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

Starting remarks:
The following document has been developed and endorsed by the EuPIA Packaging Inks for Food (PIFOOD) committee and should be understood as guidance for members and provides a methodology for the evaluation of substances used in Food Contact Material (FCM) inks and the Risk Assessment of migratable substances in such inks.

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 Regulation[1] applicable to all 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"[2,5]. Here 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 migrating 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 in order to allow them to create the Declaration of Compliance for the final packaging material.
Many substances used in printing inks for FCM have not been evaluated by an official authority. In addition, printing inks may still contain small amounts of substances which are not-intentionally added, for example from previous production steps, reaction products (e.g. from drying, crosslinking or curing of the inks or reaction with other packaging components) or from 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 and Non-Evaluated on Non-Listed substances 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 printed materials and articles intended for food contact.
Regulation (EC) No 1935/2004[1] 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 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 10/2011[3] 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 Regulation[16] 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 additives/flavourings, then the relevant restrictions such as SML or QM must be met.

Some national authorities have also evaluated substances for use in FCMs to support their national (non-harmonised) legislation. Whilst such evaluations, and any restrictions, may only apply to that country or FCM, they may be helpful when assessing the risk from migrating print components.

Regulation (EC) No 2023/2006[5] 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 Materials[2].

Article 19 of the Regulation (EU) No 10/2011[3] requires that the compliance of substances which are not covered by an inclusion in Annex I shall be assessed in accordance with internationally recognized scientific principles on Risk Assessments to be compliant with Article 3 of the Framework Regulation. The risk assessment includes hazard identification, hazard characterisation, exposure assessment and risk characterisation[6].

The responsibility for the compliance of the final FCM remains ultimately with the downstream partners. To enable shared and final responsibilities, 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 as well as 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) and FCM ink

FCM according to this paper refers to the printed packaging material. An “FCM ink” is intended to be used to print Food Contact Materials. Usually the FCM 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 FCM 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 guidance is also suitable for intended DFC inks.

Intentionally Used Substances

This covers all chemical substances which are intentionally used in the production and use of the printing ink and which have an intended and specific function within the final ink and without which the performance of the ink 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 (IAS).

Non-Intentionally Added Substances (NIAS)

Substances and raw materials used in the manufacture of printing inks may contain impurities originating from their manufacturing or extraction process. These impurities are non-intentionally added (NIAS) but present in the substance which is intentionally used in the manufacture of the printing ink. Further, during the manufacture and use of printing inks reaction and degradation products of used substances can be formed. These reaction and degradation products are non-intentionally present in the printing ink (NIAS).
As far as the impurities in the substances and raw materials intentionally used and the main reaction and degradation products in the intended application of the printing ink are relevant for the risk assessment for the final printed FCM these substances should be considered and risk assessed.

The presence of NIAS in printing inks is usually unavoidable; these substances are present only in very small quantities and they do not have an intended and specific function within the ink formulation.

Impurities from the raw material production processes are usually known 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 (e.g. isomers), degradation reactions or just by cross-contamination. Such substances could be themselves 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.

Non-Evaluated or Non-Listed Substances (NLS)
NLS are substances which are not required to be listed according the current FCM legislation and in many cases not yet officially evaluated. According to the current legislation printing inks for FCM may contain substances which are not listed or fully evaluated. The safety of such substances needs to be demonstrated in accordance with internationally recognised scientific principles on Risk Assessment. [3]

Raw materials for printing inks
Inks are made from various types of raw materials. Such raw materials may be single substances or complex mixtures of substances. The substances used in such mixtures are added in order to provide certain properties in the ink or print. In addition to these substances with an intended function, such raw material mixtures may also contain small amounts of impurities, residual starting substances etc. which are considered to be NIAS.

The polymers which are used in FCM inks as binder are usually not falling in the scope of the definition of a "plastic material" under the Regulation (EU) No 10/2011[3]. For monomers not yet officially evaluated (NLS) the approach which is described in this guidance should be used for the risk assessment. Polymers may also contain a low molecular weight (oligomeric) fraction, which should be also considered in the Risk Assessment process.

