TSC33 NIAS GUIDELINES

FOR COATED RIGID METAL PACKAGING INTENDED FOR DIRECT FOOD CONTACT

VERSION 1.7.4

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CONTENTS

1. INTRODUCTION

Currently there is an absence of industry-wide harmonised methodology on dealing with Non Intentionally Added Substances known as NIAS.

The Technical Joint Industry Group of the Coated Rigid Metal Packaging sector, which includes the value chain stakeholders: food and drink manufacturers, can makers, coatings suppliers and raw material suppliers, have worked together to develop a feasible and practical guideline on how to deal with the issue of NIAS for direct food contact coatings. However, in the absence of rigid guidelines, this proposed approach is pragmatic, particularly with regards to the level of migration of species needing identification. In line with today's convention, a level of interest (LOI) of 10 µg/kg food (often referred to as "10 ppb") will be used until accepted tests are available to demonstrate that the presence of genotoxic substances in the migrant mixture is unlikely. The LOI is based on the standard EU model of 1kg of food being packed in 6dm^2 packaging; however this can be adjusted to take account of packaging surface area to volume ratios which deviate significantly from the standard model or to account for vulnerable members of the population. For certain foods, as defined in Regulation (EU) No. 10/2011, Annex III, a fat reduction factor may be applied. When accepted genotoxicity tests for migrants from can coatings are available, they will be the next step after chemical analysis in assessing any risk from migrating species, particularly as it will equally apply to known and unknown substances. The current thinking is that excluding the presence of DNA reactive mutagens will allow the use of the TTC (Threshold of Toxicological Concern), for known and unknown migrating substances as described in the ILSI NIAS guidance (1), (upcoming ILSI paper). All references to genotoxicity from here refer to DNA reactive mutagens.

It is necessary to assess the safety of all migrating species. The first step is to identify and quantify the species wherever possible. Those identified species are 'knowns' and their potential to be genotoxic can be risk assessed in various ways, including reference to existing toxicological data. If no toxicological data exists it is possible to demonstrate that genotoxicity is unlikely by in-silico approaches (e.g. TOXTREE or DEREK). For oligomers the monomer toxicity may be used to demonstrate that genotoxicity is unlikely (2). When it is demonstrated that genotoxicity is unlikely, it is then possible to use the TTC approach and determine if each species presents a risk to human health.

However the 'unknowns' present a challenge. These guidelines propose 2 different routes to demonstrate the safety of your packaging. It is each company's decision as to which they follow or indeed if they use different approaches for different coatings. In order to use TTC approach it is necessary to apply chemical analysis along with bioassays to demonstrate that it is unlikely that genotoxic substances are part of the migrate. Alternatively, if only the chemical analysis route is pursued, then a level of interest (LOI) of 10 µg/kg food is applied and the TTC approach cannot be used.

This is a living document and as knowledge about NIAS and genotoxicity testing increase, so these guidelines will be periodically reviewed and updated.

The guidelines provide a consistent framework of identifying and risk assessing NIAS from coated rigid metal packaging.

The guidelines are not intended to cover all aspects of NIAS as there are already other documents available which do this well e.g. ILSI guidance on the risk assessment of NIAS in FCM and articles (1).

2. DEFINITION OF NIAS

The group has decided to use the definition of NIAS which is recognised at EU level in Article 3 of Regulation (EU) No. 10/2011 (3):

"'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;"

Oligomers are not excluded from consideration here, as of course they have to be considered in any risk assessment.

Examples of NIAS could be:

1. Reaction products of a monomer or oligomer containing a functional group with another substance in the coating- e.g., acid functional oligomer <1000 Daltons, with a hydroxylic solvent.
2. Decomposition products of initiators.
3. Residual starting materials of additives.
4. Impurities in starting materials, such as solvents, reaction by-products.

