FCA Guidelines on

Risk Assessment of non-listed substances (NLS) and non-intentionally added substances (NIAS) under the requirements of Article 3 of the Framework Regulation (EC) 1935/2004

Version 1.0

October 2016

This document aims to give guidance to manufacturers or downstream users of food contact substances in regard to the Risk Assessment of non-listed substances (NLS) and non-intentionally added substances (NIAS) in order to fulfill the requirements of Article 3 of the Framework Regulation (EC) 1935/2004. This document is provided for general guidance information purposes only.
This is a living document which will be updated when needed.

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EXECUTIVE SUMMARY

The present guidelines were developed by FCA – “Food Contact Additives” Sector Group of Cefic – the European Chemical Industry Council. It aims at providing guidance on risk assessment principles to manufacturers and downstream users of substances used in food contact materials. The guidelines provide an overview of methods and approaches for risk assessing so-called “non-listed substances” and “non-intentionally added substances” in order to fulfil the requirements of Article 3 of the Framework Regulation (EC) 1935/2004. This document therefore applies to substances exempted from authorization or for applications where no specific legislation exists.

Under chapters 1 and 2, the scope of the guidelines and relevant definitions are provided. Chapter 3 illustrates different internationally recognized scientific principles on toxicological assessment of substances used in various food contact materials applications. Chapter 4 highlights some tiered approaches for estimating the exposure of a given substance to the consumer. While chapter 5 indicates the principles for finalizing the risk assessment based on the findings gathered in the two previous chapters.

The present Guidelines are to be regarded as a living document, which will be regularly updated, when necessary in order to take into account latest scientific developments in this area.

1. INTRODUCTION

This document aims to give guidance to manufacturers or downstream users of food contact substances in regard to the risk assessment of non-listed substances (NLS) and non-intentionally added substances (NIAS) in order to fulfill the requirements of Article 3 of the Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food (Abbrev: “Framework Regulation No 1935/2004 on Food Contact Materials”). However, this document is provided for general guidance information purpose only. The use of any of these risk assessment methodologies is at the users own risk, and it is recommended to first seek scientific or legal advice. The procedures mentioned in this guidance do not constitute legal advice or opinions of any kind, or any advertising or solicitation. The authors of this guidance will not be liable for any damages, losses or causes of action of any nature arising from any use of risk assessment methodologies.

This is a living document which will be updated when and if needed.

Taking into account the actual state of the art, some applications like the plastic food contact materials and articles are regulated by a specific measure - the Commission implementing Regulation No 10/2011 on plastic materials and articles intended to come into contact with food (Abbrev:“ Commission implementing regulation No 10/2011 on plastic materials and articles”) - while most of the other applications, e.g. coatings, printings, paper and board, adhesives, are not subject to harmonized EU legislation. National provisions might exist in one or more countries of the EU.

Plastic food contact materials and articles

In the Commission implementing regulation No 10/2011 on plastic materials and articles, there is a mandatory listing of monomers, starting substances, macromolecules obtained from microbial fermentation and additives. There are also substances for which an exemption of listing exists. These substances need to be assessed in accordance with internationally recognised scientific principles on risk assessment as described in article 19 of the Regulation. These substances can be classified as non-listed substances (NLS) and non-intentionally added substances (NIAS) and may be present in small quantities with a potential or not to migrate into the food or food simulants. Included in those both categories, there are migrating by-products, decomposition products or other residues, but also intentionally added substances such as aids to polymerisation (AP) like e.g. catalysts, initiators and “polymer production aids” (PPA), solvents, emulsifiers, etc.

Non-plastic food contact materials and articles

In the absence of EU harmonized specific measures for the so-called “non-plastics”, a similar principle, as expressed in Article 19 of Commission implementing Regulation (EU) No 10/2011 on plastic materials and articles, is needed for those substances for which no mandatory authorisation is requested. These self-assessments based on internationally recognized principles will serve the requirements of Article 3 of the Framework Regulation No 1935/2004 on Food Contact Materials which stipulates that **all migrating substances in food contact materials have to be safe and do not bring unacceptable changes to the food**.

Based on the principle of Article 3 of the Framework Regulation No 1935/2004 on Food Contact Materials and the Responsible Care principle, all migrating substances (listed and non-listed as well as NIAS) should be present in quantities as low as reasonably and technically possible. The principles of risk assessment should never be used to whitewash avoidable migration and residues

in FCM. Appropriate quality measures should always be in place to produce a food contact material as suitable as possible in order to minimize migration.

A risk assessment consists of three components: hazard identification and characterisation, exposure assessment, followed by the risk assessment itself. Hazard is the potential of something to cause harm. Hazard typically refers to the intrinsic properties of a chemical, such as toxicity, while exposure addresses the likelihood and degree to which a human or environmental receptor will be exposed to the intrinsic hazards of a chemical. Risk is the likelihood of harm occurring.
Captured into a simple formula, this would read: **Hazard x exposure potential = risk.**

Risk assessment puts hazard and exposure together in an attempt to understand the "real world danger" posed by a chemical based on its intrinsic hazards in the light of anticipated exposure.

Risk assessment certainly requires the rigorous and objective analysis of data. However, there may be weaknesses or gaps in the data that can only be addressed by applying professional judgment. The various assumptions and uncertainties carried over from the hazard characterisation and exposure assessments also affect the risk assessment. Extrapolating from that work to reach probabilistic conclusions necessarily creates additional uncertainties.

For those non-listed substances which do not need to be authorized or which are only present as residues, the following methodology could be used:

- Verify if the substance is authorized by international recommendations or at national level; or

- Do a risk assessment on the basis of internationally recognised scientific principles according to Article 19 of Commission implementing Regulation (EU) No 10/2011 on plastic materials and articles resp. Article 3 of the Framework Regulation No 1935/2004 on Food Contact Materials.

What does this paper intend to deliver?

This Guideline aims to provide hands on support for companies which are in the process of assessing their products and/substances by giving an overview of methods how to risk assess non-listed substances and non intentionally added substances in food contact materials in order to meet Art 3 of the Framework Regulation No 1935/2004 on Food Contact Materials.The approach is similar to Article 19 of Commission implementing Regulation (EU) No 10/2011 on plastic materials and articles. Under the latter's provisions, a number of substances present in food contact plastics are exempt from the requirement to be included in the Community positive list (Union list) according to Article 6 of Commission implementing Regulation (EU) No 10/2011. The substances exempted of positive listing include: solvents, colourants, polymer production aids (PPA's), aids to polymerisation (AP's), oligomers and non-intentionally-added-substances (NIAS). NIAS include substances such as impurities, contaminants, reaction - decomposition- or degradation- products. It should therefore be made clear that this guidance document applies to substances exempted from authorisation or for applications where no specific legislation exists.

Until now, the term NIAS has not been used in European legislation for non-plastic FCMs, with the exception of the Dutch Commodities Act regulation on packagings and consumer articles coming

into contact with foodstuffs in the revision dated March 2014. Since NIAS do not only occur in plastics but may also be present in non-plastic FCMs such as paper/board, coatings, metals, cork, etc, the term NIAS used in this guideline is used in accordance with with Article 3 of Regulation EU No 10/2011 where NIAS are defined as: non-intentionally added substance means an “impurity in the substances used or a reaction intermediate formed during the production process or a decomposition or reaction product”. Depending on the physical/chemical parameters and the chemical composition of FCMs, and on the nature of the food, FCMs and articles may transfer their constituents (both intentionally added substances – IAS - and NIAS) to foods. This mass transfer phenomenon is called migration. Migration may lead to exposure to certain chemicals, which might cause or might not cause a risk for human health and so it must be evaluated and controlled. Furthermore, migration which brings about an unacceptable change in the composition of the food or brings about deterioration in the organoleptic properties of the food must be avoided.

Regarding the risk assessment, in most cases, only migrants up to a molecular weight (MW) of 1000 Daltons (Da) have to be considered. This threshold of 1000 Da is important as the European Food Safety Authority (EFSA) has conventionally assumed in its assessments of plastics starting materials that above this molecular weight, substances are not absorbed by the body and therefore may be excluded from any calculations of migration and exposure (EFSA, 2008).

2. DEFINITIONS

Absolute Barrier: A material at a given thickness which excludes any permeation of potential migrants from outside into the packed product under any foreseeable contact conditions. Examples include:

- Glass of any thickness (not: SiOx layers).
- Metal cans and lids.
- Aluminium foils at thickness when pinholes or other damages can be excluded.

CMR Substance: A substance listed as Carcinogenic, Mutagenic or toxic to Reproduction Category 1A, 1B or 2 in CLP Regulation 1272/2008 Annex VI table 3.1.

Estimated daily Intake: Amount of a substance that is daily absorbed by oral route by the consumer through food contact articles.

Exposure: In the context of food contact, exposure refers to consumer exposure, and more particularly to the quantity of a substance that a consumer is exposed to, by ingestion. It can be further refined to refer to specific consumer groups, e.g. children or infants, or to a statistical fraction of the consumer population, e.g. those consumers exposed to 95percentile level (which means that only 5% of the population is considered as not being covered).

Functional Barrier: One or more layers of any material type which limits the transfer of relevant substances into the packed product to either a) less than 10 ppb or b) below another level of regulatory or safety concern. For example, in the context of the Plastics Regulation 10/2011, Functional Barrier means a barrier consisting of one or more layers of any type of material which ensures that the final material or article complies with Article 3 of Regulation (EC) No 1935/2004 and with the provisions of the regulation. Useful information on what might constitute a functional barrier can be found in Section 5.2.7 of Technical Guidelines for Compliance Testing. The functional barrier concept does not cover substances which are mutagenic, carcinogenic or toxic to reproduction or to substances in nano form.

Hazard: Potential source of harm (adverse effect) or an intrinsic ability to cause harm

Migratable Substance: A chemical substance that is capable of transfer in detectable amounts from the food contact material and/or article into the food.

Overall migration limit (OML): The maximum permitted amount of non-volatile substances released from a material or article into food simulants.

Non-listed substance (NLS): An intentionally added substance which is exempted from the authorisation process, meaning which is exempted from a positive listing. An example of exempted substances is solvents.

Non-Intentionally added substances (NIAS): An impurity in the substances used or a reaction intermediate formed during the production process or a decomposition or reaction product.

Repeated use article: an article intended to be used several times that comes into contact with different portions of foods during its lifetime.

Risk: Risk is the chance or probability of harm (adverse effect) if exposed to a hazard. Risk is a function of hazard and exposure

Risk Analysis: Reviews and communicates the results from the risk assessment and risk management processes

Risk Assessment: A process to provide an understanding of the hazard posed in light of the anticipated exposure

Risk Management: Decision-making/policymaking based on the results of risk assessment and stakeholder input

Rubber: low shear modulus materials, either natural[1] or synthetic, made up of carbonaceous macromolecules, and characterised by long polymer chains arranged in a three-dimensional flexible network held by chemical covalent cross-links. They present, at service temperature and until their decomposition, elastic physical properties which allow the material to be substantially deformed under stress and recover almost its original shape when the stress is removed. The definition does not cover thermoplastic elastomers.

Rubber products: finished material and article constituted of rubber including thermoplastic rubber as well as blends of rubber with plastics and other materials, which are intended to come into contact with or are placed in contact with foodstuffs. A rubber product may be made almost entirely of rubber, e.g.a glove, or it may contain components and reinforcement other than rubber, as for an example in a rubber coated fabric, a tyre, a steel laminated bridge bearing and a rubber hose fitted with a metallic coupling.[2]

Set-off: The phenomenon of the transfer of substances from outer layer of materials and articles to the inner food contact layer through direct contact and not via diffusion through the material. Set-off may occur, where there is a contact between the outside and inside of the material or article during, for example, storage or transport. Such direct contact may occur when materials are wound in reels or stacked in sheets or when articles such as trays and pots are nested inside each other. Unlike migration under these conditions, set-off may occur in both materials and articles with or without a functional barrier.

Simulant: A test medium used to represent a type of packed product when measuring the migration of substances from the packaging. Food simulants are specified in Annex III of the Commission Implementing Regulation No 10/2011.

Specific migration Limit (SML): The maximum permitted amount of a given substance released from a material or article into food or food simulants.

[1] For example, caoutchoucs which are naturally derived rubber from latex originating from the sap of trees.
[2] Resolution of the Council of Europe AP (2004)4 on rubber products intended to come into contact with foodstuffs_ Version 1_10.06.2004

Thermoplastic elastomers TPE): Polymer or blend of polymers that does not require vulcanisation or cross-linking during processing, yet has properties, at its service temperature, similar to those of vulcanised rubber. These properties disappear at processing temperature, so that further processing is possible, but return when the material is returned to its service temperature. They are covered under the definition of plastics under Commission implementing Regulation (EU) No 10/2011.

Worst Case Calculation: This assumes that all the migrants will transfer from the packaging material into the packed product. To do it you need:

- Maximum concentration (MC) of substance in the material layer (in ppm).
- Maximum grammage per square metre (G) of material layer (or thickness and density) (in g/m^2).
- Maximum surface area of packaging to weight of food packed (SV) (in dm^2/ kg).

The formula to calculate maximum amount of substance that could migrate into the food is
MC x G x SV ÷ 100000 mg/kg (ppm)

3. TOXICOLOGICAL ASSESSMENT

Toxicological assessment aims to identify the adverse toxicological effects that a substance could cause (i.e. 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 (i.e. dose response assessment or hazard characterisation). So the aim of this chapter is to provide an overview on methodologies about how to define a safe dose of a given substance.

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 expected 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. The TDI concept is based on the assumption that a clear dose-repsonse relationship with a threshold exists, whereas the threshold defines the point of exposure below which no adverse effect is observable. The TDI is traditionally derived from a **NOAEL (no-adverse-effect-level)** using animal studies.
As an alternative, EFSA proposes the use of the **benchmark dose (BMD)** and the Scientific Committee concludes "*that the BMD approach is a scientifically more advanced method to the NOAEL approach for deriving a Reference Point, since it makes extended use of available dose-response data and it provides a quantification of the uncertainties in the dose-response data".*[3]

Based on the TDI and the current[4] 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

For some adverse effects a clear dose-response relationship cannot be defined or does not exist. The derivation of a safe dose is therefore impossible and other concepts need to apply.
Genotoxic, mutagens and carcinogens are examples of substances where no clear dose-response relationship may exist. 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[5]. Generally, the aim is to strictly avoid the presence of genotoxic, mutagens and non-threshold carcinogens in food contact materials.