In inks pigments are used as insoluble and inert coloured particles (crystals) which are dispersed in the polymeric ink matrix and bound in the dry print. The pigment chemistry is very complex, and many different substances are needed to produce them. These starting substances should not remain in the pigment, but are unavoidable impurities (NIAS), typically in a ppm range. Due to their crystal structure and insolubility pigments are not considered to be migratable, but the impurities from the pigment syntheses may have the potential to migrate.

Additives may have many functions in FCM inks. For example, they help to create the needed mechanical properties of the print (scratch, rub, slip, anti-blocking, flexibility); they improve the ink adhesion on the printed substrate; they improve gloss and heat resistance and they are also used to reduce antistatic effects or solvent retention.

Additives may be of varying nature: monomeric, polymeric, organic or inorganic. The additives which are used by the ink manufacturer are often mixtures of various substances. Substances used in the additives for printing inks are often not used in other FCMs and hence often not yet officially evaluated (NLS). For substances used in additives which are not yet officially evaluated, the approach which is described in this guidance should be used for the Risk Assessment.

Solvents could be needed in the FCM ink in order to bring all components in a suitable liquid form which is needed for the specific print technology. For solvents remaining in the ink film and not yet officially evaluated the approach which is described in this guidance should be used for the Risk Assessment.

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 repeated dose toxicity data to which uncertainty factors are applied, and usually expressed as mg/kg_{bw}/day (bw = bodyweight). 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).

A TDI is typically derived from an appropriate repeated dose toxicity study. Normally this uses the No Observed Adverse Effect Level (NOAEL), to which Assessment Factors (also known as uncertainty factors, safety factors, extrapolation factors or protection factors) are applied. These 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 assessment factors are used to allow for exposure duration, exposure routes, read across, data quality, data gaps or inadequacies, 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.

$$\textbf{Total Assessment Factor} = AF_{interspecies} \times AF_{intraspecies} \times AF_{duration} \times AF_{read\ across} \times AF_{other}$$

$$\textbf{TDI} = \textbf{NOAEL} / \textbf{Total Assessment Factor}$$

Derived No Effect Level (DNEL)

DNEL's describe the levels of exposure to the substance above which humans should not be exposed and has been introduced in Annex 1, number 1.0.1 of the REACH regulation.

DNELs are derived based on available data, which may be inadequate, or insufficient to make an assessment for the use as a FCM. 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.

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. Some expert knowledge is usually needed in order to judge if sufficient assessment factors have been used to derive the DNEL.

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 a 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 a person with 60 kg bodyweight consumes daily 1 kg of food containing the substance. Moreover, it is assumed that the 1 kg of food is in contact with a plastic FCM releasing the substance of the SML and that the food contact surface area is 6 dm^2 per kg food ("EU cube").

$$\textbf{SML (ppb) } [\mu g/kg_{food}] = \textbf{TDI } [\mu g/kg_{bodyweight}\ /day] \times 60\ [kg_{bodyweight}] / 1\ [kg_{food}/day]$$

Genotoxicity
Genotoxicity is a broad term for the ability of chemical substances to impair genetic material regardless of related mechanisms.
Mutagens are substances that permanently change the DNA which can cause damages in the genetic information and finally can lead to cancer.
Clastogens are agents inducing structural chromosome aberrations via chromosome breaks that end up in gain, loss or rearrangement of chromosomal segments. Clastogenic effects may also become cancerous.
Aneugens are agents inducing numeric chromosome aberrations resulting in an abnormal number of chromosomes.

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

EuPIA GMP[2] 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.

4.1. Information required from raw material 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 inks[10].

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

- Every migrating substance with MW < 1000 Dalton shall be identified, (or description of the type of substance(s) if not fully identified), including SMLs or restrictions.
- Indication of the maximum concentration in the raw material
- 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).

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

4.2. 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 depend 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.

5. EuPIA recommendation for hazard assessment methods

The advice provided in this section is derived from the guidance and opinions issued by EFSA[14,16,17,18,19]. 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 dm^2 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.