3. DETERMINATION OF NIAS

For the purposes of Risk Assessment we will only consider NIAS up to a molecular weight of 1000 Dalton (4). It is assumed that substances with molecular weight above 1000 Da or 1500 Da for fluoropolymers cannot enter the gastro-intestinal tract and as such are not absorbed by the body and are therefore not toxicologically relevant. However, polymers that hydrolyse in the body, giving monomers or oligomers <1000 Daltons which are bio available, should be evaluated. (5)

3.1 EVALUATION OF EXPECTED NIAS

The first step in determining NIAS in a coating (or coated article) is to evaluate the formulation of the coating(s) used. The coating supplier should provide their in-house analysts or external testing laboratory with:

- The complete composition of the product.
- a list of known, predicted or potential NIAS including:
    - Impurities
    - Reaction intermediates
    - Decomposition products
    - Reaction products
    - Oligomers

This information can be found from suppliers, formulators and literature. The analysts can use this information to decide which solvents and methods should be used for the detection of the NIAS during the screening process.

Some of the required information may be confidential/proprietary and therefore not accessible for all actors in the supply chain. To overcome this, some (actors) may use third party evaluation. There is a requirement for suppliers, throughout the value chain, to evaluate all sources for their NIAS.

The simulants / solvents used along with conditions for testing should be appropriate to the foodstuff(s) intended to be packaged and their processing conditions. Furthermore the information is needed for plausibility checks during identification of NIAS.

Coatings will be applied and stoved in a laboratory or industrially applied and stoved.

3.2 VOLATILE NIAS

To determine the volatile NIAS present in a coating an initial screening will be carried out. HS GC-FID (Headspace Gas Chromatography with Flame Ionisation Detection) will be used with one or more internal standards to cover the range of the chromatogram, at a level of 10 µg/kg food.

If substances are detected above 10 µg/kg food, then it is necessary to identify them, if only tentatively, using HS-GC-MS (Headspace Gas Chromatography with Mass Spectrometry Detection). It is accepted that with today's analytical techniques not all substances present above 10 µg/kg food can be identified but §4.4 contains proposals for a way forward.

3.3 Semi Volatile NIAS

Again for semi-volatile NIAS, an initial screening shall be carried out.

An extraction solvent or migration simulant is used to give a high level of NIAS. A balance is needed, as we do not want to spend resources on determining identity and quantity of NIAS which do not occur during the normal usage of the coating, however, we do want to make the detection and if required the identification of the NIAS as straight forward as possible.

It is recommended to extract the coating into acetonitrile at room temperature for 24 hours and/or 95% ethanol at 60°C for 24 hours for the initial screening and method development. Depending on the knowledge of the expected NIAS and coating and intended final use by the food manufacturer, analysts may choose to use a different solvent or simulant and/or different time and temperature conditions for the initial screening of NIAS.

GC-FID (Gas chromatography with Flame Ionisation Detection) is used with one or more internal standards at a level of 10 µg/kg food, to cover the full chromatogram.

It is generally known that with today's analytical techniques not all substances present above 10 µg/kg food can be identified. If substances are detected above 10 µg/6dm^2, then it is necessary to identify them, if only tentatively, using GC-MS (Gas Chromatography with Mass Spectrometry Detection) or GC-TOF-MS (Gas Chromatography with Time-of-Flight Mass Spectrometry detection) or a similar technique. §4.4 contains proposals for the way forward. After identification, it is necessary to risk assess the substances.

3.4 Non-Volatile NIAS

It is recommended to extract the coating into acetonitrile at room temperature for 24 hours and/or 95% ethanol at 60°C for 24 hours for the initial screening and method development. Depending on the knowledge of the expected NIAS and coating, analysts may choose to use a different solvent or simulant and/or different time and temperature conditions for the initial screening of NIAS.

High resolution techniques such as LC-MS/MS (Liquid Chromatography with Mass Spectrometry Detection) or LC-TOF-MS (Liquid Chromatography with Time-of-Flight Mass Spectrometry detection) are used with one or more internal standards at a level of 10 µg/kg food, to cover the full chromatogram.

