

EuPIA Guidance for Risk Assessment of Non Intentionally Added Substances (NIAS) and Non Listed Substances (NLS) in printing inks for food contact materials

1. Introduction

For many years, EuPIA member companies have followed a policy of Responsible Care® / Coatings Care® working for Sustainable Development, with a high level of Product Stewardship activity. Such a policy is based on a strong commitment to protect consumers' health, and, through the years, has resulted in the publication of many recommendations and position papers.

Having regard to the fact that there is a Framework Regulation¹ applicable to all food contact materials (FCM), but not yet any specific European Union legislation concerning printing inks for food packaging, EuPIA has developed the "Good Manufacturing Practice (GMP) Printing Inks for Food Contact Materials"², in which detailed recommendations, based on current European legislation, are given on how to formulate and produce inks which will allow the production of compliant printed FCM. Relevant details about potential migratable and reactive substances and solvents present in the printing inks are declared to the users of printing inks by the EuPIA Statement of Composition model to allow them to create the Declaration of Compliance for the final packaging material.

Besides intentionally added substances (IAS) however, printing inks may still also contain small amounts of substances, which are non-intentionally added (NIAS) and which may also not be listed in any official substance list approved to formulate food-packaging printing inks. Such substances in the inks may result from previous production steps of the ink raw materials, they can be reaction products of ink ingredients (for example during drying, crosslinking or curing of the inks or reaction with other packaging components), or can be caused by cross-contamination during the ink production or application.

The purpose of this document is to provide a guidance for risk assessment of non-intentionally added substances (NIAS) and non-listed substances (NLS) migrating from printing inks used for food contact materials.

2. Legislation

Whilst European harmonised legislation does not specifically cover printing inks in their supplied form, there are some legislative instruments which impact on materials and articles intended for direct contact with food, whilst being printed on the non-food-contact side of the packaging.

Regulation (EC) No 1935/2004¹ requires, in Article 3, that materials and articles in contact with food shall be manufactured in accordance with good manufacturing practices, so that, under normal or foreseeable conditions of use, they do not transfer their constituents to food in quantities which could:

- endanger human health; or
- bring about an unacceptable change in the composition of the food; or
- bring about a deterioration in the organoleptic characteristics thereof.

Inks, once printed and dried/cured, on the non-food-contact side of a packaging material in contact with food become a component of this packaging and this packaging has to comply with the requirements of Article 3.

The main specific measure pursuant to the Framework Regulation is Regulation (EU) No 10/2011³ on plastic materials and articles intended to come into contact with food. It lays down an overall migration limit (OML) of 60 mg/kg food or 10 mg/dm² of surface area. In addition, specific migration limits (SML) or maximum contents in the material or article (QM) are set for individual substances.

The Plastics Regulation (EU) No. 10/2011 contains a positive list (Union list) of substances authorised to be used in the manufacture of plastics. Packaging inks in their supplied form are not in the scope of this Regulation, although they may be subject to other EU or national rules. The Union guidelines to the Plastics Regulation¹⁶ explain, “coated and printed plastic materials and articles are covered by the scope of the Plastics Regulation. However, substances used only in printing inks, adhesives and coatings are not included in the Union list because these layers are not subject to the compositional requirements of the Plastics Regulation. If a substance used in a coating, a printing ink or an adhesive is listed in the Union list, the final material or article has to comply with the migration limit of this substance, even if the substance is used in the coating, printing ink or adhesive only.”

If there are ink components which are listed in the Union list or as food additive/flavourings, then the relevant restrictions such as specific migration limits (SML) or maximum content (QM) must be met.

Besides European harmonised substances suitable for food contact materials (FCM), in some countries national legislation for specific applications has been introduced. The most comprehensive national regulation covering printing inks is the Swiss Ordinance SR 817.023.21⁴. According to this regulation, only listed substances are allowed to be used for the manufacture of printing inks and varnishes intended for printing on the non-food contact surface of the materials and articles (packaging inks).

Regulation (EC) No 2023/2006⁵ sets out rules on Good Manufacturing Practice for the production of food contact articles. Based on this regulation EuPIA has developed the Good Manufacturing Practice (GMP) Printing Inks for Food Contact Materials².

Article 19 of the Regulation (EU) No 10/2011³ on plastic materials and articles intended to come into contact with food requires that the compliance with Article 3 of Regulation (EC) No 1935/2004 of substances which are not covered by an inclusion in Annex I to this Regulation shall be assessed in accordance with internationally recognized scientific principles on risk assessment. Such principles include hazard identification, hazard characterization, exposure assessment and risk characterization.⁶

The responsibility for the compliance of the final FCM remains ultimately with the downstream partners. To allow shared and final responsibilities to be met there needs to be cooperation

between ink manufacturer and the rest of the supply chain. This information sharing includes the total food packaging supply chain, starting from raw material suppliers, ink manufacturer, printer, packer/filler and the food producer and the relevant information has to be shared both ways – up and down the supply chain.⁹

3. Definitions

Printing Ink

The term “printing ink”, or in short just “ink”, in this paper includes not only coloured products, but also clear primers, overprint varnishes and any other components which may be added to inks to make them printable and give them the final property (so-called press side additives like waxes, extender, adhesion promoters etc.).