5.1 Toxicological Assessment

5.1.1 Listed and fully evaluated substances

For these substances, including NIAS, the official SML values are applicable. Such migration limits can be taken from:

- Regulation (EU) No 10/2011 and amendments
- Listed substances in Part A of the Swiss Ordinance SR 817.023.021[4]
- Officially evaluated substances on national authority level according to the EFSA requirements

The Tolerable Daily Intake (TDI) can be derived from the SML, which is usually given in these documents by dividing by 60 (converting $\mu g/kg_{food}$ into $\mu g/kg_{bodyweight}$) for comparison with the estimated exposure.

$$\textbf{TDI } [\mu g/kg_{bodyweight}\text{ /day}] = \textbf{SML (ppb) } [\mu g/kg_{food}] \;/\; 60\ [kg_{bodyweight}] \;/\; 1\ [kg_{food}\text{/day}]$$

5.1.2 Substances for which toxicological data are available but which are not fully evaluated

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. 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 mutagenic, then there is no safe use level – in such circumstances the exposure must be reduced to a level as low as reasonably achievable (ALARA principle). The Risk Assessment is then 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 a tolerated level of risk – typically less than one case in one million is considered to be tolerable. This means that the exposure is linked to the severity of the adverse effect and has to be extremely low.

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 a Risk Assessment.

The first step of a Risk Assessment for substances for which toxicological data are available (for example in the ECHA database) is to check if sufficient data are present to exclude genotoxicity. If this is the case, repeat dose toxicity data/studies (preferred via oral consumption) provide a NOAEL from which with sufficient assessment factors a TDI can be derived. Typically, the NOAEL shall be derived with a 90 day subchronic oral consumption study with good reliability (Klimisch score 1 or 2). If only other endpoints (like LOAEL etc) are available, or only data from shorter studies, read across data etc. are available the data may be also suitable, but more expertise is needed to make a sound decision and to select sufficient conservative assessment factors. For substances like organo-phosphates also other endpoints, like neurotoxicity, must be checked.

If a DNEL from repeat dose toxicity studies (preferred via oral consumption) for general population is available and derived with sufficient conservative assessment factors the DNEL may be used instead of the self-derived TDI. The self-derived specific migration limit can be calculated with the following formula:

$$\mathbf{SML_{self\text{-}derived}\ (\mu g/kg_{food}) = TDI_{self\text{-}derived}\ (\mu g/kg_{bw}\ /day) \times 60\ (kg_{bw}) / 1\ (kg_{food}/day)}$$

The tiered approach of EFSA for toxicity testing requires for a human exposure of more than 80 µg/kg bw per day (i.e. SML 5 ppm) additional data, such as studies on ADME, reproduction and developmental toxicity and in more than one species. In situations where this data is not available the self-derived SML based on ECHA data should not exceed 5 ppm.

For many substances in the ECHA database studies are available which allow to exclude genotoxicity, but no reliable data based on repeated dose toxicity studies are available. In such cases the data on genotoxicity can be used and the TTC approach (chapter 5.1.3) should be used to define a Cramer Class and use the TDI limits of that Cramer Class.

5.1.3 Substances missing toxicological data

The most important step is to establish, if the substance is genotoxic in terms of DNA reactivity which can lead to mutations potentially being the first step in carcinogenesis. Such types of mutagenic 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. Negative results from a well-conducted bacterial gene mutation (Ames) test would be sufficient – positive or equivocal results would need additional testing, typically *in vivo*[8]. Other types of genotoxicants which do not act via a mutagenic mechanism typically have threshold mechanisms. Therefore, they generally do not pose a cancer risk at impurity levels.

If there are data from suitable DNA reactive mutagenicity testing available, then these can be used. But if the mutagenicity data are incomplete or absent, there are several adequate (Q)SAR

models which can be used to check for any structural alerts for DNA reactivity. However, the EFSA "*Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment"* requires that DNA reactivity should not be checked with one model alone. This additional information could be in the form of read across from structurally similar chemicals, which requires a high level of toxicological expertise or the use of at least a second independent (Q)SAR model, which is based on a different training set or algorithm used to develop the models. The use of a combination of rule-based and statistical-based (Q)SAR software is one of the preferred options proposed in the EFSA guidance document.[19]

There are several (Q)SAR software tools available, which allow to predict the DNA reactivity of a substance. Potential applicable alerts are:

- in vitro mutagenicity (Ames test) alerts by ISS (ToxTree)
- mutagenicity in vitro (Sarah Nexus)
- bacterial mutagenicity OECD 471 (CaseUltra)
- bacterial mutation alerts (Leadscope)

In addition, Annex III of REACH, available on the ECHA website, consists of a compilation of (Q)SAR predicted toxicities for some 33.000 substances, including genotoxicity or carcinogenicity alerts, where applicable

If there is a structural in silico alert, it is important to obtain experimental test data or sufficiently sound evidence (as already outlined above) which adequately demonstrates that the substance is of no concern.