[3]Guidance of the Scientific Committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. The EFSA Journal (2009) 1150, 1-72
[4] This is the situation at the current point in time. EFSA is in the process of revising their note for guidance, which might have an impact on this current assumption
[5] There is on-going 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.

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 (MOE) approach** or **Derived Minimal Effect Levels** 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 do not require specific toxicological data. For Europe, under the provisions of the Regulation No 10/2011, 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 do not 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.

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:

- The determination of a tolerable daily intake (TDI), based on toxicological studies performed on the substance or a structurally similar substance (read across); or

- If no substance specific data are available, use the *Threshold of Toxicological Concern* (TTC) concept as a basis

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.

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

DATA AVAILABILITY

1) The first step is to search for all toxicological data available for the substance (including its impurities) or for similar substances / category of substances and to define the degree of purity needed for food contact materials. The focus should be especially on:

- Mutagenicity tests (in-vitro and in-vivo).
- Repeated dose studies (28-d, 90-d oral or chronic/dermal/inhalative toxicity study).
- Studies on absorption, distribution, metabolism and excretion (ADME).
- Carcinogenicity studies (oral, dermal, inhalative).
- Studies on reproduction and developmental toxicity (oral, dermal, inhalative).

Studies should be performed according to OECD test methods or international standardised test guidelines; if not available, the test methods described in the study should be judged against these standardised methods.

The following data sources[6] may be used (Peer reviewed data sources are marked in bold below)

- In-house data / owned data from other (regulatory) sources (incl suppliers).

- REACH data:

- REACH registration dossiers on ECHA website (reference as given in the document)
- ECHA/Member States peer-reviewed information on toxicological data for REACH/CLP/Biocides[7].

- ECHA Final decisions on compliance checks and testing proposals in REACH registration dossiers[8].

- **EFSA evaluations for food contact materials or food additives or other applications (cosmetics etc.).**

- Literature data and data from public available databases including databases like:
- Public literature search information
- OECD toolbox[9],
- CEFIC LRI Toolbox[10] including RepDose, FeDTex and CEMAS
- Toxtree[11] (TTC and related data)
- GESTIS substance database[12],
- ChemIDplus (Toxnet, USA)[13], Toxline[14]
- **HPV-Program[15],**
- **NICNAS (Australia)[16]**
- **Occupational Exposure Limits (OELs): see country specific lists**
- Cosmetic Ingredient Review (CIR) database[17]), **SCCS opinions**
- Council of Europe Database [18] (not publicly available)
- PubChem[19]
- Chemspider[20]

[6] Peer reviewed data sources are marked in bold
[7] https://echa.europa.eu/addressing-chemicals-of-concern
[8] http://echa.europa.eu/information-on-chemicals/dossier-evaluation-decisions
[9] http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm
[10] http://www.cefic-lri.org/lri-toolbox
[11] https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/toxtree
[12] http://www.dguv.de/dguv/ifa/Gefahrstoffdatenbanken/GESTIS-Stoffdatenbank/index-2.jsp
[13] http://chem.sis.nlm.nih.gov/chemidplus/
[14] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
[15] http://webnet.oecd.org/hpv/ui/SponsoredSubstances.aspx
[16] http://www.nicnas.gov.au/chemical-information
[17] http://www.cir-safety.org/ingredients
[18] https://fcm.wiv-isp.be/
[19] https://pubchem.ncbi.nlm.nih.gov/
[20] http://www.chemspider.com

- ESIS[21]
- TSCA[22]

- Read-across information from structural similar substances or chemical categories
  The same search criteria as above mentioned apply (see further details under section 3.5)

- Weight of evidence information (this involves assessing the relevance, reliability and adequacy of each piece of available information, holding the various pieces of information up against each other and reaching a conclusion on the hazard. This process always involves expert judgement).
  The same search criteria as above mentioned apply.

- The reliability and relevance of the information collected has to be identified:
- GLP-studies vs. non-GLP- studies
- Klimisch rating (Klimisch 1997), further developed by Schneider et al.[23]
- ToxRTool[24]
- SCIRAP tool[25]

3.2 Uncertainty factors

Once it has been demonstrated that a 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 through the ECHA guidance on information requirements and chemical safety assessment[26]. For older dietary rodent studies, where only concentrations in feed are available, guidance is provided in EFSA (2012)[27].

A self-derived Tolerable Daily Intake (sTDI) can be derived from e.g. the NOAEL (No-Observed-Adverse-Effect-Level), a benchmark dose (BMD-L) or – if these are not available - a LOAEL (Lowest Observed Adverse Effect Level) (= the so-called Point of Departure - PoD) obtained from repeated dose (chronic/sub chronic/sub-acute) toxicological studies and taking into account specific uncertainty factors.

[21] http://esis.jrc.ec.europa.eu/
[22] http://yosemite.epa.gov/oppts/epatscat8.nsf/reportsearch?openform
[23] Schneider K, Schwartz M, Burkholder I, Kopp-Schneider A, Edler L, Kinsner-Ovaskainen A, Hartung T, Hoffmann S. (2009). "ToxR Tool", a new tool to assess the reliability of toxicological data. Toxicology Letters 189(2):138-144
[24] https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam/archive-publications/toxrtool
[25] Beronius A, Molander L, Ruden C, Hanberg A (2014). Facilitating the use of non-standard in vivo studies in health risk assessment of chemicals: A proposal to improve evaluation criteria and reporting. Journal of Applied Toxicology 34(6): 607-617
[26] Chapter R8.2, the ECETOC report TR 85 - Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies; ECETOC report TR 99 - Toxicological Modes of Action: Relevance for Human Risk Assessment.
[27] http://www.efsa.europa.eu/en/efsajournal/pub/2579

sTDI (mg/kg body weight/day) = PoD (mg/kg body weight/day) / uncertainty factor

According to recent guidance by EFSA (2012)[28], the TDI is calculated by dividing the PoD obtained from a repeated dose toxicity study with one or more uncertainty factors.

INTERSPECIES/INTRASPECIES UNCERTAINTY FACTOR

The interspecies/intraspeciel uncertainty factor has been set to be "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.

It should be noted that slight differences exist between ECHA Guidance R8 and EFSA-imposed interspecies extrapolation if the PoD is based on a test species other than the rat. This adaptation accounts for differences in allometric scaling between the species. REACH DNELs might therefore deviate from the estimated TDI.

These two uncertainty factors are intended to be conservative and address a wide range of chemicals. Recent guidance provided by the International Program on Chemical Safety (IPCS) , ECHA and EFSA[29] (2012) 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. If such a decision is made, this should be based on robust scientific justification.

STUDY DURATION UNCERTAINTY FACTOR

Extrapolation from short-term or sub-chronic-studies to lifetime exposure requires the application of an additional uncertainty factor. According to EFSA (2012), a factor of 2 is sufficient to extrapolate from a high-quality 90-day (sub-chronic) study to chronic exposure conditions.

28-day oral studies might be of use in the context of a weight-of-evidence approach. EFSA (2012) suggests a case-by-case assessment to extrapolate to chronic exposure. It is noted that in case substance-specific information is not available, ECHA suggests factor 6 as a default. This factor accounts for the aforementioned factor 2 from 90-day to chronic exposure and an additional factor 3 for the extrapolation from 28-day to 90-day studies. This latter factor is based on the Rule of Haber (effect = dose x exposure duration).

In some cases, developmental endpoints may provide the most sensitive PoD for risk assessment. For example, these may be derived from a pre-natal development study (as shown below in the example of 2-ethylhexanoate) or a 2-generation reproduction toxicity study. Since the exposure

[28] http://www.efsa.europa.eu/en/efsajournal/pub/2579
[29] http://www.efsa.europa.eu/en/efsajournal/pub/2579

duration covers the entire development of the offspring, developmental PoDs do not require the application of an additional uncertainty factor for duration. In this context, it should be noted that the NOAELs for parental toxicity in OECD 414, OECD 416 or OECD 443 studies usually do not provide a preferable PoD, as the examination typically does not include important parameters used for the assessment of systemic toxicity. Therefore, these should only be used if they provide the most sensitive PoD.

NOAEL, LOAEL and BMD

While NOAELs and BMDs can be applied as such, the use of a LOAEL requires the use of an additional safety uncertainty factor of up to 10. The magnitude of this factor should be based on the overall dose-response and dose spacing in the experiments. Other regulatory guidances (ECHA R.8, SCCS Notes of Guidance rev. 8 (2012) suggest a default factor of 3 unless data indicate otherwise.

ROUTE-TO-ROUTE EXTRAPOLATION

Oral studies provide the most relevant information for the safety assessment of food contact materials. However, in some cases, oral studies are not available, or lack reliability or relevance for risk assessment purposes. In such cases, studies with a different exposure route (typically inhalation) may be used to provide the PoD for risk assessment as part of a weight-of-evidence approach. Guidance on route-to-route extrapolation can be found in ECHA Guidance R.8.

$$\text{Corrected oral } NOAEL_{rat} = \text{inhalatory NOAEC} \times sRV_{rat} \times \frac{ABS_{inh\text{-}rat}}{ABS_{oral\text{-}rat}} \times \frac{ABS_{oral\text{-}rat}}{ABS_{oral\text{-}human}}$$

With:

sRV_{rat} = standard respiratory volume of the rat in a study with a daily exposure duration of 6 hrs = 0.29 m^3/kg bw
ABS = Absorption (percentage of intake via a specific exposure route - needs either TK data or modeling). Default assumption is 100 % in all listed cases.

Since route-to-route extrapolation underlies high uncertainties, any toxicokinetic information available should be incorporated into the assessment. Highly refined approaches like biologically-based toxicokinetic (PBTK) modelling may be applied if appropriate. Care should be given to effects that may be route-specific (e.g. as indicated by information on similar substances).

UNCERTAINTY/DATA GAPS IN THE DATABASE

In those cases where available testing information is insufficient to provide information necessary for a food contact safety assessment, additional uncertainty factors may be applied. This includes hazard assessment by read across approaches if used as part of a weight-of-evidence approach. Guidance on the application of uncertainty factors for read across approaches may, for example, be found in Blackburn (2014).

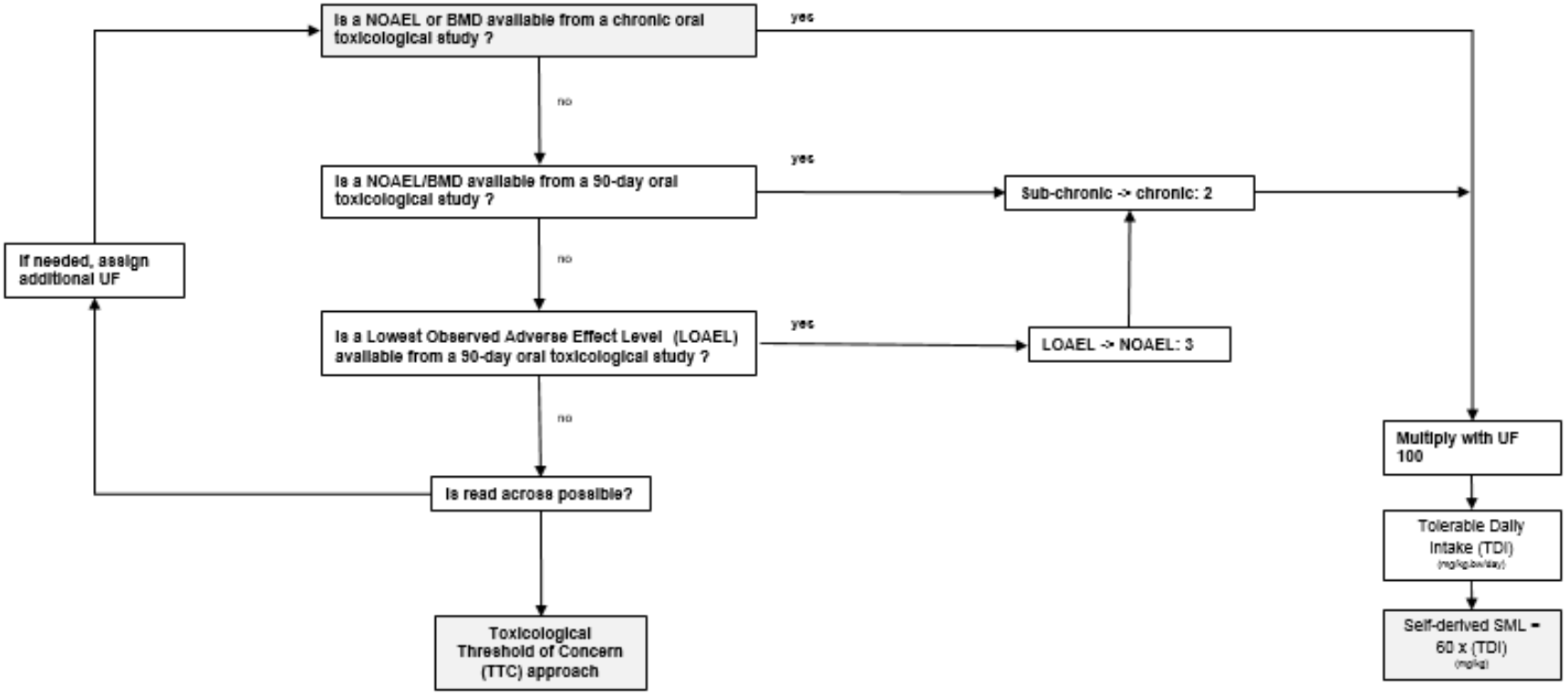
TOTAL UNCERTAINTY

The total uncertainty is the product of all uncertainty factors used in the assessment:

Total UF = $UF_{interspecies/intraspecies}$ x $UF_{duration}$ x UF_{LOAEL} x $UF_{data\ gap/read\ across}$

For substances for which toxicity data are available, it is important to use all the data for selecting the most appropriate NOAEL to determine the TDI. Only after all data, including uncertainty factors, have been assessed, can the most sensitive and appropriate PoD for the TDI be selected.

Figure1 (next page) 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.