Food Contact Material (FCM)

FCM according to this paper refers to the printed packaging material. Usually the ink does not have direct contact with the food; the printed side is the non-food contact side of FCM's or in case of laminated material the ink is sandwiched by other films. Inks with direct food contact (DFC inks) are a special case and additional requirements must be fulfilled, however this guideline is also suitable for intended DFC inks.

Intentionally Added Substances in printing inks for FCM's (IAS)

IAS in inks are all chemical substances which are intentionally added in the production and use of the printing ink and which have an intended and specific function within the final ink and without this the performance of the inks would change. These substances may be added as single components or as mixtures of various substances. The term “use” of raw materials or substances in inks in this paper means always that these raw materials or substances are added intentionally.

Non Intentionally Added Substances in printing inks for FCM's (NIAS)

NIAS are all chemical substances which are not IAS and do not have an intended and specific function within the ink formulation. Such NIAS may come from impurities in used raw materials from former production steps, but can also be created due to contamination in the ink production or handling, and also during the application process of the inks (unintended side reactions during curing, drying, crosslinking or decomposition for example).

Non Listed Substances (NLS)

NLS is an intentionally added substance, which is not required to be listed. A typical example in printing inks would be pigment additives.

IAS and NIAS in raw materials for printing inks

Ink raw materials can be single chemical substances or mixtures of various chemical substances.

They contain one or several main substances which will have a specific function in the ink (for example as film forming resin, adhesion promoter, photoinitiator, solvent and colourant). These

substances are the reason why this specific raw material is used in the printing ink and are the needed IAS in the raw material and later the ink.

There may be other needed main components in the ink raw material, for example to bring the ink raw material into the provided form (for example solvents, biocides, defoamers). These substances may also be considered as IAS in the raw material and later the inks.

But besides these main components the raw materials may also contain other substances which will not have any specific function in the ink, for example residues from the production (monomers) or residues of catalysts, solvents or defoamer. Such substances are needed to produce the raw material, but they would not be needed in the printing inks. In the raw material production these substances are intentionally added, but in an ink they are not required and hence are not intentionally added substances. However such impurities are usually known due to the production process for the raw materials and should be declared in the supply chain to allow a risk assessment as they should be considered as “known NIAS” in the inks. For raw materials with several production steps involved, it is important that compliance information is passed along the supply chain. Furthermore the ink raw materials may contain other (usually unpredicted) substances, which for example may have been created by unexpected side-reactions (for example isomers), degradation reactions or just by cross-contamination. Such substances may also already be impurities of chemical materials used for the ink raw material production. These substances are clearly not intentionally added into the ink raw material and are “unpredicted NIAS” in both the raw material and the inks.

Raw Material selection

Due to the lack of harmonised legislation on inks the EuPIA members have agreed to the “Exclusion Policy for Printing Inks and related Products”⁷. The Good Manufacturing Practice (GMP) Printing Inks for Food Contact Materials² defines more requirements on the selection of ink raw materials.

Specific Migration Limit (SML)

According to EU legislation, specific migration limit (SML) means the maximum permitted amount of a given substance released from a material or article into food or food simulants. The SML is based on the safety evaluation of the substance by EFSA, taking into account information on the toxicity and the migration behaviour of the substance. In setting the SML, it is conventionally assumed that 1 kg of food containing the substance is consumed daily by a person with 60 kg bodyweight. It is assumed that the 1 kg of food is in contact with a plastic food contact material releasing the substance at the SML, and that the food contact surface area is 6 dm² per kg food (EU cube).

Tolerable Daily Intake (TDI)

Tolerable Daily Intake (TDI) is an estimate of the amount of a substance in air, food or drinking water that can be taken in daily over a lifetime without appreciable health risk. TDIs are calculated on the basis of repeat dose toxicity data to which uncertainty factors are applied, and usually expressed as mg/kg bodyweight/day. TDIs are used for substances that do not have a reason to be found in food (as opposed to substances that do, such as additives, which are assigned Acceptable Daily Intakes or ADIs).

4. Examples for IAS and NIAS in ink raw materials and inks

Water based ink based on a styrene acrylic dispersion polymer

During the production of the dispersion polymer the styrene and the acrylic monomers react to form the polymer. This polymer has the function of the film-forming resin in the ink and is IAS. The styrene-acrylic co-polymer may contain residual amounts of the starting monomers, but they are not needed in the ink, hence they are known NIAS (including catalysts). The water is part of the polymer dispersion, and is also an IAS since it has a function in both the raw material and ink. The polymer dispersion may also contain biocides and defoamers or coalescent which remain in the raw material as (unreacted) substances, i.e. they are IAS in the raw material. In the ink these additives may or may not have a function (usually additional defoamers, biocides etc. are used in the ink formulation which are clearly IAS in the inks), but in any case the additives are IAS in the ink raw material and so irrespective of whether they are IAS or NIAS in the ink they should therefore be declared to downstream users.