If a substance is not genotoxic, it may additionally be suitable for assessment using the Threshold of Toxicological Concern (TTC) approach. This can be applied to substances of known chemical structure where there is low human exposure and few or no toxicity data available[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, if 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 into the Cramer Classes 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, 19].

If absence of mutagenicity is the only information available, the applicable limit should be no higher than Cramer Class III (corresponding to self-derived SMLs up to 90 ppb). For the use of

Cramer Class II and I clastogenicity must be excluded, which requires experimental data. A check list on suitable experimental methods can be found in attachment 4.

Although the TTC value for Cramer Class II is based on very few substances, the latest advice from EFSA and WHO is that the Cramer Class II can continue to be used and applied to the TTC approach [19]. The domain of applicability of TTC has to be taken in consideration. The Cramer decision tree is automated in the open-source application ToxTree. It is recommended to use the decision tree „Cramer Rules with Extensions“ in ToxTree.

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

$SML_{self\text{-}derived}$ (µg/kg_{food}) = Exposure Threshold (µg/kg_{bw} /day) x 60 (kg_{bw}) / 1 (kg_{food}/day)

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

5.2 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 using two approaches, the EFSA Food Consumption database and FACET.

5.2.1 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_{bw} per day" and the "95th percentile of consumption in grams / kg_{bw} 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.

5.2.2 FACET tool

FACET is a software tool that can be used for exposure assessment. It uses migration modelling and dietary survey data, along with databases of pack surface area to food weight ratios, packaging structures, and substances used in the different packaging materials, in order to create a more accurate exposure assessment.

However, some country dietary survey information is missing in FACET, and the data for substances in FCM is aging and so FACET is not always the default tool for exposure assessment.

6. EuPIA recommendation for the final Risk Assessment for non-listed NIAS

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

The final Risk Assessment step must consider the consumer exposure data in the daily diet.
The EU default approach considers a food consumption of 1 kg food per person, day and lifetime. Based on this approach the SML is calculated. If the migration of a substance into the food is below the SML there is no concern for that substance in that application.

$$\text{Specific migration is} \quad < \quad \text{SML or SML}_{\text{self-derived}}$$

In case more realistic food consumption data are available (for example from the EFSA food consumption database or FACET) the Estimated Daily Intake (EDI) can be calculated with the concentration of the substance in the food (for example from migration testing) and the real food consumption. However, it must be considered that the consumer may be also exposed to this substance by other routes. The EDI can be compared with the maximum tolerable daily intake levels (TDI) based on the toxicological assessment. If the EDI is:

$$\text{EDI}_{\text{Substance}} \quad < \quad \text{TDI or TDI}_{\text{self-derived}}$$

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

7. EuPIA Reporting format to downstream users

Migrating substances present in the dry ink film, which are sufficiently evaluated to have an official SML will be declared by EuPIA members to the downstream users by a Statement of Composition[9]. 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 potentially migrating known NIAS and NLS in the printing inks. In the SoC the safety for any NIAS or NLS can be only given exemplarily, for example by a worst-case calculation based on the EU default assumption. Such exemplary safety demonstration may be based on SML's if available or can be based on exposure data in comparison on (self-derived based on toxicological data or TTC based) TDI's.

However, 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, the information in the SoC shall allow the downstream user to do the necessary Risk Assessment, by either worst-case calculation, modelling or migration testing for the final printed packaging material.

