a real situation, the maximum concentration of one proprietary surfactant, already used in cosmetic formulations and in certain Food Contact Materials, is below 1.5% in the final pure acrylic-methacrylic copolymer used as impact modifier. In the normal conditions of use, the maximum level of the impact modifier into the final plastic material polymer is below 5%.

The Cramer Class of the specific surfactant used is III. Consequently the exposure threshold for the substance is 90 µg/person/day or 0.09 mg/person/day. So, for a European eating 1 kg food per day, the SML based on TTC approach will be:

SML_{TTC} = 0.09 mg/kg food.

For this proprietary surfactant a NOAEL value of 155 mg/kg bw/day has been determined derived from a 90 days sub chronic oral toxicity study on rats. Based on 3 negative mutagenicity studies, this surfactant is considered as a non-genotoxic chemical. Following the pathway given by the Figure 1, the Tolerable Daily Intake can be derived from the NOAEL by applying the safety factor 100.

TDI = NOAEL / 100 = 1.55 mg/kg bw/day

The self-derived SML for a 60 kg European eating 1 kg of food per day will be:

Self-derived SML = TDI * 60 = 93 mg/kg food

The comparison of these two SML's shows again that the TTC approach is conservative compared to real toxicological data. The SML calculated, on the basis of toxicological data is higher than the overall migration limit of 60 mg/kg food set by the Regulation.

The concentration of this specific surfactant used to prepare an acrylic-methacrylic copolymer is below 2 % of the active ingredients (monomers, additives, PPA's, AP's excluding water). The commercial product is a water solution containing 30 % the surfactant. The maximum level of the surfactant in the acrylic-methacrylic copolymer is 0.6%. After the different finishing steps, this concentration could be lower. The impact modifier is often incorporated at 2 % in a PVC resin. So in the PVC polymer the maximum concentration of the surfactant is: **120 mg/kg**.

Assuming a 100 % migration from a 6 dm2 surface packaging of 100 µm thickness and 1.4 g/cm3 density, the migration level into the food will be: **1 mg/kg food**.

This worst-case migration is a factor 93 below the SML of 93 mg/kg food as derived from toxicological data and above the SML_{TTC} of 0.09 mg/kg food given by the TTC approach.

As the TTC approach is very conservative compared to the real toxicological data measured on the substance, the conclusion of the risk assessment is that the final materials containing this specific surfactant as component in the impact modifier, are safe for the consumer in the intended use.

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