Example to show the principle:

Raw Material	Substances used in the raw material production	Status of substances in the ink raw material	Substances in ready ink raw material	Status of substance in the ink
Styrene acrylic dispersion	Styrene	IAS	Styrene-acrylic polymer	IAS
	acrylic acid		styrene and acrylic acid	NIAS
	Water	IAS	water	IAS
	Biocide	IAS	biocide	NIAS*
	Defoamer	IAS	defoamer	NIAS*
	Initiator	IAS	reactions products of initiator	NIAS
	Emulsifier	IAS	emulsifier	NIAS

* depending on the ink formulation, biocides and defoamers originating from the raw materials may sometimes have an intended function in the ink and in this specific case must be considered to be IAS

Water based ink based on dry styrene-acrylic resins

The styrene and the acrylic monomers react to form the polymer, for example in a solvent-based polymerization process. The residual amounts are known NIAS in the raw material. The solvents which have been used in the polymerization process should have been removed from the dry resin and residual amounts are known NIAS. Initiators or catalysts should have reacted - residual amounts are known NIAS; however, unknown NIAS may have been created from unintended side reactions. The polymer is the IAS of the raw material and intentionally used in the ink formulation (film forming resin).

Solvent based ink containing a PU resin solution

The starting polyols, isocyanate, chain extension amines, etc., react to form the polymer which is the key substance of the PU resin solution and which is used (IAS) in the ink. Residues of these starting substances from the PU resin production have no intended function in the ink and are NIAS. The solvent which has been used for the polymerization process and in which the resin is dissolved has a function (acts as solvent in the ink), and hence is an IAS. Residual amounts of polymerisation catalyst are considered as NIAS.

Pigments

The starting components react during the pigment production. Residual amounts do not have a function in the ink and are NIAS. The additives used to define the particle size of the pigment crystals in the pigment production (for example precipitation) are not needed and have no specific function in the ink so are NIAS. The additives to post treat (coat) the pigment crystal (for example to make it friendly for water based, solvent based or oil based systems) however have a specific function in the pigment and are considered to be IAS in the raw material and ink. However, in the existing regulations^{3,4} pigment additives are not in scope, so they may not be listed (NLS) and compliance needs to be demonstrated by a risk assessment.

5. Requirements for IAS and NIAS

To comply with the Swiss Ordinance polymers used as IAS in inks must be produced from listed monomers^{3,4}, and in cases where the molecular weight is above 1000 Dalton (for fluoropolymers 1500 Dalton) such polymers are considered not to migrate or be absorbed through the gastrointestinal tract. However, polymers may contain a low molecular weight (oligomeric) fraction, which should be also considered in the risk assessment process.

IAS used by EuPIA members in inks for FCM's and with a molecular weight less than 1000 Dalton should be listed in any official European or recognised national list (for example the Union list in (EU) No 10/2011³ or in Annex 1 or 6 of the Swiss Ordinance⁴). For such substances either a toxicologically derived specific migration limit (SML) into food exists or the legislation defines a regulatory non-detection limit (for non-CMR substances usually 0.01 mg/kg food^{3,4}).

NIAS can be divided into two groups, "known NIAS" and "unpredicted NIAS".

"Known NIAS" are usually added by the producer of an ink raw material during the production of the raw material as starting monomers, catalysts or process aids. Substances to initiate the polymerization process or to control the polymerization process (chain extension, transfer or termination) are currently not subject to a harmonized legislation. Usually such substances should no longer be present in the final polymer. Any "known NIAS" should be declared to downstream users to allow a risk assessment if there is evidence that such substances are still present in the raw material/inks at levels that could cause a non-compliance of the FCM.

"Unpredicted NIAS" may result from side reaction or degradation reactions, may be residues from previous production steps of the raw materials or can come from unintended cross-contamination in the production or handling of substances during the production of ink raw

materials or the ink itself. The chemical structure of such substances is often unknown and their presence unexpected. Such substances may or may not be listed in any official substance list. Their simple presence in raw materials or inks however does not mean that the raw material, ink or the printed material is not compliant to existing legislations (for example^{3,4}).

6. EuPIA recommendation for the identification of substances in ink raw materials and inks

EuPIA GMP² requires a raw material selection and approval process for the introduction of new raw materials. After completion of this process, information on every substance present in the raw material in quantities relevant for its intended use should be in place, including non-intentionally added substances (NIAS), to enable the ink formulator to conduct a risk assessment.

6.1. Information required from raw materials suppliers

Information from the supplier of the raw material is requested using the EuPIA Raw Material Compliance Questionnaire (2016), or equivalent, and shall include the following specific information on the suitability of raw material ingredients with regard to their use in FCM inks¹⁰.

Swiss Ordinance Confirmation: All intentionally used ingredients which are in scope of the Swiss Ordinance (substance used as such, or as monomer in a polymeric ingredient) should be listed in Annex 1 or 6 of the Swiss Ordinance.

Information on migratable substances (intentionally used substances, and NIAS which are known to be present):

- Every migratable substance with MW < 1000 g/mol shall be identified, including SML or restriction.
- In case of raw materials to be used in inks for Direct Food Contact applications, every substance used or known to be present must be disclosed, including monomers used in the manufacture of polymers, and independent of MW.
- Information on substances not intentionally used in the manufacture of the raw material which are known or can be expected to be present (such as traces of monomers or additives used, decomposition products, typical contaminants), including hazard information (if available).