EuPIA, 2017-01-20
1st amendment 2017-08-10
2nd amendment 2019-02-28
3rd amendment 2020-03-12
4th amendment 2020-08-14
5th amendment 2021-05-11

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 intended to come into contact with foodstuffs (SR 817.023.21), Eidgenössisches Departement des Innern (EDI), 16.12.2016
https://www.admin.ch/opc/de/classified-compilation/20143393/index.html

5 COMMISSION REGULATION (EC) No 2023/2006 of 22 December 2006 on good manufacturing practice for materials and articles intended to come into contact with food, Official Journal of the European Union, L 384/75, 29.12.2006.

6 ILSI Europe, Guidance on best practices on the risk assessment of non-intentionally added substances (NIAS) in food contact materials and articles, July 2015
http://www.ilsi.eu

7 Exclusion Policy for printing inks and related products, 3rd edition, EuPIA, November 2016
http://www.eupia.org/index.php?id=3

8 Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment, EFSA Journal 2011;9(9):2379 [69 pp.].
https://www.efsa.europa.eu/de/efsajournal/pub/2379

9 Customer Guidance Note for using ink Statements of Composition when considering compliance of food packaging, EuPIA, 01.07.2012
http://www.eupia.org/index.php?id=29

10 Explanatory note for suppliers of ink raw materials regarding regulatory compliance of printed food packaging, EuPIA, 19.02.2013
http://www.eupia.org/index.php?id=29

11 ILSI Europe, Threshold of toxicological concern, 2005
http://www.ilsi.eu

12 JRC Scientific and Technical Reports, Analyses of the Cramer classification scheme for oral systemic toxicity – implications for its implementation in Toxtree, 2011
http://publications.jrc.ec.europa.eu/repository/handle/JRC66022

13 Kroes 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

14 EFSA (European Food Safety Authority) and WHO (World Health Organisation) , 2016, Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree, EFSA supporting publication 2016. EN-1006. 50 pp
www.efsa.europe.eu/publications

15 Istituto Superiore di Sanita, Environmental and Health Department, Rome,
http://www.iss.it

16 Union Guidelines on Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, 21.02.2014
https://ec.europa.eu/food/sites/food/files/safety/docs/cs_fcm_plastic-guidance_201110_en.pdf

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 Jounal, 31.07.2008
http://www.efsa.europa.eu/de/efsajournal/pub/21r

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.europe.eu/publications

19 Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment, EFSA Journal 2019; 5708
www.efsa.europe.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