Is a NOAEL or BMD available from a chronic oral toxicological study ?
yes
no
Is a NOAEL/BMD available from a 90-day oral toxicological study ?
yes
Sub-chronic -> chronic: 2
no
If needed, assign additional UF
Is a Lowest Observed Adverse Effect Level (LOAEL) available from a 90-day oral toxicological study ?
yes
LOAEL -> NOAEL: 3
no
Multiply with UF 100
Is read across possible?
Tolerable Daily Intake (TDI)
(mg/kg.bw/day)
Toxicological Threshold of Concern (TTC) approach
Self-derived SML = 60 x (TDI)
(mg/kg)

3.3 The Use of the DNEL (REACH) for Risk Assessment in Food Contact

As explained under 3.1. and 3.2. the Tolerable Daily Intake (TDI) is derived as the safe dosage of a substance migrating from food contact materials into food and which is therefore orally consumed via the human diet. Thus, exposure from food contact materials only happens via the oral-gastro route. In contrast, DNELs (Derived-No-Effect-Level) are derived for various routes (e.g. dermal, inhalation, oral) and exposure groups (workers and general population). The REACH Regulation also describes the methodology to define the PoD (point of departure, see 3.2.), the use of assessment factors and the calculation of other DNELs based on DNELs in case of lacking of appropriate data.

The DNEL is a value described in the REACH Regulation under Article 119 Section 1f, and which can also be used for finding a safe exposure limit of a substance in food contact materials. The DNEL is defined under Annex I, Section 1.0.1 of the REACH Regulation:
"The objectives of the human health hazard assessment shall be to determine the classification of a substance in accordance with Regulation (EC) No 1272/2008; and to derive levels of exposure to the substance above which humans should not be exposed. This level of exposure is known as the Derived No-Effect Level (DNEL)."
In accordance with the provisions laid down in the REACH Regulation, the registrant has to derive such limits for all substances as of 10 tons/year (production or import) to gain quantitative values based on the toxicological properties of that material. In general, the registrant does this in the form of a self-assessment for all substances. The DNEL is described in detail in the ECHA –Guideline R8

Since DNELs are not officially approved or confirmed by ECHA (only checked according to a defined procedure), an unreflective use for the risk assessment of NLS or NIAS from food contact materials is not recommended. However, since there are clear rules in the ECHA-Guideline R8 for deriving DNELs, these values are the outcome of an ECHA prescribed methodology and the current state of the art. Nevertheless, it is advisable to realise on which data basis (oral, dermal or inhalative route) and calculation method including safety factors the DNEL has been generated in order to be able to take a decision whether this value is suitable or not suitable for food contact use. Therefore, it is recommended to consult expert knowledge (toxicologist) to confirm the use of a DNEL. In some cases, it might be useful to add additional uncertainty factors.

For the risk assessment of a substance the DNEL is used similar to the TDI and results in the following two scenarios: If the ratio between level of exposure to DNEL is below 1, it is considered safe (e.g. Exposure = 1 mg/kg Food and DNEL = 2 mg/kg Food = > ½ = 0,5). If the ratio between level and DNEL is above 1, it is considered unsafe (e.g. Exposure = 10 mg/kg Food and DNEL = 1 mg/kg Food = > 10/1 =10). The ratio between DNEL (or TDI or uncorrected NOAEL etc.) and exposure level is often defined as *margin of exposure (MoE)* or *margin of safety (MoS).* It is always desirable to have a MoS or MoE of several magnitudes.

A straightforward Dose – Response – Correlation with a threshold mechanism is necessary to derive a DNEL for a toxicological effect. The threshold marks the dose under which the toxicological effect does not occur anymore. Effects which do not correlate with a specific dose cannot be used to derive a DNEL. However, it is sometimes helpful to at least define a level where the occurrence of an adverse effect is minimal. The so-called DMEL (Derived-Minimal-Effect-level) corresponds to a Dose-Response-relationship without a threshold. The DMEL should only be used as an exception

and only together with appropriate uncertainty factors (e.g. for risk assessment of a carcinogenic residue present in the product in trace levels).

In general, DNELs for REACH-registered substances are publically available on the ECHA-website: Registered substances .For food contact uses the preferred DNEL to be used is “General Population - Hazard via oral route – systemic effects – long term exposure” (hereinafter referred to as $DNEL^{GP\_oral\_longterm}$). If this $DNEL^{GP\_oral\_longterm}$ is calculated based on solid tox data (e.g. PoD, NOAEL or LOAEL) and appropriate uncertainty factors (the terminology “assessment factor” is used the REACH context), the value can directly be used for the Risk Assessment of NLS or NIAS. The $DNEL^{GP\_oral\_longterm}$ should be based on chronic feeding studies with the original substance; if this is not the case always seek for toxicological support to determine how valid the figure is. Cross calculation using read across data or other DNEL (e.g. based on inhalation or dermal) may be not valid enough to be used for food contact application.

A value for the used “overall assessment factor” can also be found in the REACH Dossier for the substance. This factor is a combined value used to calculate the DNEL from a point of departure, such as a NOAEL (No-observed-adverse-effect-level), NAEL (No-adverse-effect-level) or a LOAEL (lowest-observed-adverse-effect-level). The uncertainty factors are adapted according to the studies available. The REACH guideline for DNELs advises which assessment factors should be combined. The NOAEL levels etc. are in general the outcome of animal studies and the various factors (incl. safety factors) are used to translate the value into a safe dosage for humans. If the approach of deriving a $DNEL^{GP\_oral\_longterm}$ using many uncertainty factors appear too conservative it may be easier to refer to the TTC-Concept and use these generic exposure limits based on the criteria applied there (e.g. structure, no-CMR, etc.).

3.4 Read across

READ ACROSS (Q)SAR

When testing data are insufficient or lacking, toxicological properties can be read across from toxicity information of similar substances. If the prediction is based on modelling, the term (Q)SAR (quantitative structure-activity relationship) would apply, with a toxicological activity being the function of one or more physicochemical parameters of the substance. Detailed guidance for toxicity prediction is beyond the scope of this guidance; however, some key elements are summarised to improve the understanding. For any prediction of a toxic effect, with or without computational support, the following principles should be considered:

- Sound expertise in both toxicology and chemistry is required for a critical appreciation of the results.
- Any prediction requires complete and transparent documentation. Ideally, the level of documentation should be equal to that provided in a QMRF (QSAR Model Reporting Format and QPRF (QSAR Prediction Reporting Format) (ECHA, 2012)
- In general, results of actual testing are considered to be of higher relevance for risk assessment; only in case of severe doubts of the reliability of the existing test may non-testing data be applied as part of a weight of evidence approach.
- The (Q)SAR model applied should fulfil the validity criteria outlined by OECD (2007), which are defined as follows:

- *A defined endpoint:* A defined endpoint might be mechanistic (e.g. estrogenic activity), a test protocol endpoint (e.g. liver weight) or regulatory (NOAEL). Clear distinction should be made on the applicability of the endpoint to risk assessment).
- *An unambiguous algorithm:* Thorough documentation should ensure that the rationale underlying the prediction is transparent and the results are reproducible.
- *A defined domain of applicability:* For example, a model based on hydrocarbon data should not be used for organic acids. The chemical space is defined by a border of physicochemical parameters that should always be checked before a model is applied.
- *Appropriate measures of goodness-of-fit, robustness and predictivity:* Models should be statistically robust, and the predictor variables should be chosen to be independent from each other (e.g. not using both boiling point and vapour pressure, or molecular weight and size).
- *A mechanistic interpretation, if possible:* The model should ideally be plausible, with a causal link between physicochemical property of the chemical substance and biological effects existing. For statistical models, this might not always be possible.

For the assessment of food contact materials, genotoxicity/carcinogenicity and repeated dose systemic toxicity are the key hazard classes of interest and are described in more detail.

a) Genotoxicity / Carcinogenicity

The TTC approach requires a decision of presence or absence of the potential for (direct) genotoxicity. The reactivity with DNA is dependent on the presence of electrophilic functional groups (structural alerts), and various computational tools exist to predict whether a molecule is likely to bind to DNA. Computational tools can either be knowledge-based (rule-based) (providing information on the existence of known structural alerts), statistical (comparison with test results of similar molecules, e.g. with identical fragments), or hybrids of these two.

The use of *in silico* methods to confirm the absence of structural alerts for genotoxicity is accepted in several regulatory frameworks (EFSA, 2012; ICH, 2014), but regulators do not provide clear guidance on *how* to confirm the absence of a structural alert. However, some considerations may offer support:

- The Benigni-Bossa rule base in Toxtree is reported to predict genotoxicity with an accuracy of 80 % (Benigni, 2008), which is comparable to the Ames test.
- Various publications suggest several models to be used in parallel, to reduce false negative predictions. The increased probability of false positive predictions caused by that approach is accepted based on the fact that the TTC is meant to provide a "safety net", and a false positive would only result in an unnecessary Ames test to be conducted.
- For impurities in pharmaceutical actives, regulators provided a more defined guidance: "*The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no mutagenic concern, and no further testing is recommended"* (ICH, 2014)

- The OECD QSAR Toolbox is a meta-database, including key elements of Toxtree, OncoLogic and additional lists of strong electrophilic groups with potential DNA reactivity. It also includes both a rule-based and a statistical element.

Note that some substances (e.g. chloroform, CAS# 67-66-3) may induce carcinogenicity in rodent bioassays in the absence of any genotoxic mode of action. Typically, non-genotoxic carcinogenicity is a secondary effect of target organ toxicity or endocrine activity and underlies a dose-response relationship, including a NOAEL that can be used for risk assessment.

b) Repeated dose systemic toxicity

Due to great uncertainty in both toxicokinetics and toxicodynamics, non-genotoxic systemic oxicity has shown to be the biggest challenge in predictive toxicology. Computational (Q)SAR models to predict systemic toxicity underlie rapid development and are not further described here. Examples may be found in Schilter (2014).
Regulatory bodies differentiate between read across from one of few analogues or from a group/category of chemicals. Detailed guidance has been published by regulators (ECHA, 2008; ECHA, 2015 and WHO, 2014), joint initiatives such as ILSI (Schilter, 2014), SEURAT-1 (Schultz, 2015) and by industry (see e.g. Wu, 2010; Blackburn, 2011; Blackburn, 2014, Patlewicz, 2015).

The figure below shows three possible ways how prediction of toxic effects can be applied:

- **Property 1/Activity 1 (read across/SAR):** Both properties (log Kow, electronegativity,..) and activities (e.g. covalent binding to DNA or proteins, ligand receptor interaction) may be read across from one source substance to a target substance (Chemical 1->2, Chemical 3 -> 4)

- **Property 2/Activity 2 (Interpolation):** Properties of the target substances (Chemicals 2 and 3) are predicted from properties *within the chemical space* of a group of source substances (Chemicals 1 and 4). This means, the group consists of source substances that are expected to be either less (e.g. Chemical 1) or more (e.g. Chemical 4) lipophilic, electronegative, DNA-reactive, hydrolytically unstable than the target substances. All predictions of properties or activities stem from interpolation within a defined group.

- **Property 3/Activity 3 (Extrapolation):** In this example, also a group (category) approach is applied. Source substances (Chemicals 2 and 3) are not believed to represent the boundaries for specific properties or activities, but the predictions for the target substances (Chemicals 1 and 4) are believed to be *outside the chemical space* of the group.

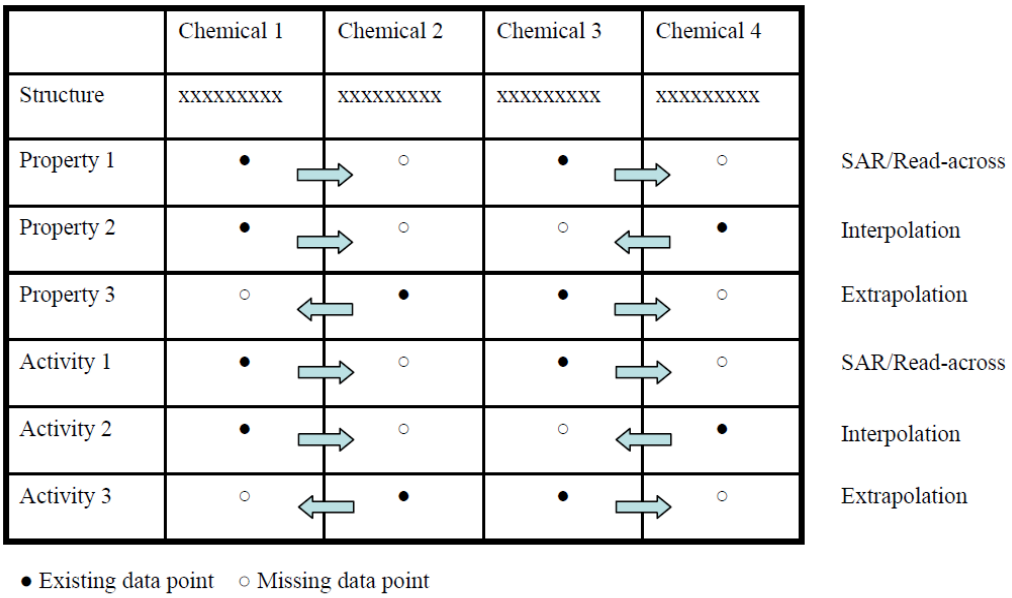


Figure 2. Graphical representation of a chemical category and some approaches for filling data gaps (OECD, 2014)

In general, the category (group) approach is regarded to be more robust than read across from one analogue substance, and interpolation (within a defined applicability domain/chemical space) is believed to be more reliable than extrapolation to a target substance outside the boundaries defined by the properties of the source substance(s).

Typically, the rationale for read across is a common mode of action, identical metabolites, and/or strong similarity of the parent molecules (both based on physicochemical properties and presence/absence of specific functional groups). The OECD QSAR Toolbox may aid in the search for a suitable category for read across.

Other strategies for the definition of a category or the search for an analogue may include a similarity search via the Tanimoto Index (e.g. via www.chemspider.com, Toxmatch or the OECD QSAR Toolbox). This should always include a prediction of potential metabolites
Toxtree and the QSAR Toolbox are freely available examples for metabolism prediction.

Current research focuses on the identification of Adverse Outcome Pathways (AOP) that will aid to break down the complexity of systemic toxicity to a sequence of simple steps that are easy to model.

While a detailed guidance is beyond the scope of this document, some examples will highlight the uncertainty/possible pitfalls related to read across:

Hydrocarbons/hexane: Short-chain aliphatic linear hydrocarbons (e.g. C2 to C8) may form a homogenous group of chemicals with similar toxicological properties. However, hexane has been found to be an outlier within this group, inducing chronic and reproductive toxicity that is unique to this compound. Therefore, even interpolation within a group of very similar category members should be interpreted with care.

Benzene/Toluene/Ethylbenzene/Xylenes: Even though these molecules differ by only one methyl group, each of the mentioned substances induces unique target organ effects that have not been observed with any of the other compounds. While these molecules seem to be very similar to each other, prediction of their metabolic breakdown would show the formation of different degradation products, resulting in great variation of toxicity.