For IAS and NIAS the raw material supplier shall give the following information to the ink manufacturer:

- The identity of the substance/s, or description of the type of substance/s (if not fully identified),
- Indication of max. quantity (or range),
- Indication of MW (if MW < 1000 g/mol)

The raw material supplier takes responsibility for any information that is withheld.¹⁰

6.2. Analytical Work: Screening for unpredicted NIAS

Depending on the completeness of the information from the supplier and the projected end-use, analytical work may be defined to screen for unpredicted NIAS in the raw material with the potential to migrate. Information from the raw material supplier as well as the rationale for defining the analytical work and its results shall be documented in the raw material evaluation and approval files.

Analytical work may be done in-house, at external laboratories, or by the supplier of the raw material. It may be part of the raw material specification.

The analytical method(s) selected must be suitable for the type of raw material in question.

Selection of analytical method/s, detection limit, and effort depends on the projected percentage of the raw material in the final printed FCM.

This work is intended to identify NIAS in raw materials, however it will normally not be possible to find or identify all NIAS.

7. EuPIA recommendation for hazard assessment methods

The advice provided in this Section is derived from the guidance and opinions issued by EFSA. [14.16.17](#) The greater the exposure through migration, the more toxicological information is required. The quantity of ink present in printed FCM is small (typically 120 mg per 6 dm² EU cube) and any exposure due to migration is unintentional; consumer exposure via this route is usually considerably lower (parts per million, or less) than from other uses of chemicals. Consequently, we believe it is more appropriate to follow EFSA, rather than ECHA, guidance on chemical risk assessment.

7.1 Toxicological Assessment

7.1.1 Listed and fully evaluated substances

For such substances, be they IAS or NIAS, the official SML values are applicable. For NIAS listed in Swiss Annex 6 B⁴ but toxicologically not evaluated a 10 ppb detection limit (in the food or food simulant) applies, as long as it cannot be shown by an accepted scientific method that a higher migration limit is safe. The Tolerable Daily Intake (TDI) can be derived from the SML by dividing by 60 (converting mg/kg food into mg/kg bodyweight) for comparison with the estimated exposure.

$$\text{SML [ppb (}\mu\text{g/kg food)]} = \text{TDI [}\mu\text{g/kg bw/day]} \times 60 \text{ [kg bw]} / 1 \text{ [kg food/day]}$$

7.1.2 Non listed substances for which toxicological data are available

If a substance has not been assessed or assigned a TDI or SML, it may still be possible to make a risk assessment depending on the extent of available toxicity data and toxicological expertise. The general approach is outlined in this Section, but it is expected that a level of expert knowledge is required. The most important step is to establish if the substance is genotoxic or has a genotoxic potential, since genotoxic carcinogens are considered to act via a

non-threshold mechanism (one-hit hypothesis). This typically requires data of acceptable quality to demonstrate absence of gene mutations and structural and numerical chromosome abnormalities. Negative results from a well-conducted bacterial gene mutation (Ames test) and an *in vitro* micronucleus assay would be sufficient – positive or equivocal results would need additional testing, typically *in vivo*.⁸

If a substance is determined to be genotoxic, then there is no safe use level – in such circumstances the exposure must be reduced to a level as low as reasonably practicable. The risk assessment is based not on demonstrating that the level of exposure is below an acceptable threshold, but by a determination of the likely number of additional adverse effects (cancer) in the population and deciding whether these constitute an acceptable level of risk – typically less than one case in one million is considered to be acceptable. This means that the exposure is linked to the potency and has to be extremely low.

A TDI is typically derived from an appropriate repeat dose toxicity study. Normally this uses the No Observed Adverse Effect Level (NOAEL) or the Bench Mark Dose Lower confidence limit (BMDL) as a point of departure, to which uncertainty factors (also known as assessment factors and safety factors) are applied. These uncertainty factors are used to allow for extrapolation from the test species (usually rat or mouse) to humans (interspecies), and for individual variation amongst the human population (intraspecies). Typically these two factors are both set at 10 (resulting in a total uncertainty factor of 100), although specific knowledge about toxicokinetic or toxicodynamic effects can be used to set different values. Additional factors are used to allow for data gaps or inadequacies, read across, data quality, etc. With appropriate expertise, it is possible to calculate a self-derived TDI, which can then be used to calculate a self-derived SML, if required.

$$\text{TDI} = \text{NOAEL or BMDL} / \text{composite uncertainty factor}$$

$$\text{composite uncertainty factor} = \text{UF}(\text{interspecies}) \times \text{UF}(\text{intraspecies}) \times \text{UF}(\text{data gaps}) \times \text{UF}(\text{data quality}) \times \text{UF}(\text{etc.})$$

$$\text{SML}_{\text{self-derived}} (\text{mg/kg food}) = 60 (\text{kg body weight}) * \text{TDI} (\text{mg/kg body weight/day}) / 1 \text{ kg food/day}$$

As a consequence of the EU REACH Regulation, many substances now have toxicity data, which can be found on the ECHA website (<https://echa.europa.eu/>). Although the information is only in the form of a robust study summary, rather than the actual toxicity test study report itself, this is usually sufficient for the purposes of risk assessment. In addition to the toxicity information, various Derived No Effect Level (DNEL) values are also available. In principle, these DNELs also represent a tolerable daily intake, but it is important to understand that the basis for their derivation may be significantly different – reflecting the differences in the guidance and approach between EFSA and ECHA. DNELs are derived based on available data, which may be inadequate, or insufficient to make an assessment for use as a food contact material. Furthermore, DNELs are specific exposure thresholds for a targeted population. For that reason different DNELs could be available for the same substance and same exposure

pathway. However, a number of DNELs are based on extensive datasets of good quality, with appropriate selection and justification of uncertainty factors, and after suitable assessment and evaluation, could be used as a surrogate TDI.