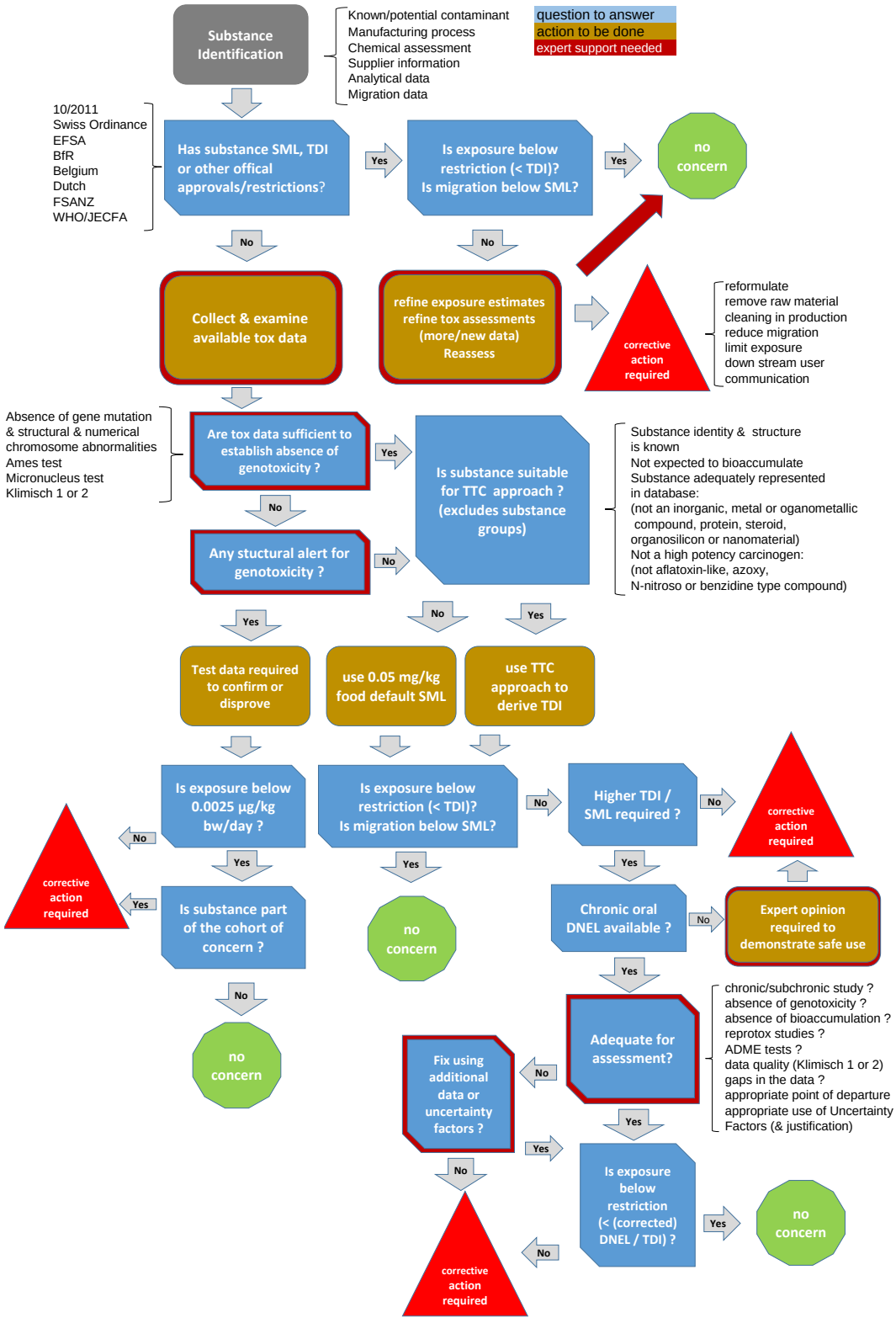
Software for calculating log Octanol/Water partition coefficient
http://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

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

FACET exposure assessment tool
http://expofacts.jrc.ec.europa.eu/facet/

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 (logP)

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 surface area 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. Use the EU default approach
    The SML is based on the EU default approach that an adult person of 60 kg eats daily 1 kg food packed in 6 dm^2 packaging material.

    Note: For specific consumer groups or in case the surface/volume ratio in the application is different to the EU default value, the SML may not be applicable.

    b. EFSA food consumption database
    EuPIA recommends using the following settings:
        i. Use “Chronic” 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 g/kg body weight per day and

vi. 95th percentile of consumption in g/ 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.

c. FACET

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 (µg/kg$_{bw}$/d) = migration (µg/kg$_{food}$) x food consumption (kg$_{food}$/kg$_{bw}$/d)

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 tree
      i. In vitro mutagenicity (Ames test) alerts by ISS[15]
   e. If no alerts appear in ToxTree further evidence of the absence of genotoxicity by need to be searched. This can be done using a second (statistical) QSAR tool, Read Across or expert knowledge for example.
   f. In case genotoxicity alerts with QSAR tools are found these alerts must be further evaluated before deriving the Cramer Class:
      Options are: experimental data, expert knowledge or Read Across. For this detailed evaluation usually deeper toxicological knowledge is necessary.
   g. **In case sufficient evidence for the absence of mutagenicity is available only Cramer Class III as maximum can be applied. For the use of Cramer Class II and I clastogenicity must be excluded, which requires experimental data.**
      If no alerts appear then include justification to continue in step 7.

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):