Benzophenone/4-methylbenzophenone: In its risk assessment of the finding of 4-methylbenzophenone in breakfast cereals in 2009, EFSA found that there was very little information useful for the toxicological assessment of 4-methylbenzophenone itself, but there was much more information available for the structurally similar benzophenone. 4-Methylbenzophenone is expected to be metabolised by the same metabolic pathways as benzophenone, with the addition of oxidation of the 4-methyl group to the corresponding alcohol and further oxidation to the carboxylic acid with its glycine and glucuronide conjugates. Based on structural considerations and experimental results on the structurally related benzophenone, it can be concluded that 4-methylbenzophenone does not raise concern for genotoxicity, and like benzophenone, 4-methylbenzophenone is expected to be a non-genotoxic carcinogen. In addition to the usual uncertainty factor of 100 to allow for inter- and intraspecies differences in sensitivity, EFSA applied a further uncertainty factor of 2 to allow for the read across of data from benzophenone to 4-methylbenzophenone.

In conclusion, read across of systemic toxicity is related to great uncertainty and should be done with care. However, this field is subject to broad interest and rapid development.

3.5 Determination Threshold of Toxicological Concern (TTC)

In cases where no or insufficient animal testing data are available for a chemical substance and no read-across is possible, pragmatic approaches to determine acceptable threshold limits have been developed over more than four decades. In particular, the threshold of toxicological concern (TTC) is a concept defining exposure thresholds for substances below which no appreciable risk for human health is assumed (Kroes et al. 2000, 2005; Kroes and Kozianowski 2002).

The TTC concept has been used for years in the assessment of impurities of food contact materials, drinking water, and pharmaceuticals (for a comprehensive overview of existing values for the TTC, see Hennes 2012). For example, the US Food and Drug Administration (FDA) adopted the concept of a threshold of regulation (TOR) for substances used in food contact articles: If a substance or an impurity has not been shown to be a carcinogen in humans or animals and there is no reason, based on the chemical structure of the substance, to suspect that it is a carcinogen, a threshold of regulation is defined as a dietary concentration of 0.5 ppb (=µg/kg diet) or 1.5 µg/person/day assuming a consumption of 3 kg diet per day. The threshold was derived from linear extrapolation of TD_{50} values from animal experiments to the risk of one in a million for tumor development in humans.

Other concepts have further developed the general TTC approach, based either on the structure of groups of substances (Munro et al. 1996; Kroes et al. 2004) or on information on certain endpoints (Cheeseman et al. 1999) which would allow setting higher threshold concentrations under certain conditions with a high degree of certainty to predict that a substance is safe if the concentration is not exceeded. Based on an analysis of a comprehensive database of 2,944 entries for 600 substances on repeated dose studies and studies on reproductive toxicity and developmental

toxicity, Munro et al. (1996) proposed human exposure thresholds for three structural classes as defined by Cramer et al. (1978) using the 5th percentiles of the NO(A)ELs based on the lowest NO(A)EL for each substance.
The human exposure thresholds were 1,800, 540, and 90 µg/person/day for Cramer class I, II, and III respectively.

An overview of the most important threshold values **(Figure 3)**:

Classification	**TTC (µg/person/d)**	**TTC(µg/kg b.w./d)**	**Reference**
Cramer class I	1800	30	Munro 1996
Cramer class II	540	9	Munro 1996
Cramer class III	90	1.5	Munro 1996
Organosphosphates and carbamates	18	0.3	Kroes 2004
No structural alerts for carcinogenicity	1.5	0.025	TOR
Genotoxic substances (without aflatoxin-like, azoxy- or N-nitroso compounds)	0.15	0.0025	Kroes 2004

In 2012 the European Food Safety Autority (EFSA) published a scientific opinion on exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC):

The Scientific Committee concluded that the TTC approach should not be used for the following categories of substances: high potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines), inorganic substances, mixtures of substances containing unknown chemical structures, metals and organometallics, proteins, steroids, nanomaterials, radioactive substances, and substances that are known or predicted to bioaccumulate. Furthermore, special attention has to be paid if there is data showing that a substance has endocrine-mediated adverse effects and if the TTC approach is used for risk assessments including infants and children the low body weight has to be taken into account.

The TTC value of 0.15 µg/person per day, derived by Kroes et al. (2004) for substances with a structural alert for genotoxicity, is considered to be sufficiently conservative to be used in EFSA's work, excluding high potency carcinogens (see above). Possible genotoxic metabolite has to be considered. Non-genotoxic carcinogens are considered to have a threshold and, in general, NOELs for these are in the same range or higher than NOELs for other types of toxicity.

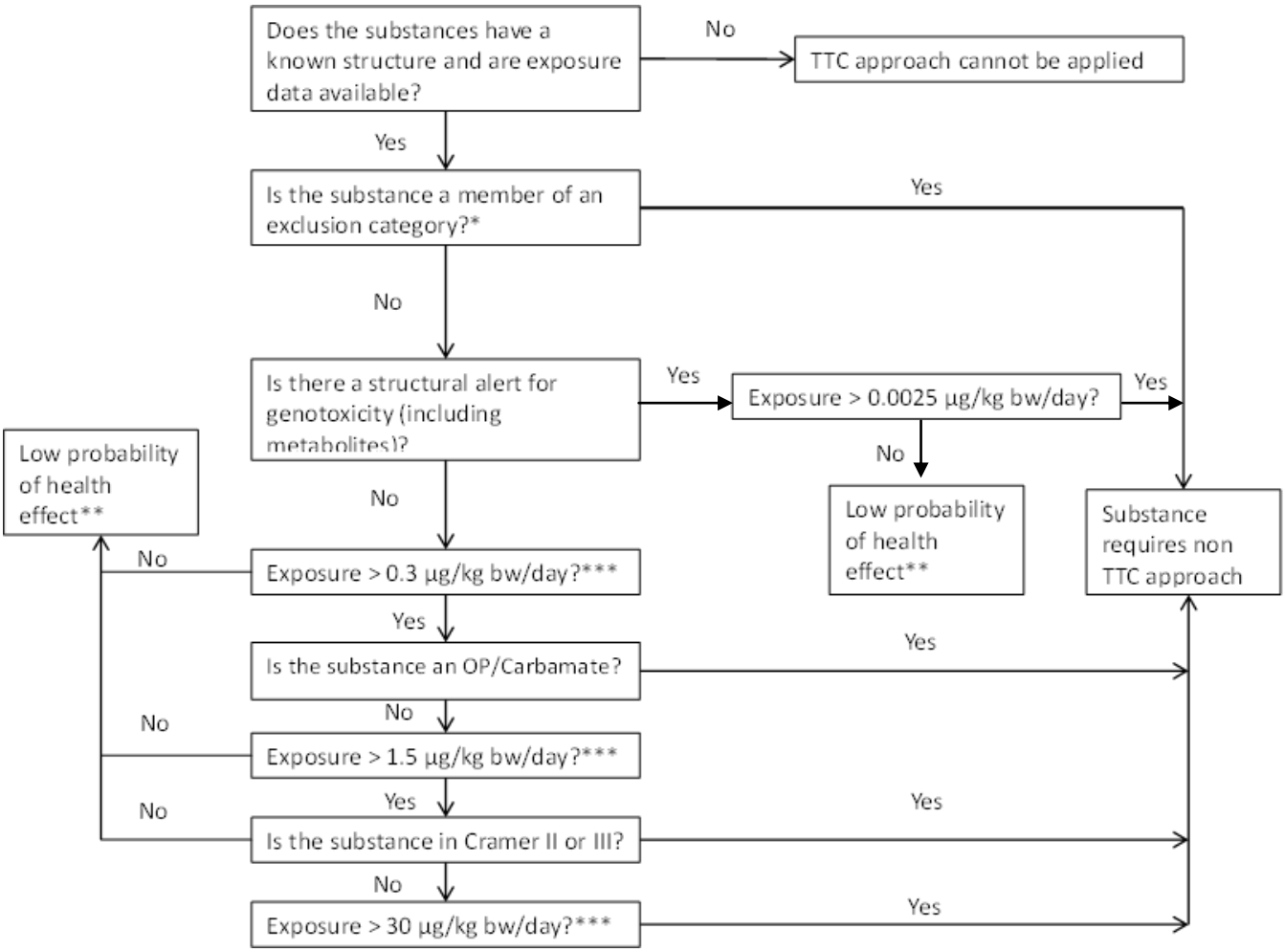
Also the TTC value of 18 µg/person per day, first proposed by Kroes et al. (2004), is considered sufficiently conservative to cover the anti-cholinesterase activity of substances with organophosphate or carbamate structural features. The Scientific Committee concluded that the original FDA Threshold of Regulation (TOR) value of 1.5 µg/person per day is of historical importance, but has little practical application in the overall TTC approach. However, it should be

noticed that this threshold value is the only threshold value really established by law (21 CFR (FDA), §170.30) until now.

Only a very low number of substances formed the basis for the calculation of the Cramer class II threshold value. Therefore, the Scientific Committee concluded that consideration should be given to treating substances that would be classified in Cramer Class II under the Cramer decision tree as if they were Cramer Class III substances.

All in all, the Scientific Committee concluded that the science supports the application of the TTC approach in any area of chemical risk assessment for which human exposures are low, whether exposure is from deliberate addition or due to contamination. Within EFSA, the Scientific Committee recommends that the TTC approach can be used to assess impurities, breakdown and reaction products, metabolites, and low-level contaminants in food and feed, where an exposure assessment can be conducted, but on which there are few or no toxicological data. Therefore, the TTC approach can be recommended as a useful screening tool either for priority setting or for deciding whether exposure to a substance is so low that the probability of adverse health effects is low and that no further data are necessary (EFSA Journal 2012;10(7):2750).

EFSA proposed the following generic scheme **(Figure 4)**:

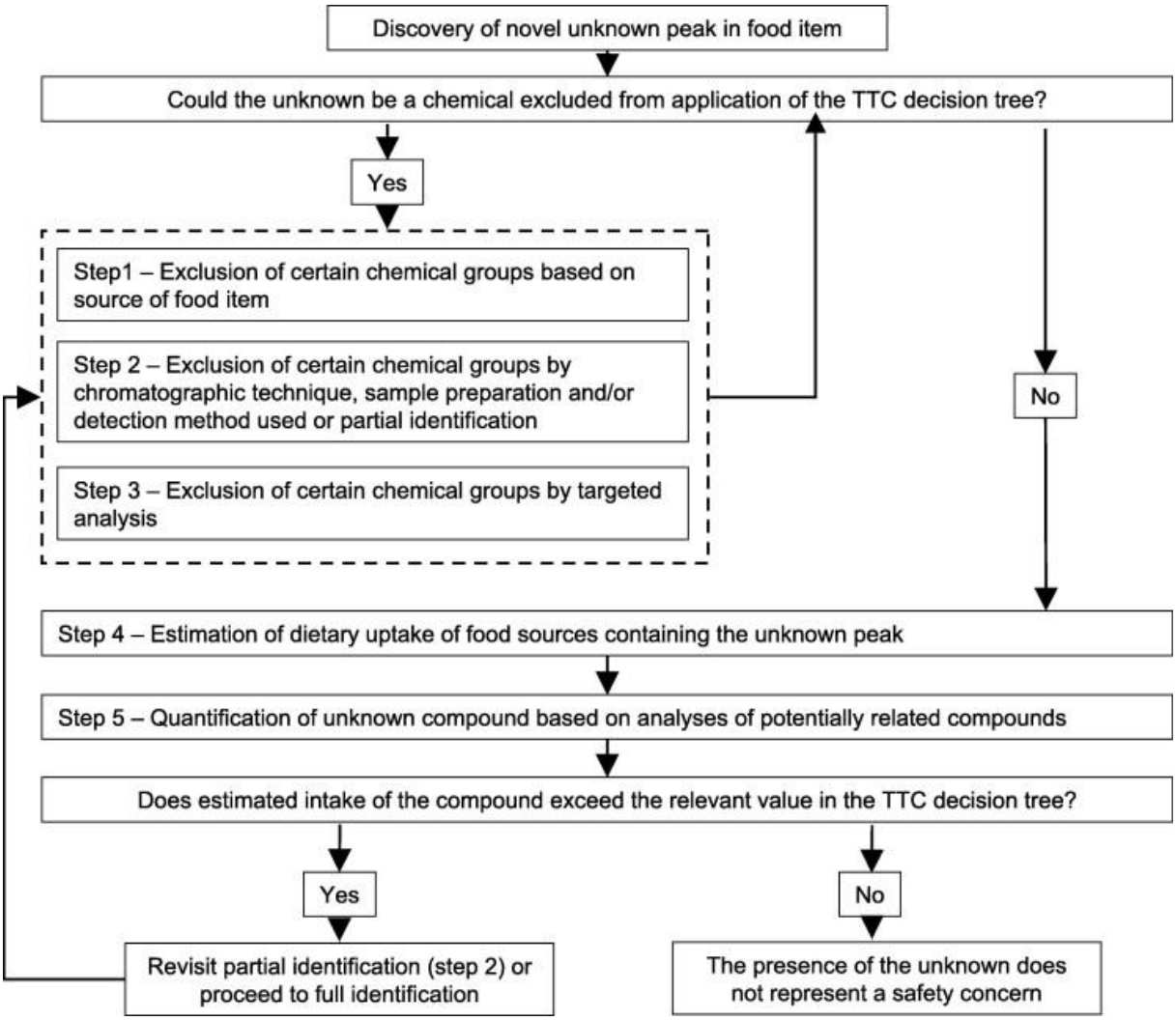


*Exclusion categories: high potency carcinogens, inorganic substances, metals and organometals, proteins, steroids, substances known/predicted to bioaccumulate, nanomaterials, radioactive substances, mixtures
**If exposure of infants < 6 months is in range of TTC -> consider if TTC is applicable
***If exposure only short duration -> consider margin between human exposure and TTC value
Please notice, that a proposed revised decision tree was published on the 10th of March 2016 in the EFSA report "Review of the Threshold of Toxicological Concern (TTC) approach and development of new decision tree."