7.1.3 Substances without toxicological data

Although having data is always preferable to not having data, it may be easier, and require much less toxicological expertise, when there is little or no relevant data available. As above, it is important to establish first if the substance has a genotoxic potential. If there is data from suitable mutagenicity testing, then this can be used, but if incomplete or absent, there are several adequate (Q)SAR models which can be used to check for any structural alerts for genotoxicity. The open source software ToxTree contains in vitro mutagenicity (Ames test) alerts by ISS, carcinogenicity (genotox and nongenotox) and mutagenicity rulebase by ISS, structure alerts for the in vivo micronucleus assay in rodents and DNA binding alerts. In addition, Annex III of REACH, available on the ECHA website, consists of a compilation of (Q)SAR predicted toxicities for some 65,000 substances which are due to be registered by 2018, including genotoxicity/carcinogenicity alerts, where applicable. If there is a structural alert for genotoxic potential, it is important to obtain test data which adequately demonstrates that the substance is not genotoxic.

The current EFSA guidance regarding submission of substances for evaluation as food contact materials indicates that a SML of 0.05 mg/kg food is acceptable for substances which are not genotoxic.¹⁷ Such substances may additionally be suitable for assessment using the Threshold of Toxicological Concern (TTC) approach, which can be applied to substances of known chemical structure to which there is low human exposure, but for which there are few or no toxicity data.^{11,12,13,14} It utilises generic human exposure threshold values (also called TTC values) that have been established for substances grouped according to their chemical structure and likelihood of toxicity. There is a range of human exposure threshold values that have been developed based on data from extensive toxicological testing in animals, covering both cancer and non-cancer endpoints. Application of the TTC approach requires only knowledge of the chemical structure of the substance concerned and information on human exposure, for which there is confidence that it is not an underestimate.

The TTC concept has its origin in one of the fundamental principles of toxicology, that toxicity is a function of dose and duration of exposure. For toxicity endpoints with a threshold, when comprehensive, substance-specific toxicity data are available, they usually allow risk assessors to identify a dose or exposure, below which no adverse effects of the substance can be detected, i.e. there is an exposure that is so low that the probability of adverse effects is low and no further data are necessary. The classification and grouping of chemicals according to chemical structure is an essential component of the TTC approach. EFSA considers that the application of the Cramer classification scheme in the TTC approach is conservative and therefore protective of human health.¹⁴

The TTC value for Cramer Class II is not well supported by the presently available databases and therefore substances that would be classified in Cramer Class II under the Cramer decision

tree should be treated as if they were Cramer Class III substances. In addition, the TTC approach should not be used for the following (categories of) substances:

- a. High potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines)
- b. Inorganic substances
- c. Metals and organometallics
- d. Proteins
- e. Steroids
- f. Substances that are known or predicted to bioaccumulate
- g. Nanomaterials
- h. Radioactive substances
- i. Mixtures of substances containing unknown chemical structures

The Cramer decision tree is automated in the open source application ToxTree.

Chemical structure	Exposure Threshold [µg/kg bw/day]	Exposure Threshold [µg/person/day]	SML _{TTC} [µg/kg food]
Structural alert for genotoxicity (including metabolites)	0.0025	0.15	0.15
Organophosphate or carbamate	0.3	18	18
Cramer Class III	1.5	90	90
Cramer Class II*	9	540	540
Cramer Class I	30	1800	1800

* Due to limited data supporting the Cramer Class II the use of this group is disputed. Besides the proposal of EFSA to evaluate under the Class III TTC threshold all the chemicals categorized as Class II ¹⁸, an EFSA/WHO expert group recommended that Cramer Class II continues to be used and applied to the TTC approach ¹⁴. A change of the decision scheme and the merge of different non-cancer databases has been proposed 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 can be expected in the future.

Calculation of a TTC-based SML can be done taking the relevant TTC exposure threshold into consideration:

$$\text{SML}_{\text{TTC}} \text{ (mg/kg food)} = 60 \text{ (kg body weight)} * \text{exposure threshold (mg/kg body weight/day)} / 1 \text{ kg food/day}$$

7.2 Consumer Exposure Assessment

Consumer exposure assessment shall be used to define the amount of a non-listed substance a person may be exposed to in a certain population. It should be mentioned that consumers may be exposed to substances via various routes and not only from FCM's.

EuPIA recommends to use two approaches, the EFSA Food Consumption database and FACET.

7.2.1 EFSA Food Consumption database in conjunction with migration data

In order to get a realistic consumption scenario it is important to use the correct data from the database. Due to the broad variation of food consumption in the various countries and also consumer groups, it is not possible to give a general recommendation on how to filter the data. The highest food consumption data should be used, depending on the setting of the filters (country, consumer group, food type), to be on the safe side. As consumption data the "Mean consumption in grams/ kg body weight per day" and the "95th percentile of consumption in grams/ kg body weight per day" shall be used. The 95th percentile consumption is normally the value used by regulators to represent the worst case for a high level consumer, and the chronic dataset is used for assessing ongoing repeated exposure. The acute dataset would be more appropriate for assessing isolated, one-off exposures.