It is generally known that with today's analytical techniques not all substances present above 10 µg/kg food can be identified, if only tentatively, but §4.4 contains proposals for the way forward. After identification, it is necessary to risk assess the substances.

3.5 QUANTIFICATION OF NIAS

The quantification of NIAS is particularly challenging and, as of today, no universal detector with the same response for all species exists for liquid chromatography. In many cases only semi-quantification is feasible, as it is not possible to obtain the specific standards required to perform quantitative analysis, due to lack of commercial availability, inability to synthesise the substance or expense. . It is necessary to select appropriate standards which are representative of the chemistry(ies) of the coating(s). It is accepted that this is not ideal, but this is a major step in the right direction. If the coating consists of more than one type of chemistry, then it is necessary to use representative standards for each type of coating. ILSI are initiating an expert group to standardise protocols for identification and quantification of migrants in FCM.

3.6 POTENTIALLY GENOTOXIC NIAS

As part of the evaluation of NIAS following the ILSI / EFSA protocols (4), it is required to demonstrate that the presence of genotoxic substances is unlikely by chemical analysis, argumentation or bioassays. At the moment there are bioassays available, however an accepted strategy of which to use for which purpose is still missing.

An ILSI expert group of the packaging materials Task Force is evaluating available bioassays and the coated rigid metal packaging industry will wait for the ILSI report before deciding which bioassay method or methodology to choose. Once accepted methodology is available, bio-assays for genotoxicity testing will be introduced into the protocol for risk assessing migrants from rigid metal packaging as an initial step before proceeding with the step wise risk assessment outlined later. It is for each company to decide if they want to pursue the bio-assay route.

4. RISK ASSESSMENT

A risk assessment for those species present in the migrate which have been tentatively identified can be carried out using internationally recognised toxicological approaches (e.g. toxicological data from the literature, read across Cf. ILSI guidance document for more details) (1) . When acceptable genotoxicity test methodologies for extracts of rigid metal packaging are available then risk assessment of unknowns can also be performed. This will permit the application of the TTC approach.

The risk of a substance is a function of hazard and exposure. Therefore both have to be determined prior to risk characterization.

4.1 DETERMINATION OF CRAMER CLASS

In the absence of toxicological data, based on the chemical identity of the substance, the chemical classification can be determined using the TTC decision tree which includes the classification as published by Cramer (see ILSI document). There are a number of freely and commercially available tools to determine Cramer Class. E.g., Toxtree is freely available from

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

It should be borne in mind that some in-silico tools can and will give different levels of toxicity, so the input of a toxicologist is highly desirable in interpreting the result from whichever tool(s) is(are) used.

The Cramer classification can only be used in cases where it can be demonstrated that the substances do not belong to one of the special categories for which use of TTC is excluded:

- High potency carcinogens
- Inorganic substances
- Metals and organometallics
- Proteins
- Steroids
- Known or predicted bio accumulative substances
- Nanomaterials
- Radioactive substances
- Organophosphates & Carbamates (TTC 0.3 µg/kg bw/day)

If the presence of these substances cannot be ruled out by expert judgement, then they must be ruled out using analytical techniques.

4.2 DETERMINATION OF EXPOSURE

To determine exposure, it is necessary to know the concentration of the migrant in the foodstuffs and how much of each foodstuff is consumed. The concentration can be obtained

using food simulants under time and temperature conditions as outlined in the migration testing guidelines for coated rigid metal packaging (6).

For a first screening the consumption levels proposed by EFSA (4) are useful.

If needed, the exposure can be refined by using specific data from the EFSA food consumption database available at

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

Alternatively FACET has preloaded consumption databases.

The exposure of the population to a substance can be found from a number of sources such as FACET available from

http://expofacts.jrc.ec.europa.eu/facet/login.php

FACET has the advantage that migration/extraction levels of migrants can be direct inputs; however it has the disadvantage that the food consumption databases are limited to eight countries.