EFSA recently reviewed the TTC approach and proposed a new version of the TTC decision tree (EFSA event report, 2016). In this new decision tree the threshold levels are the same as given above, besides the reintroduction of the Cramer class II value of 9 µg/kg bw/day. Despite acknowledgement that there are very few chemicals in Class II and therefore the TTC value for this class is not well supported within the current TTC approach, and the previous proposal to evaluate under the Class III TTC threshold all the chemicals categorized as Class II (EFSA, 2012), the expert group recommended that Cramer Class II continues to be used and applied to the TTC approach. A change of wording and a change in the order of the asked questions were suggested. Furthermore, it was stated that a merge of different non-cancer databases is desirable to increase statistical power and improve transparency in the database, and that after the merge of the databases the "overall TTC's" should be recalculated. Thus, the TTC approach is still under revision and further changes of the TTC decision tree should to be expected in the future.

Currently the TTC approach is used by several authorities like EFSA and FDA for risk assessment of substances. However, there are several limitations for the use of the approach, which have to be considered. The chemical structure of the compound has to be known, specific substance classes are excluded (see above) and the TTC approach will only be used if there is no useful animal testing data and no read across is possible.

Despite these limitations, there are considerations made about whether or not the TTC concept could also be used for the evaluation of NIAS. Because the chemical structures of the NIAS are often not known there is a difficult discussion which is still ongoing. In 2011, Koster et al. proposed a TTC approach for the regulation of unknown substances found in food samples including non-intentionally added substances (NIAS), but the confident identification of NIAS and, particularly, genotoxic substances remains an unresolved issue. A step wise approach was suggested for the evaluation of NIAS:



Several published studies have demonstrated that the application of the Cramer classification scheme in the TTC approach is in general conservative and therefore protective of human health. However, it should be pointed out that substance specific toxicological data or the read across to

similar substances would always be preferred, and that the use of the approach demands a high level of Expert Judgement. All in all, the TTC concept is of great utility and of high interest due to the pragmatic approach, conservativeness, and applicability in several areas. Furthermore, the use of the approach for risk assessment of specific substances or as a screening tool for the prioritisation of toxicological testing contributes to save animal lives and high costs.

3.6 10ppb- approach / 50 ppb- approach

The "10 ppb threshold" utilised in Europe is a limit of detection for the validated analytical determination of migrants in food or food stimulant (0.01 mg/kg). Under the EU Regulation 10/2011 for plastics it is referred to in article 13 (specific provisions for plastic multi-layer materials and articles): a substance whose migration is not detectable with a detection limit of 0,01 mg/kg is exempted from authorisation, when it is in a layer not in direct contact with food, it is not classified as 'mutagenic', 'carcinogenic' or 'toxic to reproduction' category 1A, 1B or 2 according to the CLP Regulation 1272/2008 and it is not in nano form. In addition, the detection limit of 0.01 mg/kg applies to substances listed in annex I and which are subject to a non detectable migration limit (including among others also carcinogenic substances like ethylene oxide and propylene oxide). However, it should be pointed out, that in such cases, when the analytical methods enable a determination even below 10 ppb, this has to be considered to be the applicable detection limit.

Furthermore, the 10 ppb concept has been introduced in industry code of practices and in national legislation dealing with non plastics materials. Examples are the Dutch Commodities Act Regulation on packagings and consumer articles coming into contact with foodstuffs (Warenwet) which allows the use of non-listed components provided they are not CMR classified and their migration is less than 0,01 mg/kg, or the CEPE code of practice (edition 4, version 9) for coated articles where the food contact layer is a coating and which allows the use of monomers and additives provided they are not CMR classified and their migration is less than 0.01 mg/kg . The Swiss Ordinance on packaging ink on non food contact side (SR 817.023.21, section 8b) also allows the use of substances which are listed but not yet toxicologically evaluated (part B of the lists), provided their migration is not detectable with a detection limit of 0.01 mg/kg.

Lastly the detection limit of 0.01 mg/kg food is widely used as a cut off limit by testing laboratories for the assessment of food contact materials, especially during screening tests (e.g. by GC-MS) on extracts/migration solutions. The recently published ILSI guidance on best practice on the risk assessment of NIAS in FCMs recommends the 10 ppb threshold during the non targeted chemical analysis step (section 5.1). Its use is however conditioned to the exclusion of CMR substances based on expert judgment or otherwise.

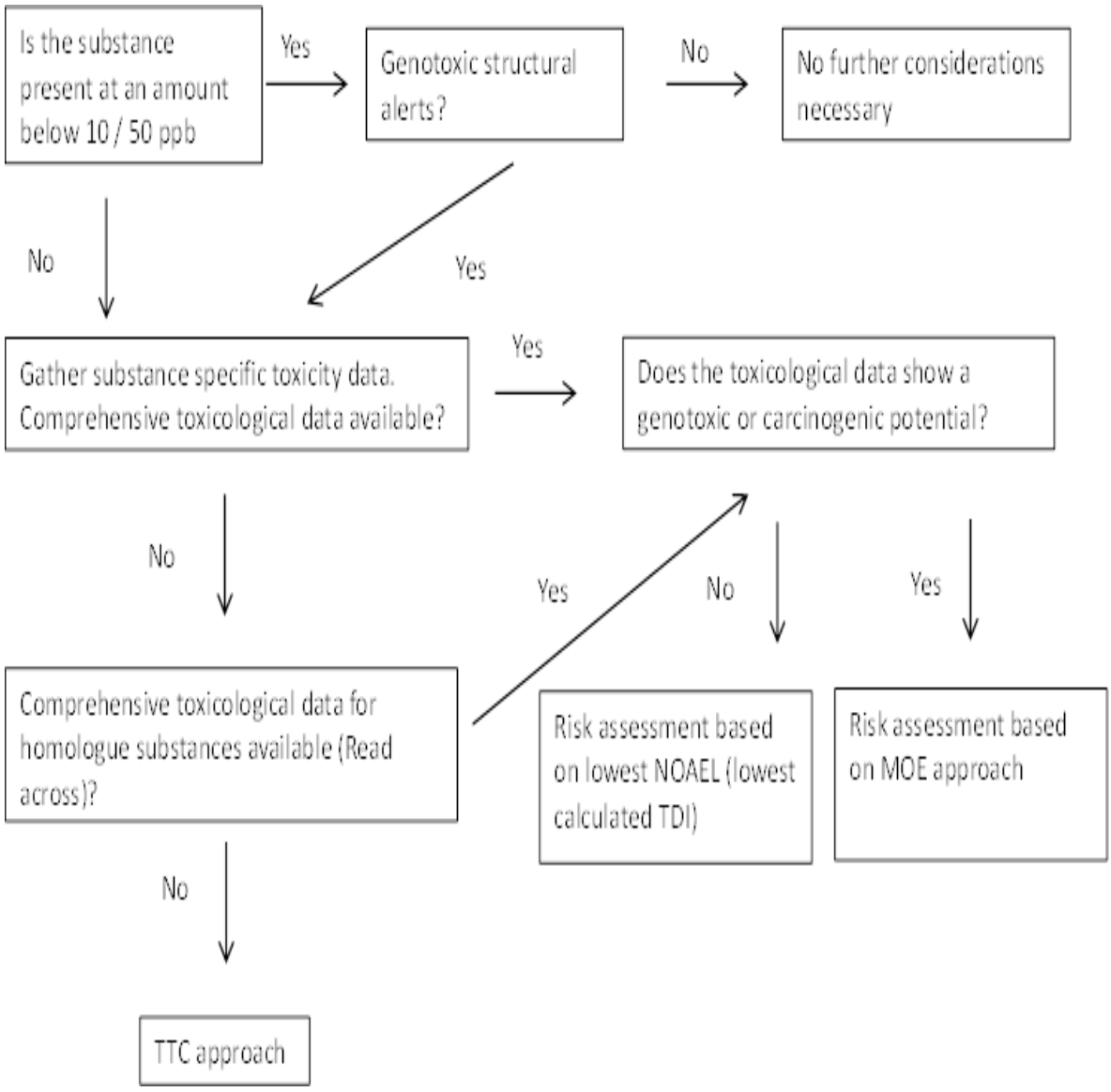
In the US a similar approach is used by industry and law firms, working as consultants and performing substance evaluations for food contact applications. Due to this approach an analytical sensitivity level of 50 ppb, a finding of "non-detected" is found to be reasonable. This limit value is based on the "Ramsey Proposal", a notice of proposed rulemaking circulated by FDA in 1969, and a precursor and historical part of the development of the Threshold of Regulation (TOR) and the TTC concept. Although never adopted by FDA, this concept has received wide acceptance in the scientific community. Furthermore, due to the definition of a food additive as: "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food *(including any substance intended for use in . . . . . packaging, . . . or holding food . . .*).", it can be assumed that a

food-contact substance must be expected to become a component of food in more than a toxicologically insignificant amount to be properly considered a food additive. An analytical sensitivity level, a “non-detection” level of ≤ 50 ppb can be seen as a toxicologically insignificant amount for substances for which a genotoxic potential does not have to be expected due to missing genotoxic structural alerts or in vitro genotoxicity studies demonstrates that the substance is not genotoxic.

FDA's tiered requirements for toxicological data for substances with a potential dietary exposure between 0.5 ppb and 50 ppb mandate two in vitro genotoxicity studies demonstrating that the substance is not genotoxic. Also in Europe when submitting a petition for the listing of substances to EFSA for food contact applications the requirements regarding the toxicological data package are depending on the specific migrating of the substance into food simulants in the used application. If the specific migration is found to be below 50 ppb only a reduced data set of three in vitro genotoxicity tests has to be delivered. These set limits also support the use of a “50-ppb approach” as a limit below which no risk of harm has to be anticipated if a lack of genotoxicity has been shown by in vitro testing or no genotoxicity testing is necessary due to the lack of structural alerts based on expert judgement.

In conclusion, if it can be shown that the migration of a substance, which is not CMR classified and shows no genotoxic structural alerts, is less than 0.01 / 0.05 mg/kg food (simulant), then no further assessment is needed. These conservative approaches have however the drawback of a very limited applicability, due to the low values (EU: 10 ppb, US: 50 ppb). As a next step following a tiered approach the possibilities of applying the TTC concept can be considered (see chapter 3.8).

Suggested step wise approach for the evaluation of non-listed substances/impurities present at low concentrations/amounts **(Figure 5)**:



3.7 Nano

According to the EU definition, engineered nanomaterial means a manufactured or processed material in an unbound state or as an aggregate or an agglomerate where one or more external dimension is in the size range 1 nm – 100 nm. These particles can be present in food contact materials as IAS or NIAS.

According to EFSA, the safety of nanomaterials in FCM should be evaluated ‘case-by-case’ as there is uncertainty of characterisation, detection and measurement of the nanoparticles in food and these materials have specific properties, which may affect their toxicokinetic ant toxicology profiles. If it can be convincingly demonstrated, that there is no migration of the nanomaterial to the food matrix then there is no exposure to the substance and thus no toxicological concern. EFSA has used this “no

exposure – no risk”-concept in the approval of TiN nanoparticles (FCM #807) as food contact material.

3.8 Endocrine Disruptors

While as of today no legal definition is in place, the European Commission presented in June 2016 criteria to identify endocrine disruptors in the field of plant protection products and biocides. The Commission proposed to adopt a science-based approach to the identification of endocrine disruptors and to endorse the WHO definition. In 2013, EFSA published a Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA, 2013). EFSA supported the OECD conceptual framework substances testing of potential endorcrine disrupting properties, which is based on the presence of an adverse effect caused by an endocrine mode of action. EFSA concluded "EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment." However, hazard assessment should pay attention to possible gaps in the test data set. ECETOC (2009) suggests the application of additional uncertainty factors in some cases.

3.9 Bioaccumulation / bioavailability in the human body

Another major aspect with respect to risk assessment is the molecular weight of a substance or in case of polymers the fraction < 1000 Dalton. Substances with a molecular weight > 1000 Dalton are unlikely to pass biological membranes meaning they are non-bioavailable and therefore they are not expected to cause adverse systemic effects, unless they hydrolyze in the gastrointestinal tract and liberate toxic substances or cause a local effect like irritation of the mucosa. If this can be excluded, only substances or oligomers with a molecular weight < 1000 Dalton normally need a risk assessment.

Bioaccumulation in the human body occurs when a substance is absorbed by the body to a higher extent than it is excreted. As substances with a molecular weight > 1000 Dalton are normally not absorbed by the body, bioaccumulation cannot occur. Thus, this toxicological endpoint is relevant only for substances < 1000 Dalton.

Extract from the note for Guidance, annex 4 to Chapter III: In the case of food contact materials the interest centers on the potential for direct accumulation in mammalian tissues and not on biomagnification through the food chain. However, normally a log ko/w value below 3 would be considered sufficient evidence for the lack of accumulative potential in the mammalian body, unless special considerations, e.g. chemical structure, give cause for concern. On the other hand, a log ko/w of 3 and higher will not by itself be proof of accumulation as a substance may not be absorbed or be metabolised to substances with no accumulation potential. In these circumstances other evidence for the absence of accumulative potential is needed.

4. EXPOSURE ASSESSMENT

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 EDIs 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 requires 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 water during contact events (migration data), and data that allows 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 (Temperature, S/V). The findings of exposure are determined by how much food and water are consumed by the consumer and what types and shapes of packaging are used for the food and water.

4.1 Tiered approach

The consumer exposure to a given migrant can be determined by various basic to complex means, depending on how much refined value is needed for the risk assessment, i.e. depending on substance hazard. Consequently, a tiered approach is proposed, starting with a simple worst case determination and ending with a refined determination which requires analytical data and knowledge of intended uses (FCM structure, storage conditions, food categories and consumption data…). The latter approach is more difficult to conduct at an early stage in the supply chain e.g. for a food contact additive manufacturer, and the exposure data is then only relevant to very specific uses of the product.

In any case, the exposure assessment necessarily first requires the determination of the migration level of substance of interest from intended FCMs (refer to paragraph 4 b), either by calculation (100% transfer or migration modeling) or by a combination of extraction data (residual content in intermediate or final material) and calculation or by migration tests on final material.

Migration values have then to be converted into consumer exposure (amount of substance /pers/day) for comparison with "tolerable intake values". Here also a tiered approach is proposed to estimate the "FCM consumption" (expressed e.g. as dm^2 /pers/day), refer to paragraph 4d.

4.2 Migration Estimation

The amount of migration of substances from Food Contact materials into food can be derived from worse case calculations (assuming 100% migration), migration models (diffusion model), extraction studies in solvent (experimental data) or migration studies in food simulants (experimental data). Migration is normally expressed in mg/dm^2 Food Contact material or in mg/kg food.