7.2.2 FACET tool

FACET is still under development and in the future EuPIA plans to use this tool for exposure assessment.

8. EuPIA recommendation for the final risk assessment for non-listed NIAS

In the final risk assessment step the consumer exposure data in the daily diet (EDI – Estimated Daily Intake) shall be compared with the maximum tolerable exposure levels based on toxicological assessment data. If the EDI is:

$$EDI_{\text{substance}} < TDI \quad \text{or}$$

$$\text{Specific migration is} < SML \quad \text{or} \quad SML_{\text{self derived}} \quad \text{or} \quad SML_{TTC}$$

it means the substance coming from that FCM is not a concern in this application.

However EuPIA members can only communicate adequate information to allow downstream users to do their risk assessment and demonstrate the safety of the final FCM. Also for NIAS parameters like handling of the ink, the final application (for example drying and curing), applied dry weight and packaging design may play a major role but cannot be controlled by the ink producers.

9. EuPIA Reporting format to downstream users

Migratable substances present in the dry ink film which are sufficiently evaluated to have an official SML (for example in^{3,4}) will be declared by EuPIA members to the downstream users by a Statement of Composition⁹. In order to allow the downstream users to demonstrate compliance with existing regulations for the final FCM, EuPIA members give detailed information about the chemical nature of the substance (description, CAS-, FCM-, E- or FL-number, existing migration limit and the amount of the substance in the dry ink film (“Customer Guidance Note for using ink Statements of Composition (SoC) when considering compliance of food packaging”⁹ and the “Explanatory note for suppliers of ink raw materials regarding regulatory compliance of printed food packaging”¹⁰).

The SoC also shall contain relevant information about known NIAS in the printing inks. As the processing of the inks, the packaging design and other parameters are not under control by the ink suppliers, the ink supplier cannot take responsibility for the conformity of the final FCM. Therefore, in the SoC the safety for any NIAS or NLS can be only given exemplarily. Such exemplary safety demonstration may be based on SML’s if available, or can be based on exposure data in comparison on (self-derived or TTC based) TDI’s. The information is given in the SoC to allow the downstream user to do the necessary risk assessment, by either worst-case calculation, modelling or migration testing.

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References

- 1 REGULATION (EC) No 1935/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC, Official Journal of the European Union, L 338/4 13.11.2004
- 2 Good Manufacturing Practice (GMP) Printing Inks for Food Contact Materials, 4th completely revised version, EuPIA, March 2016
<http://www.eupia.org/index.php?id=29>
- 3 COMMISSION REGULATION (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food, Official Journal of the European Union, L 12/1, 15.01.2011
- 4 Ordinance of the FDHA on Materials and Articles (SR 817.023.21), Eidgenössisches Departement des Innern (EDI), 23.11.2005
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- 17 Guidance document on the submission of a dossier on a substance to be used in Food Contact Materials for evaluation by EFSA by the Panel on additives, flavourings, processing aids and materials in contact with food (AFC), EFSA Journal, 31.07.2008
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- 18 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
www.efsa.europa.eu/publications

Attachment 1: EuPIA recommendation for risk assessment tools

EuPIA recommends to use the following publicly available tools for the risk assessment.