4.3 Determination of Risk

When it can be demonstrated that the presence of genotoxic substances is unlikely, that no other source of toxicological information are available, and that substance do not belong to the TTC exclusion groups, the TTC approach can be followed (Risk Assessment). Otherwise the LOI of 10 µg/kg food can be used (Risk Management) as a pragmatic compromise until the analytical techniques are developed such that they allow to measure NIAS efficiently at 0.0025 µg/kg bw day. It should also be borne in mind that the sensitivity of bio-assays maybe such that the limit of detection of genotoxic or non-genotoxic mixtures may be greater than that required for a rigorous application of the TTC concept. This is however also true for characterisation by chemical analysis only, for which the LOD may not be sufficient to detect substances known to be genotoxic at the relevant level, nor does analytical chemistry allow the exclusion of unidentified and non-detected substances which could be genotoxic since a portion of the migrate cannot be identified today. In these cases the unlikely presence of genotoxic substances as demonstrated by e.g. bio-assay will be used as the basis for applying the proposed (interim) decision tree approach for assessing risk from migrants including NIAS from rigid metal packaging.

When it is not possible to demonstrate unlikely presence of genotoxic substances or to demonstrate that migration of the substance does not exceed 0.0025µg/kg bw/day, then the TTC approach cannot be used and an LOI of 10 µg/kg food should be used.

4.4 FLOWCHART FOR THE DETERMINATION OF NIAS

The flowchart in the ILSI guidance is appropriate for use by the coated rigid metal packaging sector

All safety assessments of coatings will need to start by evaluation of the information already available from the coating recipe. In addition, information from literature or knowledge from the lab should be assessed to evaluate whether NIAS can potentially be formed and their toxicity should be assessed. If available, existing toxicological data should be used before using the TTC approach.

A: Chemical Analysis - the approaches for analysis of the migrant extract are in section 3.

B: In-vitro bioassays - in the first instance only the genotoxicity and cytotoxicity of the migrant extract will be tested by bio-assays. Cramer class III is considered conservative enough to cover endocrine activity. Without demonstration that genotoxic substances are unlikely to be present in the migrate, then a TTC approach cannot be used, an LOI of 10 µg/kg food can be used as a pragmatic compromise until the analytical techniques are developed such that they allow to measure NIAS efficiently at 0.0025 µg/kg bw day. The left hand side of the flow chart can then be followed. As stated earlier, it is not possible with today's knowledge to test at very low levels, but if it can be demonstrated that genotoxic substances are unlikely to be present using today's tests, then a TTC approach can be used.

C: Identified NIAS - If oligomers are detected and tentatively identified, then it is necessary to use the oligomer flow chart along with this one.

D: Performing hazard characterisation of unidentified NIAS - it will not be easy to use this route if the NIAS are unknown, but if there are differences in molecular weight of different species (e.g. C_2H_4) which would suggest a homologous series then it may be possible to assign tentative structures.

E: Exposure - this can be used for both routes. However, for TTC approach it is necessary for genotoxicity to be tested. Refer to section 4.2 for assessing exposure.

F: Exposure and Hazard Identification - in principle you can have the situation that you have a positive genotoxic response and then the answer is yes. If not genotoxic, the answer is no.

G: Risk Management - this step focuses on risk management. Identification is required, if only tentatively of those peaks/masses detected >10 µg/kg food. For those peaks tentatively identified it is necessary to determine if any present a risk. A follow-up expert group will be initiated to provide more guidance on this topic. With today's knowledge this is as far as one can realistically go in demonstrating that the NIAS do not present a risk to human health. Suppliers should provide documentation explaining how to improve their safety assessment in the future as part of risk assessment documentation.