WORSE CASE MIGRATION

The following formulas can be used to calculate the worse case migration in the food assuming 100% migration:

Option 1

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

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

Option 2

$$C_{Food} = C_{polymer} \times [d_{Polymer} / d_{Food}] \times [S_{Packaging} / V_{Food}] \times e_{Packaging}$$

$$C_{Food}\ (ppm) = C_{polymer}\ (ppm) \times [d_{Polymer} / d_{Food}] \times 0.1 \times [S_{Packaging} / V_{Food}](dm^{-1}) \times 10^4 \times e_{Packaging}\ (\mu m)$$

Where:
C_{Food} = concentration of the substance into food (mg/kg or ppm)
$C_{Polymer}$ = concentration of the substance into polymer (mg/kg or ppm)
$d_{Polymer}$ = density of the polymer (g/cm^3 or kg/dm^3)
$S_{Packaging}$ = contact area of the food contact material (cm^2)
$e_{PackagingM}$ = thickness of the food contact material (cm or 10^4 µm)
V_{Food} = volume of food (cm^3)
d_{Food} = density of the food (g/cm^3)

* NOTE: Difference between options 1 and 2 are units

EXAMPLES

Printing Inks. In case the substance is used in printing ink applications, EuPIA (European Printing in Association) has published some default values which can be used to calculate the worse case migration[30].
When substances are used in printing inks an average ink weight per area is required to be able to calculate the worse case migration. The following dry ink film weight (indicative values) can be used.

Printing technology	Ink film weight (dry)
Flexographic ink	1-1.5 g/m²
Gravure ink	1-2 g/m²
Offset ink	1-2 g/m²
Dispersion varnish	2-3 g/m²
White basecoat	12-16 g/m²
Clear basecoat	1-2 g/m²
UV varnish	4-7 g/m²

The following formula can be used to calculate the worse case migration in the food assuming 100% migration originating from the printing ink.

$$C_{Food}\ (mg/kg) = \frac{W\ (g/m^2) * C_{Ink}\ (\%) * S_{Packaging}\ (dm^2)}{M\ Food(kg) * 10}$$

Were:
C_{Food}: concentration of the substance into the food
C_{Ink}: concentration of the substance in the dried ink
M_{Food}: weight of the food in contact with the material
$S_{Packaging}$: contact area of the packaging material
W (g/m^2): Dry Ink weight of the printed article

Coatings. CEPE (European Council of Paint, Printing Ink and Artists' Colours Industry) describes in its "Code of practice for coated articles where the food contact layer is a coating" the typical film thickness used in different coating applications[31]

Application	Film Thickness
Coated light metal packaging	5 – 15 µm
Drums and Pails	12 – 13 µm
Heavy duty coatings	250 – 500 µm

[30] http://www.eupia.org/uploads/tx_edm/2011-11-14_EuPIA_Guideline_for_Food_Packaging_Inks_-_November_2011__corr_July_2012.pdf
[31] http://www.cepe.org/epub/easnet.dll/ExecReq/Page?eas:template_im=100087&eas:dat_im=05043D

Adhesives. In May 2016, the Association of the European Adhesive & Sealant Industry (FEICA) published a guidance paper called "Migration testing of adhesives intended for food contact materials"[32]. The guidance paper forms part of a package on migration testing of non-plastic food contact materials developed by several sector associations from the packaging supply chain.

Due to the wide range of applications and the complexity of the chemistry, no unified testing conditions can be defined for adhesives. Testing adhesives according to the rules of the plastics regulation without substrate or the construction material will usually overestimate the migration of constituents into foodstuff, as contributing factors to real migration are not sufficiently considered. Contributing factors can be:

- Curing times and conditions
- Interaction of adhesive with other FCM layers
- Barrier properties of other FCM layers
- Distribution of constituents within the FCM
- Ratio of adhesive amount to filling good

The Guidance includes material-specific properties to be considered when testing. Also, general migration testing recommentations for i.e typical application in paper and board packaging, as well as specific recommendations for pressure-sensitive adhesives and cold and heat seal application are included.

EXTRACTION TESTS

Another way of obtaining information on the possible worst case migration of substances from food contact materials is to perform extraction tests on the food contact material with an appropriate solvent. By applying extraction test information on the possible migration can be obtained relatively easier than by performing migration studies. However it has to be ensured that a suitable extraction solvent is used obtaining a 100% extraction of the component of interest.

It has to be pointed out that from the results obtained from extraction studies non-compliance may not be concluded. Actual migration studies or analysis in packed food itself are required.

MODELING

For predicting the migration of substances, mathematical modeling can be applied, which has been significantlydeveloped in recent years. These tools have been validated for some of the common used plastics and provide an over estimation of the possible actual migration. For guidance on migration modelling JRC (Joint Research Centre) issued a guidance document[33].

[32] http://www.feica.eu/information-center/news/feica-guidance-paper---migration-testing-of-adhesives-intended-for-food-contact-materials.aspx

[33] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC59476/reqno_jrc59476_mathmod_v10_cs_2010_09_24_final.pdf%5b1%5d.pdf

Modeling on plastics has been accepted by EFSA as an option to calculate migration[34]. Modeling is only applicable under “non-swelling” conditions. For other materials, like paper and paperboard the development of a modeling tool is in progress.
Modeling is not yet applicable for rubbers or other elastomers.

It is known that in most cases the migration of substances from polymeric materials follows Fick’s law of diffusion. In order to be able to use the modeling tools at least the following information is needed; molecular weight of the substance with a polymer specific parameter (Ap) and a polymer specific activation energy (t) to obtain the diffusion coefficient D of the organic substance in the polymer, amount of substance in the polymer, layer thickness, area to volume ratio and the contact condition of the food contact material.

SOME AVAILABLE SOFTWARE TOOLS (non-exhaustive list of tools)

There are a few companies who offer software systems for migration modelling such as: INRA Safe Food Packaging Portal version 335, MIGRATEST software36 or AKTS-SML Software[37], FACET v3.0.0, among others.

NOTE: The first three are designed to overestimate migration and are valiadated, while FACET offers a more realisitic calculation but is not validated.

MIGRATION TESTS

The European Commission together with the Joint Research Center (JRC) is currently finalising the “Technical Guidelines for migration testing compliance”. These technical guidelines are part of a series of documents to provide guidance on application of Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food and are ***only applicable to plastic materials and articles*** in the scope of this Regulation. It covers the following topics related to compliance testing of plastic materials and articles: sampling, testing in food, choice of food simulants and test conditions, testing in food simulant, verification testing, screening testing, calculation of migration test results and reporting of test results. Although these technical guidelines are not legally binding, they give the state-of-the-art of compliance testing in the framework of Regulation (EU) No 10/2011 and they give all the elements for the supporting documentation related to the compliance testing of the material or article. Once finalised, the guidelines will be made available on the EC’s website.

In parallel industry stakeholders associations, covering the so-called “non-plastics”- value chain have formed a task force to propose testing conditions better adapted to the specificity of various FCMs. The Task Force is developing compliance guidelines with separate chapters for each non-harmonized FCM. The guidelines explain that in the Plastics Regulation (EU/10/2011) some of the simulants, times and temperatures are inappropriate for some non- plastic FCMs. However in the absence of harmonised regulations, the conditions used in the Plastics Regulation are often applied to non-plastics. Plastic simulants and/ or conditions and may cause physical damage or changes to

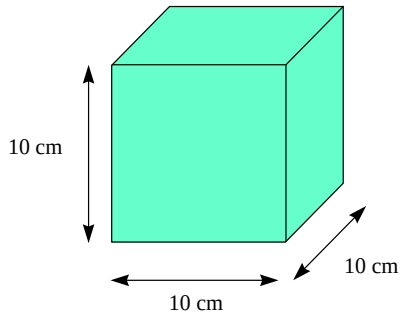
[34] http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3635.pdf
[35] http://modmol.agroparistech.fr/SFPP3/SFPP3download.html
[36] http://www.fabes-online.de/software.php?lang=en&mode=migratest
[37] http://www.akts.com

the non-plastic FCM leading to wrong results. Each sector assesses the applicability or not of the plastics 10/2011 migration testing guidelines for their own sector, assessing gaps and collecting technical solutions for improved compliance testing. Test proposals are based on technical and scientifically demonstrated justification. The guidelines will contain a common introduction and the majority of association's guidelines will be on their corresponding website.

4.3 Food consumption and packaging use data

At this point in time[38], the default conventional assumption for packed food 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

4.4 Derivation Estimated Daily Intake number – three steps approach

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 resource intensive than the conservative approach.

STEP 1: WORST CASE EXPOSURE CALCULATION BASED ON EUROPEAN DEFAULT ASSUMPTIONS

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.

[38] This might change in light of the revision of EFSA's note for guidelines, which is currently on-going.

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

STEP 2: FRF CORRECTED EXPOSURE CALCULATION FOR LIPOPHILIC SUBSTANCES IN FATTY FOOD[39]

At this time, to account for the fact that 95% of the population consumes less than 200 g of fat per day, the Regulation facilitates 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 (EU) No. 10/2011 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[40].

Under FDA approach, the term "Consumption Factor" (CF) is used to describe the fraction of the daily diet expected to contact specific packaging materials. 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 CF represents the fraction of daily consumed packaged food that is packed in a certain packaging material. It somehow reflects the fact that only a certain part of the daily food is packaged and especially packaged in a certain material. Table 1 of the a.m. FDA guidance document shows specific packaging materials e.g. PET with a CF of 0.16. This means

[39] http://www.tandfonline.com/doi/pdf/10.1080/02652030500157700

[40] FDA guidance document for submission of a Food Contact Notification http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081818.htm#iie1a)

that 16 % of the daily diet (of 3 kg liquid and solid food) is packaged in PET. Or around 20 % of the daily diet is packaged in metal cans (CF is 0.17 for coated and 0.03 for uncoated metal containers). Since consumer behavior changes these CF-values need to be adapted from time to time.
(http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm081818.htm#aivti);.

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 values take into account the fact that certain packaging materials are used for specific foods of the daily diet. i.e. Coated paper are rarely used (<5%) for foods which fall in the category acidic or alcoholic. However, they are mostly used (95%) for foods of type aqueous or fatty (e.g meat).

For the calculation of the overall migration of a food contact substance from a specific material the analytical results of migration testing with food simulants (<M>) are combined in that way using Food-type distribution factors (f_T) to reflect the real life use of that packaging material. In a second step Exposure (EDI) is calculated from Migration (<M>) considering market share and usage of that material (CF).

These data (consumption factors and food type distribution factors) are available on the FDA website[41]

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):

$$\mathbf{EDI_{FDA}\ (mg/person/day) = 3\ kg\ food/person/day * CF * <M>\ (mg/kg\ food)}$$

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:

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

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].

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

4.5 European consumer exposure assessment tools

4.5.1 Risk Assessment of non-intentionally added substances (NIAS) using the MATRIX

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 respective 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.

For specific packaging not often used in a country or specific food not consumed often, the average real surface exposure can be very low compared to the standard 600 cm2 (i.e. Aluminium foil in Italy the surface exposure is 0.06 dm2/person/day) can lead to a high Limit of Interest. However, it was agreed by industry, that even if the calculated LOI was above 100, we would apply a maximum conventional LOI of 100 µg/dm2, for negligible or low surface exposure (Surface < 0.1 dm2/person/day).

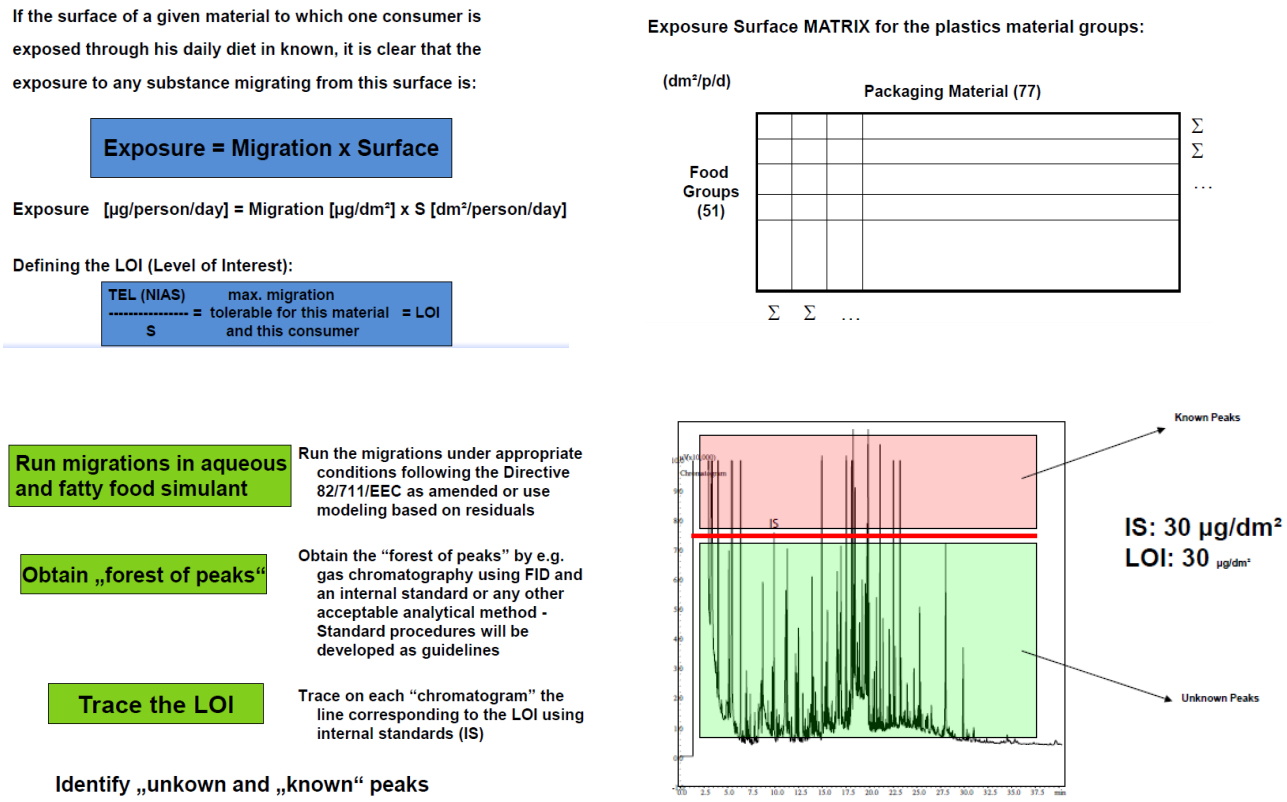
The Matrix Project derived country data sets for Germany, France, Italy, Spain and United Kingdom with the respective packaging surface to which consumers are exposed per plastic material group and per consumed food and the respective calculation of LOIs.