Chemical drawing & substance naming software*

<http://www.acdlabs.com/resources/freeware/chemsketch/>

*only free for private persons, may not be free for companies

Software for calculating log Octanol/Water partition coefficient

<http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface>

EFSA food consumption database

<http://www.efsa.europa.eu/en/food-consumption/comprehensive-database>

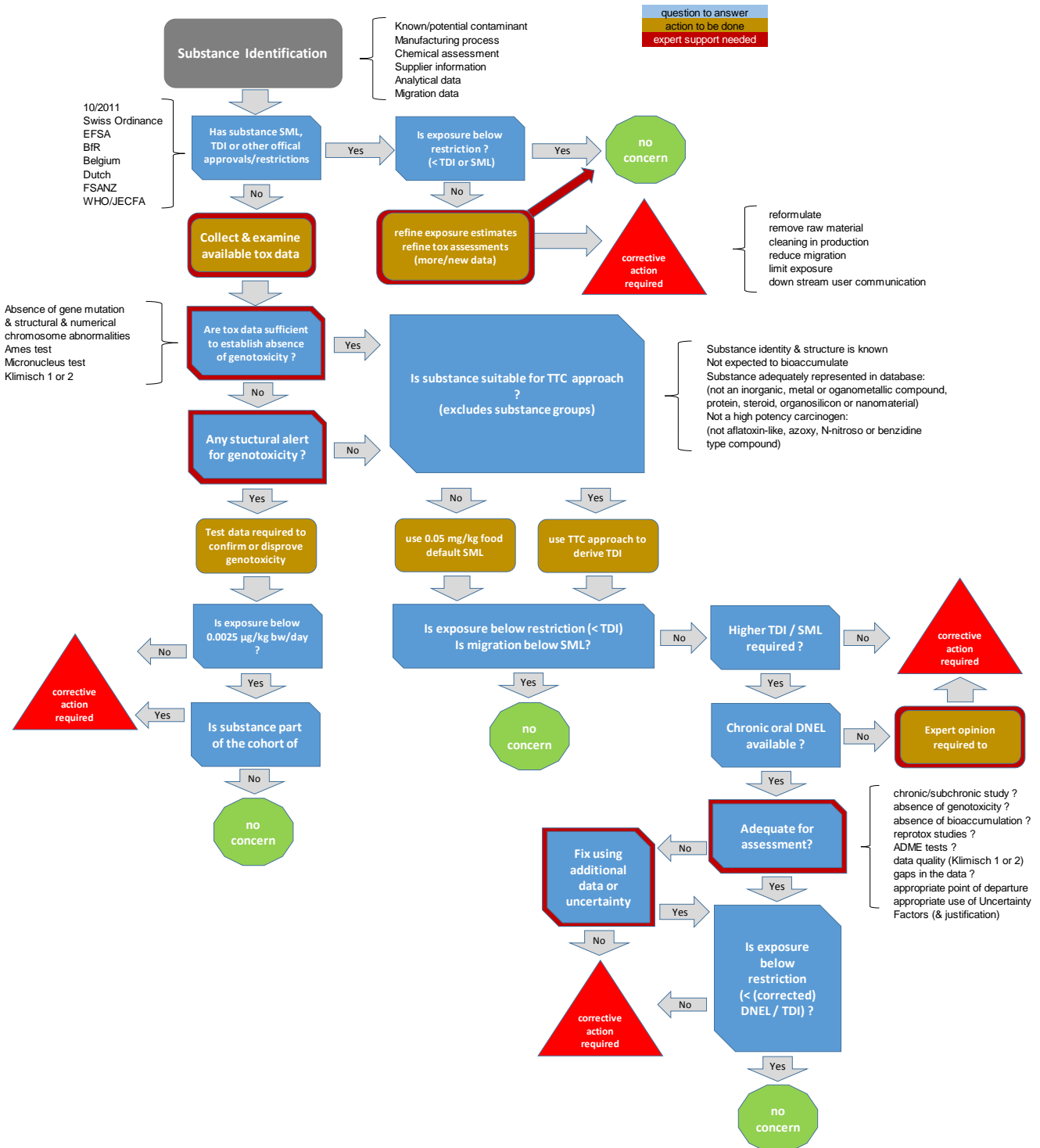
FACET exposure assessment tool

<http://www.cremeglobal.com/modelling-software/facet-download>

Toxicological assessment tool

<http://sourceforge.net/projects/toxtree/>

Attachment 2: Flow Chart of the EuPIA Risk Assessment Approach



Attachment 3 – Risk Assessment Steps and Questionnaire

1. Identification of the substance
 - a. Chemical structure
 - b. Molecular weight
 - c. CAS number if available
 - d. SMILES
 - e. Log Octanol/water partition coefficient

2. Information about the packaging material and types in which the substance is used
 - a. Structure of packaging material
 - b. Type of packed food
 - c. Ratio weight of packed food versus size of packaging material
 - d. Consumer type for this food (infant, adult, toddlers)
 - e. Concentration of substance in (the layers of) the packaging materials

3. Migration results for the substance
 - a. Worst Case Calculation
 - b. Data from Migration measurements or modelling

4. Exposure results for consumers based on step 2
 - a. EFSA food consumption database
EuPIA recommends to use the following settings:
 - i. Use “Acute food consumption statistics, all days”
 - ii. Level 2_all days
 - iii. Select the relevant country or search for all countries
 - iv. Select the relevant consumer group (infants, toddlers, adults) or use all
 - v. Mean consumption in grams/ kg body weight per day and
 - vi. 95th percentile of consumption in grams/ kg body weight per day

The highest food consumption data (point v. and vi.) should be taken depending on the setting of the filters to be on the safe side.

b. FACET

FACET is still under development and in the future EuPIA plan to use this tool for exposure assessment.

The results of the migration evaluation (step 3) must be multiplied with the food consumption data (step 4) to get the consumer exposure data.

Consumer exposure ($\mu\text{g}/\text{kg}$ bw per day) = migration (mg/kg) * food consumption (g/kg bw per day)

5. Hazard assessment of the substance based on existing toxicological data

- a. REACH database
- b. Other sources

if data are available (DNEL, NOAEL) assess the suitability and derivation of the data and if ok jump to step 8

6. Hazard assessment via Threshold of Toxicological Concern (TTC) approach

- a. Not of a family that is unsuitable
- b. Not highly reactive
- c. Not obviously bio-accumulative
- d. No obvious structure alerts
If above questions are answered "OK" then test suitability for TTC using ToxTree decision trees
- e. Carcinogenicity (genotoxic and non-genotoxic) and mutagenicity rule base by ISS¹⁵
- f. In vitro mutagenicity (Ames test) alerts by ISS¹⁵
- g. DNA binding Alerts
- h. Protein binding Alerts
- i. Structure Alerts for the in vivo micronucleus assay in rodents

If no alerts appear then include justification to continue in step 7.

If one or more alerts appear than cross-reading with the properties of a similar molecule may be possible. For this cross-reading usually deeper toxicological knowledge is necessary.