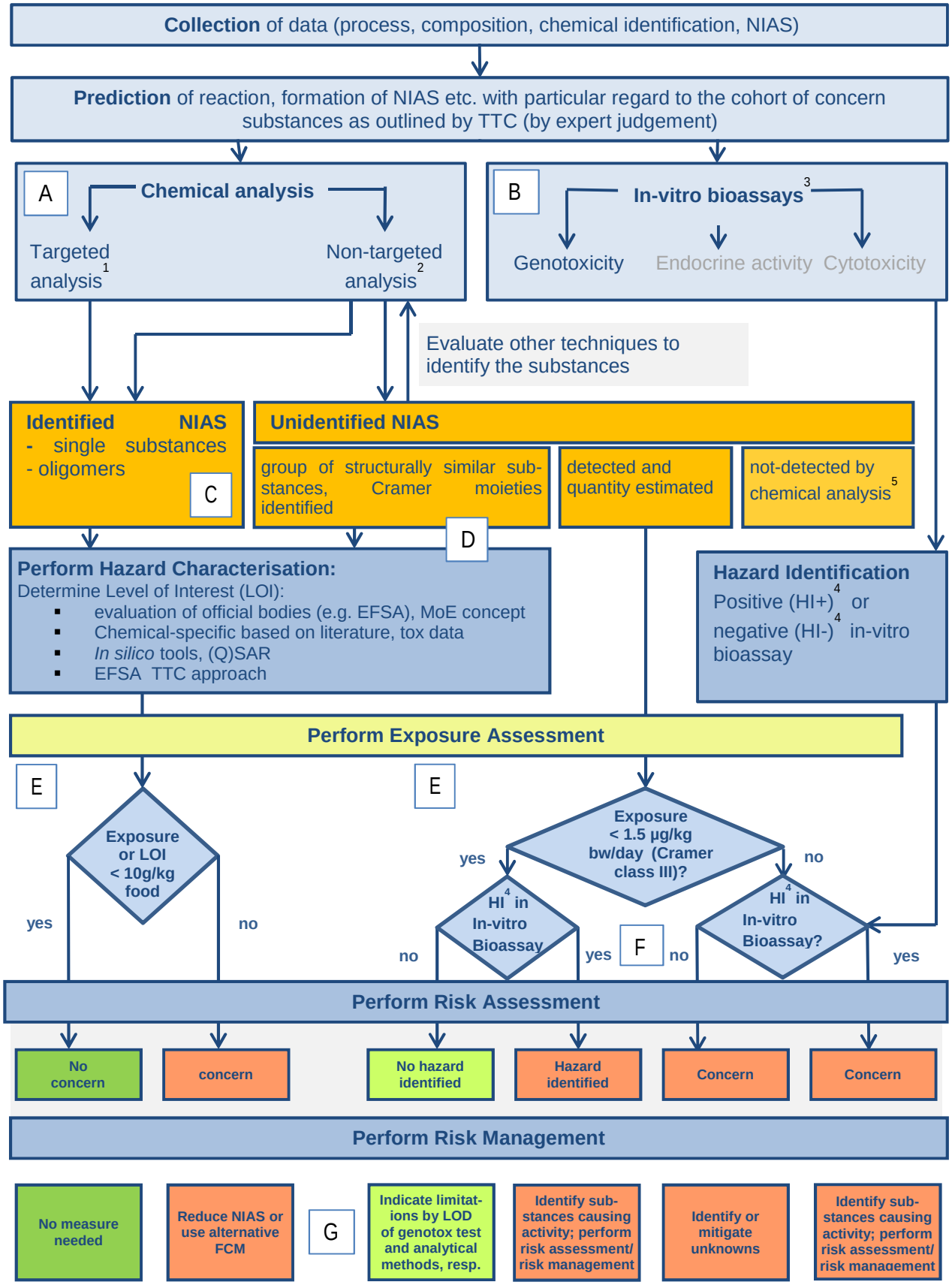


CHART 1 – ILSI NIAS FLOWCHART

[1] LOD depending on substance