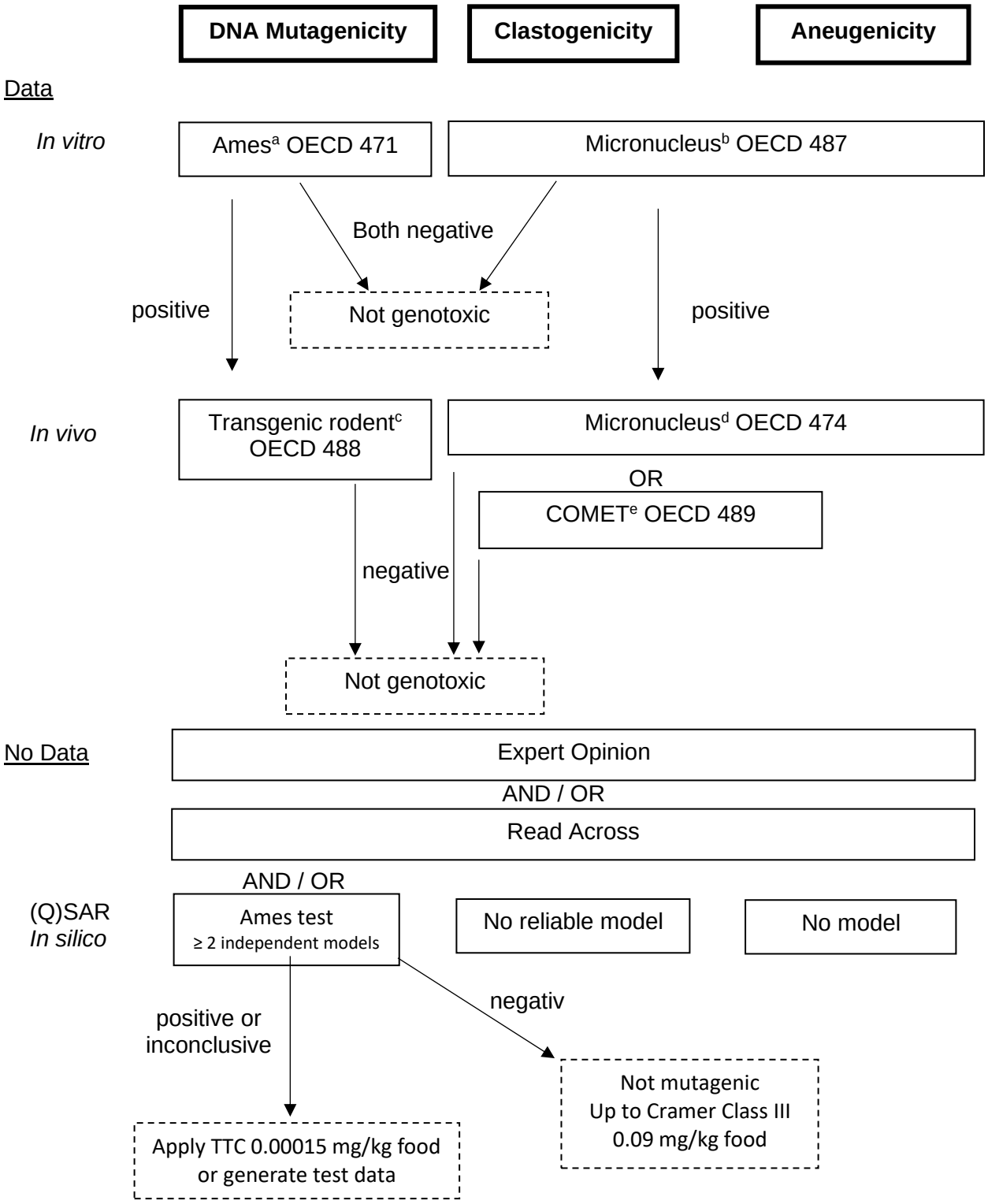
$$EDI_{Substance} < TDI$$

or

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

   <u>Then the substance can be considered to be safe in the evaluated application!</u>

Attachment 4: Genotoxicity decision tree



[a] The *in vitro* mammalian gene mutation assay OECD 476 has also been used but was found to reduce specificity with no substantial gain in sensitivity (false positives). Since 2015, mammalian cell gene mutation testing using the tk locus is covered by a separate test guideline (OECD 490) and OECD 476 now includes only testing using the hprt and xprt locus

[b] Previously the *in vitro* mammalian chromosome aberration assay OECD 473 was used.

[c] The *in vivo* unscheduled DNA synthesis (UDS) assay OECD 486 has also been used but is of questionable sensitivity.

[d] Previously the *in vivo* mammalian bone marrow chromosome aberration assay OECD 475 was used.

[e] The *in vivo* mammalian alkaline COMET assay can also be combined with DNA repair enzymes to detect DNA base damage.