7. Hazard assessment result

If step 6 shows no alerts, or a cross-reading with a similar substance allows to use the tiered TTC approach, then the substance can be considered in one of the 3 Cramer Classes, with respective NOAEL, Exposure Threshold or derived SML value (see section 7.1.3 of the Guideline).

8. Final Risk Assessment

The results of the consumer exposure evaluation (step 4) have to be compared with the results of the hazard assessment of the substance (step 5, 6, 7).

The consumer exposure must be lower than the tolerable daily intake (TDI).

$EDI_{\text{substance}} < TDI$ or

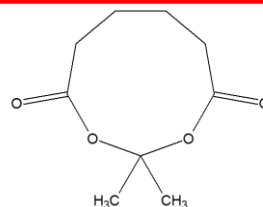
Specific migration is $< SML$ or $SML_{\text{self derived}}$ or SML_{TTC}

Then the substance can be considered to be safe in the evaluated application.

Attachment 4: Risk Assessment - Example

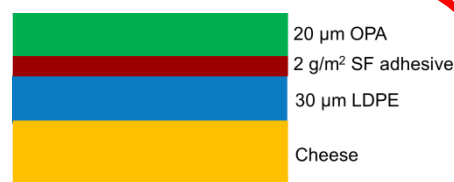
Section 1 Information about the substance.

Chemical structure	2,2-dimethyl-1,3-dioxonane
Molecular weight	186 (C ₉ H ₁₄ O ₄)
SMILES Ref	<chem>O=C1CCCCC(=O)OC(C)(C)O1</chem>
CAS Number of substance (if one exists)	Not Known
Log Octanol / Water partition coefficient (Kow)	
From literature reference	
From structure calculation (EPI Suite)	4.76



Section 2 Information about the structure in which the substance is used

Indicate layers and starting concentration of substance in each layer.



800 ppm Cyclic Oligomer is present in the adhesive layer

Indicate the likely pack geometries and pack surface area to food weight.

1 Kg cheese wrapped in 0.06 m² of packaging.

Indicate the basis for the exposure calculation.

- Migration Worst Case Calculation and EFSA Food Consumption database.
 - 95th% 0.17 µg/Kg bw/day
- Migration modelling and EFSA Food Consumption database.
- Migration testing and EFSA Food Consumption database.
- FACET
 - 95th% 0.00176 µg/Kg bw/day For existing laminated cheese packaging
 - 95th% 0.55 µg/Kg bw/day For all laminated packaging

Ideally pick more than one from the list above.

Section 3 Migration results

Indicate the migration data obtained (mg substance migrating into food / m² food contact material)

0.096 mg/Kg food migration (WCC)

0.0955 mg/Kg food migration (migration model) – conclusion, most of the substance migrates into food.

Section 4 Exposure results

Indicate the food types considered, the dietary surveys used and the exposure results, include both the mean and 95th percentile results.

Food: All Cheese

Consumption database: EFSA Acute food consumption statistics, All Days, L2, UK

(also compared to FACET consumption database for UK 19-64 yr olds)

Mean exposure = 0.69 g/day x 0.096 mg/Kg food = 0.066 µg/Kg bw/day

95th% exposure = 1.77 g/day x 0.096 mg/Kg food = 0.170 µg/Kg bw/day

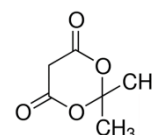
Section 5 Hazard Assessment – Search for available toxicological data for substance, or very similar substances (Read Across).

Data from ECHA No data on substance found

Data from other sources No data on substance found

Some data found on substance with similar structure

CAS Number 2033-24-1, Mol Wt 144 – confirmed not CMR.



Genotoxicity studies, 90 day studies, Accumulation studies, ADME (Adsorption / Distribution / Metabolism / Excretion) studies, Developmental studies, Long term studies, Carcinogenicity studies

Section 6 Hazard Assessment – Confirmation that using TTC approach is valid.

Data to suggest that substance is:

- No obvious structure alerts ✓
- Not obviously bio-accumulative ✓
- Not of a family that is unsuitable ✓
- Not highly reactive ✓

If above Ok then test suitability for TTC using ToxTree decision trees

- Carcinogenicity (genotox and nongenotox) and mutagenicity rulebase by ISS ✓
- In vitro mutagenicity (Ames test) alerts by ISS ✓
- DNA binding Alerts ✓
- Protein binding Alerts ✓
- Structure Alerts for the in vivo micronucleus assay in rodents **X**

One structure alert QSA34, H-acceptor path3-H-acceptor

If any alerts then include justification to continue.

Justification to continue based on non-CMR nature of similar molecule, see section 5.

Section 7 Hazard Assessment result

Allowed maximum ($\mu\text{g}/\text{Kg}$ bw day)

Using Cramer rules, with extensions, molecule is classified Cramer Class III (high) = 1.5 $\mu\text{g}/\text{Kg}$ bw /day

Section 8 Risk Assessment – Comparison of Exposure and Hazard assessments.

Include the Margin of safety.

95th% exposure = 0.170 $\mu\text{g}/\text{Kg}$ bw/day

Maximum allowed exposure = 1.5 $\mu\text{g}/\text{Kg}$ bw/day

Risk characterization ratio is: 8.8 times (must be > 1)

State final conclusion

The presence of this molecule in lamination adhesives for cheese packaging does not pose a risk to human health