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.

MATRIX EXAMPLE



* Further information about MATRIX can be found under: http://matrixcalculation.eu/

PACKAGING USE DATA FROM THE EXPOSURE MATRIX PROJECT

The Exposure Matrix project collected information on the composition and amount of food packaging in five EU countries (DE, UK, IT, FR, ES) in the period 2003-2006. The scope of the project can be described as direct food contact packaging for pre-packed food sold to consumers in retail channels. The packaging use data is a combination of data obtained from third party market survey organisations and information collected from member companies of the participating associations. More background information can be found here (registration and log-in required)[42]

The collected packaging use data has been combined with official dietary surveys from the five countries by methods of stochastical modelling to result in a value for the average daily consumer exposure to an area of food packaging, split up per food type and per packaging type. The calculated values are an average (i.e. the 50th percentile of the distribution) because the intention was to look at results over the entire diet or large parts of it and no person can be the extreme consumer for every food. Nevertheless several factors of over-estimation remain (100% market shares, 100% packaging loyalty, 100% packed foods, certain double-counting in the data, etc.) and also the average value was seen to be higher than the median. Therefore the average packaging area exposure value is seen to represent a sizeable majority of consumers.

[42] https://matrixcalculation.eu/matrix/matrix.nsf/mv-exposure-matrix-14-01-2008.pdf

The results from the Exposure Matrix project can be used in certain cases to get a more refined insight into the use of specific packaging materials than what is possible with the standard EU convention that the diet consists of 1 kg food in contact with 6 dm² of each packaging material.

The following points need to be considered:

- The data only covers the scope of the project as outlined above. If a substance is being assessed for an application outside the scope, this cannot be done on the basis of this Exposure Matrix project.
- This methodology would likely give a false result if the substance or material is known to have a disproportionally large contribution to consumer exposure from FCM applications not covered by the scope. An example would be polystyrene, known to be heavily used in vending and fast food outlets, or paper & board known to be heavily used in secondary packaging and fast food. Exceptions may apply when assessing substances only used in specific grades and/or specific applications which are known to be within the scope of the Exposure Matrix project.
- This method is not intended as an assessment for "all foods, all materials" as then the numbers add up to being significantly more severe than the standard EU 6 dm²/kg scenario (which is proof that there are still significant overestimations in the Exposure Matrix methodology).

Refer to the Exposure Matrix results tables giving the average exposure (in dm²/person/day) for 51 food groups (50 for Germany) against 77 packaging materials (54 for Germany). In extracting information from these tables, several different scenarios are possible depending on the origin of the substance and the information available about the use of the substance or its parent material. It is recommended to look at all five countries and select the highest result.

The following considerations can be made:

a) Do not look at the value of an individual matrix cell. These tables were not designed to be used at this level of detail. First of all, they are an average value instead of a 95th percentile. Also, there are inevitably data inaccuracies both in the underlying packaging data as well as (and possibly even more) in the dietary survey data. These will only average out if a larger consumption pattern is being looked at.

b) When the substance being assessed is known to be present in one or more specific components (e.g. a polymer type), the relevant result is the value reported at the bottom of the column (i.e. the sum over that entire column) in which that component is present.

    1) If the component is present in more than one column, add up all relevant results.

    2) Take into account that in certain material descriptions, certain components may be present "anonymously":

        i. **Example 1:** acid/ester copolymer PE types are listed as an individual material description, nevertheless they will also make up a certain percentage of any other column that mentions the more generic term "PE" or "plastic".

ii. **Example 2:** adhesives can be assumed to be present in all material descriptions described as having two or more substrate layers (e.g. materials such as “APET/PE”). Refinements based on type of adhesive chemistry, would depend on expert judgement, to be documented.

iii. **Example 3:** the presence of inks or coatings cannot be easily derived from the material descriptions listed, but may be allocated based on expert judgement. Refinements based on type of ink or coating chemistry, would depend on expert judgement, to be documented.

3) For niche products known and documented to have a very small market share, it is allowed to take a fraction of the values reported, but not less than 10% *[value to be discussed]*.

c) The procedure described under point (b) may be modified by not making the sum over all food groups, but only a sub-set of them, if there is documented justification for doing so:

- When the substance is known not to migrate in all simulants, then the food groups can be selected for which the relevant simulant(s) is/are applicable according to the table in Annex III of Regulation 10/2011.

  i. **Example 1:** A non-volatile substance can be considered not to migrate into dry food (possibly to be confirmed by testing in Tenax), in which case the food groups corresponding to dry food can be eliminated.

  ii. **Example 2:** A lipophilic substance is expected to migrate only into fat/oil, therefore the food groups for which simulants D1 or D2 are assigned, can be selected for the evaluation.

  iii. **Example 3:** An FCM substance marketed only for non-fatty food contact applications, can be evaluated by eliminating food groups for which *only* simulant D1 or D2 has been assigned.

- When the substance has a very specific function related to a very specific food packaging application, the food group(s) that cover this packaging application can be selected – but taking into account the point (a) above.

  I. **Example:** A substance known (but see point e) to be only used in can coatings, would be only relevant for those food groups where cans are used, and only for the column covering metal packaging (“other packaging” in the German data; “other mono-substrate non-plastic” for the other countries).

d) When the substance being assessed is known to be associated to a specific FCM substance, e.g. a NIAS resulting from an additive, the parent substance can be used in this methodology if that makes it easier to collect information about the use and presence of the substance.

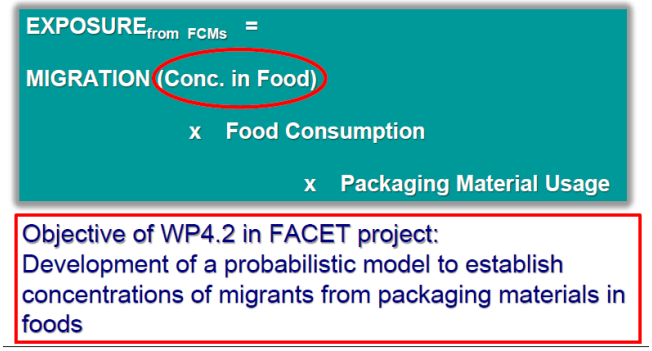
e) It can be difficult to know where in the market / in which kinds of materials a certain substance is used or present. Expert judgement usually only extends to that specific market segment the company is active in. Inventory lists may be an indication of the various uses of certain substances.

The result of the exercise carried out along the previous points (a) through (e) is typically a single value which is the average consumer exposure to the relevant materials, in dm²/person/day, for the worst case country of the five countries included in the project. Knowing the migration into food or food simulants allows a calculation of the concentration in the diet of the substance at hand. This then constitutes an exposure assessment relevant for the risk assessment of the substance:

- If the migration is not known, certain assumptions can be made based on concentration in the material, typical worst case thickness of the material, and assuming complete transfer of the substance.
- If the migration level is known to be different in different simulants (which would typically be the case) then the exercise under points (a) through (e) can be carried out by splitting the food groups according to the simulant assignment. This results in double counting for those food groups where more than one simulant is assigned – this is seen as an extra safety margin.

4.5.2 FACET Project

Within the 7th Framework Research Programme, 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, flavourings and migratable substances from food contact materials. The FACET project which was officially finished in October 2012 developed a software tool that models 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.[43]



The FACET software allows to calculate the consumer exposure to direct food additives and flavouring substances, as well as to migrants from food contact materials. In the area of FCM migrants, distinction is made between metal packaging and non-metal packaging. In what follows, only non-metal packaging is considered.

In order to calculate the exposure, the model combines the following information inputs:

- food consumption, as recorded in national dietary surveys;

[43] See http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/chemicals_in_food/FACET

- structure, size and market share of the various FCM used for each food;
- composition of each component used in the FCM structure – identity of substances, concentration range, probability of presence in the FCM;
- contact conditions (range of temperature and time) during conditioning, storage and use of the packed food product.

The FACET model originally had the intention of recording industry-collected data covering the three last bullet points in the list above. This information is embedded as encrypted data files in the FACET software. The user only has to run a “pre-population” (once per country) which performs a calculation of the migration levels into food, and can then proceed to run the “assessment” which is the actual exposure calculation.

The big advantage of this approach is that it allows an exposure calculation across the consumer’s complete diet (per country, per dietary survey) without requiring extensive knowledge by the user of the use and composition of all FCM in all packaging sectors – a level of expertise considered unrealistic for any user.

Experience has shown however that severe data gaps exist in the encrypted background data, so that the results may be completely unreliable. In particular, the presence of certain substances in polymers was not correctly recorded. Therefore the use of this pre-loaded data within the FACET software is not recommended.

Two alternative methodologies exist within the FACET software to by-pass the unreliable background data: the “new substance wizard” and the “new packaging wizard”.

In the “new substance wizard” the user has the option to create a “new substance” or a “NIAS” – there is no fundamental difference between the two. The substance is defined by a name and its molecular weight and log P (octanol/water partitioning). The option to “replace existing substance” or “NIAS associated with existing substance” should not be chosen as this refers back to the unreliable encrypted background data. Instead, the user should select the material(s) containing the substance or NIAS and self-define the concentration and market share of the substance in each of the materials selected. Running the new substance wizard results in the new substance appearing in the list of substances to be selected (at the very end, as “NS-1, NS-2” etc.) in the pre-population wizard (to calculate the migration). In doing this, the program uses the encrypted background data on use and structure of the FCM, but by-passes the background data on composition of the individual components in the FCM. After running the pre-population, the exposure assessment can be started.

In the “new packaging wizard” the user first defines a substance (again with name, molecular weight and log P) or selects it from the listed existing substances, and then proceeds to define the structure of the food contact material in which the substance is present. This requires layer thickness(es), concentration, surface/volume ratio. The user also has to define the food, pack size and food contact conditions.An advantage of running the new packaging wizard, is that it gives the user access to the results of the migration calculation. This is under “My Migration Data” in the “My Data” tab. The “view pack table” button gives the migration results in mg/kg food. It should be noted that this is a probabilistic migration model and is not designed to over-estimate the migration level. It is not a validated model that can be used in the context of SML compliance. Running the new packaging wizard includes a migration calculation, so no separate pre-population run is needed before starting

the exposure assessment. When starting the exposure calculation, select “use my concentration data” and find the appropriate entry under “my migration data”.

In summary, the new substance wizard (NSW) and the new packaging wizard (NPW) allow the user to perform a targeted investigation but have as disadvantage that they require the user to have some expert knowledge as input into the software:

- NSW requires that the user find the molecular weight of the substance, and knows which material(s) the substance is present in along with concentration and market share.
- NPW requires that the user find the molecular weight of the substance, and knows which material(s) the substance is present in along with concentration and market share, what the structure is of the FCM in which the material in question is used, and what the food type and food contact conditions are for each application.

The NSW can be used to calculate the exposure from a substance present in a particular material or even several materials, integrated over all FCM structures in which those materials are present, and integrated over all foods for which those FCM are used. The output of an “all foods, all materials” exposure run could therefore be seen as an exposure in the diet. Some care is needed in the interpretation of these results, as it is unlikely that the user has sufficient knowledge of the use of a substance across all different packaging sectors.

The NPW is more suitable for the risk assessment of a single packaging application known to the user. It takes much more effort (separate runs) to generate information across a range of foods, and is therefore unlikely to ever approach an exposure result in the diet. The NPW gives access to the migration calculation which is very useful in itself, but is not a validated model for SML compliance purposes.

The NSW and NPW have been tested for metal packaging and for plastics and inks. They are likely to work equally well for plastic-like materials such as adhesives. Other materials, most notably paper & board, remain to be investigated.

As a final note, the user should be aware of the limitations of the scope of the FACET project. This can perhaps best be described as “consumer retail”. This implies that other stages in retail e.g. B2B trade of bulk foods or food ingredients, as well as food outlets such as vending, restaurants, fast food outlets etc., or drinking water infrastructure, or home cooking and food storage, are not covered at all.

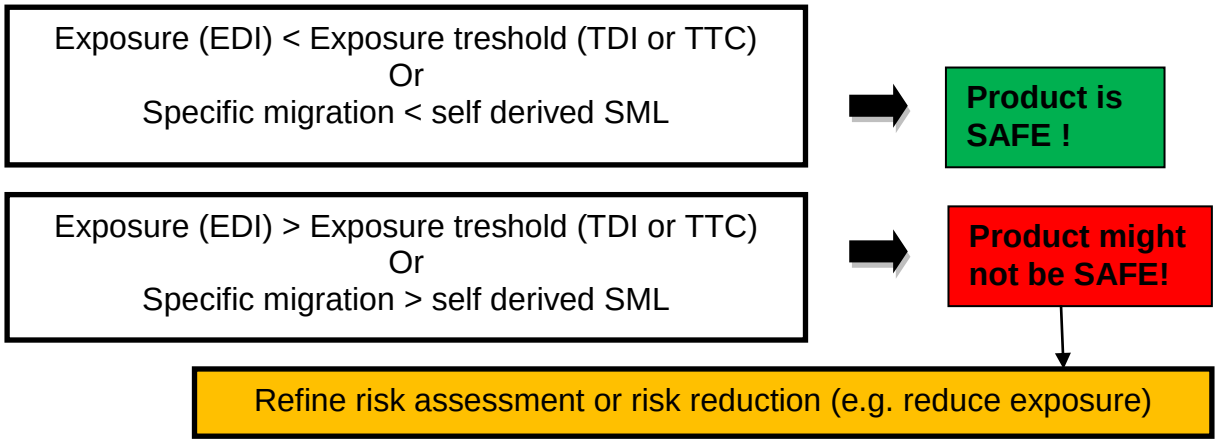
5. RISK CHARACTERISATION OR RISK ASSESSMENT

In the final risk characterisation 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.

Exposure (EDI) < exposure threshold (TDI or TTC) or Specific migration < self-derived SML ⇒ SAFE

If a safe use in the specific application cannot be immediately concluded, then either the risk assessment could be refined (refine the exposure estimation or generate more toxicological data) or the exposure to the substance (migration level) could 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.



REFERENCES

PlasticsEurope Guidance on Risk Assessment of non-listed substances (NLS) and non-intentionally substances (NIAS° under Article 19 of Regulation 10/2011/ EU

Koster S, Boobis AR, Cubberley R, Hollnagel HM, Richling E, Wildemann T, Würtzen G, Galli CL. Application of the TTC concept to unknown substances found in analysis of foods. Food Chem Toxicol. 2011 Aug;49(8):1643-60.

Technical guidance safety assessments under REACH:
http://guidance.echa.europa.eu/guidance_en.htm

EFSA note for guidance for food contact materials:
http://ec.europa.eu/food/food/chemicalsafety/foodcontact/documents_en.htm

FDA guidance document - Toxicological assessment:

http://www.fda.gov/Food/default.htm_(Document UCM081825)

FDA guidance document - Consumer Exposure assessment :

http://www.fda.gov/Food/default.htm_(Document UCM081818)

ILSI publications (http://www.ilsi.org/Europe/Pages/HomePage.aspx)

- Threshold of Toxicological Concern (2005)
- The Acceptable Daily Intake: A Tool for Ensuring Food Safety (2000)
- Guidance for Exposure Assessment of Substances Migrating from Food Packaging Materials (2007)
- Exposure from food contact materials (October 2002)
- Guidance for Exposure Assessment of Substances Migrating from Food Packaging Materials (2007)
- Food Consumption and Packaging Usage Factors (1997)
- The Use of an Additional Safety Factor or Uncertainty Factor for Nature of Toxicity in the Estimation of Acceptable Daily Intake and Tolerable Daily Intake Values

FDA CEDI/ ADI database
http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/default.htm

Benford D, Bolger PM, Carthew P, Coulet M, DiNovi M, Leblanc JC, Renwick AG, Setzer W, Schlatter J, Smith B, Slob W, Williams G, Wildemann T. Application of the Margin of Exposure (MOE) approach to substances in food that are genotoxic and carcinogenic. Food Chem Toxicol. 2010 Jan; 48 Suppl 1:S2-24.

ECHA Guidance on information requirements and chemical safety assessment.

Chapter R.8: Characterisation of dose [concentration]-response for human health. May 2008.

http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

Opinion of the Scientific Committee on a request from EFSA related to a harmonized approach for Risk Assessment of substances which are both Genotoxic and Carcinogenic. The EFSA Journal (2005) 282, 1-31. http://www.efsa.europa.eu/en/scdocs/scdoc/282.htm

ECETOC report TR 085 - Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies December 2002.

ECETOC report TR 099 - Toxicological Modes of Action: Relevance for Human Risk Assessment July 2006.

IPCS, 2005. Chemical-Specific Adjustment Factors for Interspecies Differences And Human Variability: Guidance Document For Use Of Data In Dose/Concentration–Response Assessment. World Health Organisation, the International Labour Organisation and the United Nations Environment Programme. Harmonisation Project Document No. 2.

ECHA Guidance on information requirements and chemical safety assessment. Chapter R.6: QSARs and grouping of chemicals. May 2008.

http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

Kroes, R. et al., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to Substances present at low levels in the diet. Food and Chemical Toxicology 42: p 65-83.

Kroes, R. et al., 2000. Thresholds of Toxicological Concern for chemical substances present in the diet: A practical Tool for Assessing the Need for Toxicity Testing, Food and Chemical Toxicology 30: p 255-312.

Cramer GM, Ford RA, Hall RL. 1978. Estimation of toxic hazard--a decision tree approach. Food Cosmet Toxicol. 16(3):255-76.

Munro IC, Ford RA, Kennepohl E, Sprenger JG. 1996. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. Food Chem Toxicol. 34(9):829-67.

ToxTree version 2.5.8 (http://toxtree.sourceforge.net/) and Patlewicz G, Jeliazkova N, Safford RJ, Worth AP, Aleksiev B. An evaluation of the implementation of the Cramer classification scheme in the ToxTree software. SAR QSAR Environ Res. 2008;19(5-6):495-524. PubMed PMID: 18853299.

Walker R, Kroes R. [The threshold of toxicological concern]. Vopr Pitan. 2002; 71(1):42-4. Review. Russian. PubMed PMID: 12018155.

Barlow SM, Kozianowski G, Würtzen G, Schlatter J. Threshold of toxicological concern for chemical substances present in the diet. Report of a workshop, 5-6 October 1999, Paris, France. Food Chem Toxicol. 2001 Sep;39(9):893-905. PubMed PMID: 11498266.

Kroes R, Kozianowski G. Threshold of toxicological concern (TTC) in food safety assessment. Toxicol Lett. 2002 Feb 28;127(1-3):43-6. Review. PubMed PMID: 12052639.

Renwick AG. Toxicology databases and the concept of thresholds of toxicological concern as used by the JECFA for the safety evaluation of flavouring agents. Toxicol Lett. 2004 Apr 1;149(1-3):223-34. Review. PubMed PMID: 15093268.

Kroes R, Kleiner J, Renwick A. The threshold of toxicological concern concept in risk assessment. Toxicol Sci. 2005 Aug;86(2):226-30. Epub 2005 Apr 13. PubMed PMID: 15829616.

Renwick AG. Structure-based thresholds of toxicological concern--guidance for application to substances present at low levels in the diet. Toxicol Appl Pharmacol. 2005 Sep 1;207(2 Suppl):585-91. Review. PubMed PMID: 16019047.

Munro IC, Renwick AG, Danielewska-Nikiel B. The Threshold of Toxicological Concern (TTC) in risk assessment. Toxicol Lett. 2008 Aug 15;180(2):151-6. Epub 2008 May 22. Review. PubMed PMID: 18573621.

Felter S, Lane RW, Latulippe ME, Llewellyn GC, Olin SS, Scimeca JA, Trautman TD. Refining the threshold of toxicological concern (TTC) for risk prioritisation of trace chemicals in food. Food Chem Toxicol. 2009 Sep;47(9):2236-45. Epub 2009 Jun 14. PubMed PMID: 19531369.

Union Guidelines on Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food -http://ec.europa.eu/food/safety/docs/cs_fcm_plastic-guidance_201110_en.pdf

Chapter 3.1

http://apps.echa.europa.eu/registered/registered-sub.aspx

http://www.efsa.europa.eu/en/publications.htm

http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm

http://www.cefic-lri.org/lri-toolbox

https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/qsar_tools/toxtree

http://www.dguv.de/dguv/ifa/Gefahrstoffdatenbanken/GESTIS-Stoffdatenbank/index-2.jsp

http://chem.sis.nlm.nih.gov/chemidplus/

http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE

http://webnet.oecd.org/hpv/ui/SponsoredSubstances.aspx

http://www.nicnas.gov.au/chemical-information

http://www.cir-safety.org/ingredients

https://fcm.wiv-isp.be/

https://pubchem.ncbi.nlm.nih.gov/

http://www.chemspider.com/

http://esis.jrc.ec.europa.eu/

Klimisch H., Andreae M. and Tillmann U. (1997) - A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul Toxicol Pharm,* 25, 1-5. and Schneider K, Schwartz M, Burkholder I, Kopp-Schneider A, Edler L, Kinsner-Ovaskainen A, Hartung T, Hoffmann S. (2009). "ToxR Tool", a new tool to assess the reliability of toxicological data. Toxicology Letters 189(2):138-144

https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam/archive-publications/toxrtool

http://www.scirap.org/Page/Index/1e69f488-36b4-4660-9986-c529b9d9b40d/toxicity-framework

Beronius A, Molander L, Ruden C, Hanberg A (2014). Facilitating the use of non-standard in vivo studies in health risk assessment of chemicals: A proposal to improve evaluation criteria and reporting. Journal of Applied Toxicology 34(6): 607-617

Chapter 3.2 Uncertainty factors

Blackburn K, Stuard SB (2014). A Framework to Facilitate Consistent Characterisation of Read Across Uncertainty. Regulatory Toxicology and Pharmacology 68: 353-362

ECETOC (2002). Report TR 085 - Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies.

ECETOC report TR 099 - Toxicological Modes of Action: Relevance for Human Risk Assessment July 2006.

ECHA (2012). Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1. Available at http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

IPCS (2005). Chemical-Specific Adjustment Factors for Interspecies Differences And Human Variability: Guidance Document For Use Of Data In Dose/Concentration–Response Assessment. World Health Organisation, the International Labour Organisation and the United Nations Environment Programme. Harmonisation Project Document No. 2.

EFSA (2012). Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 10(3):2579. Available at http://www.efsa.europa.eu/en/efsajournal/pub/2579

Chapter 3.3 The use of DNELs for Risk Assessment in Food Contact

Guidance on information requirements and chemical safety assessment

https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

REACh Registered Substances

https://www.echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Guidance on Derivation of DNEL/DMEL from Human Data

https://echa.europa.eu/documents/10162/13632/r8_dnel_hd_draft_rev1-1_after_peg_en.pdf

Chapter 3.4 Read across

Benigni R, Bossa C (2008). Structure alerts for carcinogenicity, and the Salmonella assay system: A novel insight through the chemical relational databases technology. Mutation Research 659: 248-261

ECHA (2008). Guidance on information requirements and chemical safety assessment. Chapter R.6: QSARs and grouping of chemicals. Available at http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

Blackburn K, Bjerke D, Daston G, Felter S, Mahony C, Naciff J, Robison S, Wu S (2011). Case studies to test: A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. Regulatory Toxicology and Pharmacology 60: 120-135

Blackburn K, Stuard SB (2014). A framework to facilitate consistent characterisation of read across uncertainty. Regulatory Toxicology and Pharmacology 353-362

ECHA (2012). Practical Guide 5: How to report (Q)SARs. Version 2.0. Available at http://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf

ECHA (2015). Grouping of Substances and Read across. http://echa.europa.eu/support/grouping-of-substances-and-read-across

EFSA (2009). EFSA statement on the presence of 4-methylbenzophenone found in breakfast cereals. The EFSA Journal (2009) RN-243, 1-19.

EFSA (2009). Scientific Opinion of EFSA prepared by the Panel on food contact materials, enzymes, flavourings and processing aids (CEF) on Toxicological evaluation of benzophenone. The EFSA Journal (2009) 1104, 1-30.

EFSA Scientific Committee (2012): Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC). EFSA Journal 10(7):2750 [103 pp.]. Available at http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2750.pdf

ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) (2014). Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. ICH Harmonised Tripartite Guideline M7. Public available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf

OECD (2007). Guidance Document on the Validation (Quantitative) Structure-Activity Relationships ((Q)SAR) Models. OECD Environment Health and Safety Publications. Series on Testing and Assessment No. 69. ENV/JM/MONO(2007)2. Public available at http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2007)2&doclanguage=en

OECD (2014). Guidance on Grouping of Chemicals, Second Edition. Environment Health and Safety Publications. Series on Testing and Assessment No. 194. ENV/JM/MONO(2014)4. Public available under: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)4&doclanguage=en.

Patlewicz G, Ball N, Booggaard PJ, Becker RA, Hubesch B (2015). Building Scientific Confidence in the Development and Evaluation of Read Across. Regulatory Toxicology and Pharmacology 72: 117-133

Schilter B, Begnini R, Boobis A, Chiodini A, Cockburn A, Cronin MTD, Lo Piparo E, Modi S, Thiel A, Worth A (2014). Establishing the Level of Safety Concern for Chemicals in Food without the Need for Toxicity Testing. Regulatory Toxicology and Pharmacology 68:275-296

Schultz TW, Amcoff P, Bergren E, Gautier F, Klaric M, Knight DJ, Mahony C, Schwarz M, White A, Cronin MTD (2015). A Strategy for Structuring and Reporting a Read Across Prediction of Toxicity. Regulatory Toxicology and Pharmacology 72: 586-601

Wu S, Blackburn K, Amburgey J, Jaworska J, Federle T (2010). A framework for using structural, reactivity, metabolic and physicochemical similarity to evaluate the suitability of analogs for SAR-based toxicological assessments. Regulatory Toxicology and Pharmacology 56: 67-81

Chapter 3.5 TTC

EFSA event report (2016). “Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree.” EFSA Supporting publication 2016:EN-1006.

Kroes R, Galli CL, Munro I, Schilter B, Tran L-A, Walker R, Würtzen G (2000) Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. Food and Chemical Toxicology 38, s. 255–312.

Kroes R, Kleiner J, Renwick A (2005) The threshold of toxicological concern concept in risk assessment Toxicological Science 86 (2), s. 226–230.

Kroes R, Kozianowski G (2002) Threshold of toxicological concern (TTC) in food safety assessment. Toxicology Letters 127, s. 43–46.

Munro IC, Ford RA, Kennepohl E, Sprenger JG (1996) Correlation of structural class with no-observed-effect levels: A proposal for establishing a threshold of concern. Food and Chemical Toxicology 34, s. 829–867.

Kroes R, Renwick A, Cheesman M, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Wurtzen G (2004) Structured-based thresholds of toxicological concern (TTC): Guidance for application to substances present at low levels in the diet. Food and Chemical Toxicology 42, s. 65–83.

Hennes EC (2012) An overview of values for the threshold of toxicological concern. Toxicology Letters 20;211(3), s. 296-303.

Cheeseman MA, Machuga EJ, Bailey AB (1999) A tiered approach to threshold of regulation. Food and Chemical Toxicology 37, s. 387–412.

Cramer GM, Ford RA, Hall RL (1978) Estimation of toxic hazard – a decision tree approach. Food and Chemical Toxicology 16, s. 255–276.

EFSA (2012). “Scientific Opinion on exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC).” EFSA Journal 2012;10(7):2750.

Koster, S. et al. (2011). “Application of the TTC concept to unknown substances found in analysis of foods.” Food Chem Toxicol 49:1643-60.

Chapter 3.7 Nano

EFSA Scientific opinion “Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain” 2011

EFSA Scientific opinion “Recent Development in the risk assessment of chemicals in food and their potential impact on the safety assessment of substances used in food contact materials” 2015

EFSA Scientific “Opinion on the safety evaluation of the substance, titanium nitride, nanoparticles,for use in food contact materials” 2012

Chapter 3.8 Endocrine Disruptors

EFSA (2013). Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. EFSA Journal 11(3):3132

IPCS (2002). Global assessment of the state-of-the-science of endocrine disruptors. Geneva, Switzerland, World Health Organization, International Programme on Chemical Safety.

ECETOC (2009). Guidance on Identifying Endocrine Disrupting Effects. Technical Report No. 106.

Chapter 3.9 Bioaccumulation / bioavailability in the human body

Regulation (EU) N° 10/2011on Plastic Materials and Articles Intended to Come into contact with Food

EFSA Draft Scientific Opinion on Recent Developments in the Risk Assessment of Chemicals in Food and their Potential Impact on the Safety Assessment of Substances Used in Food Contact Materials

ILSI Guidance on Best Practices on the Risk Assessment of Non Intentionally Added Substances (NIAS) in Food Contact Materials and Articles

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