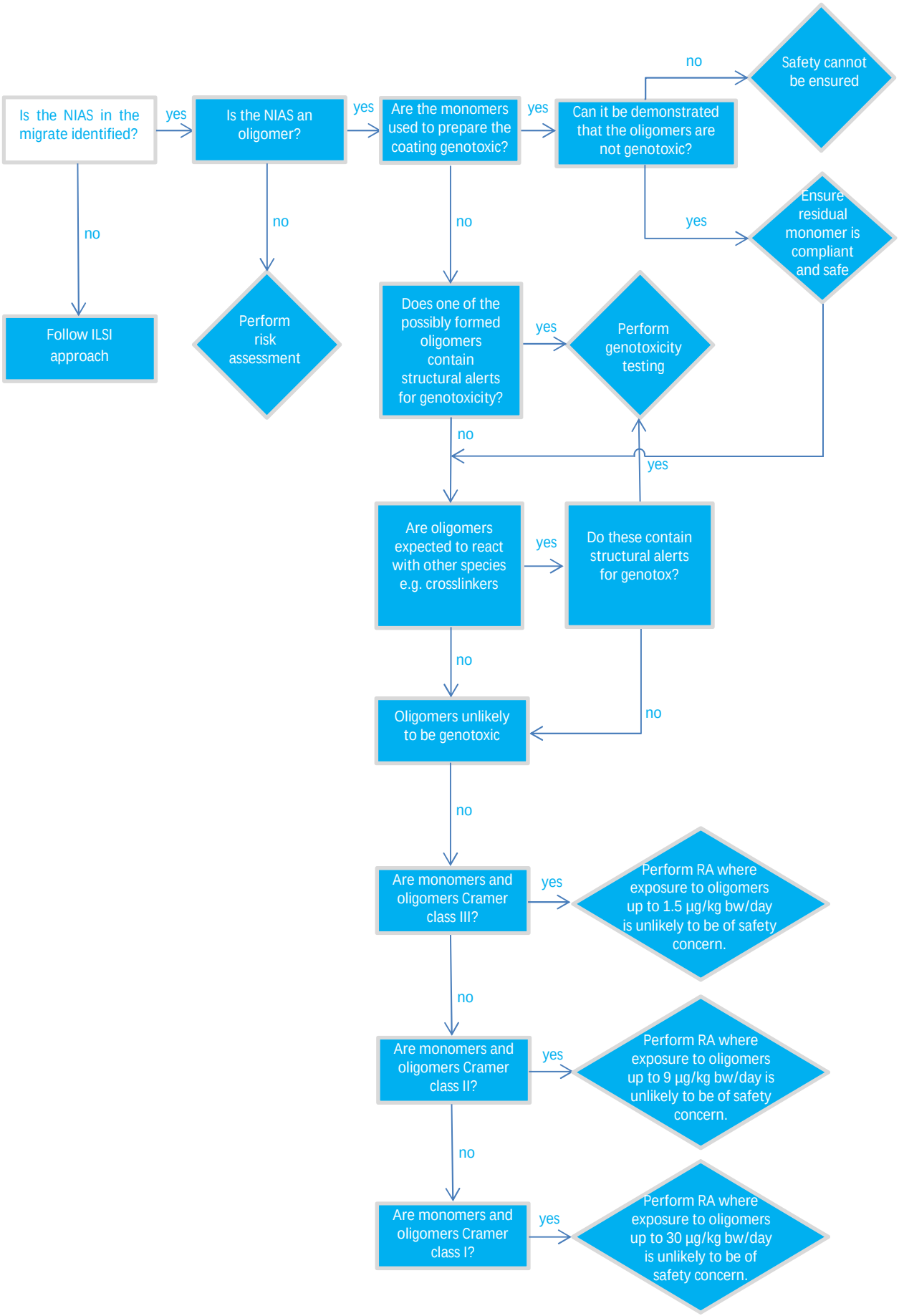
[2] 10 µg/kg food threshold. Target should be to exclude CMR based on expert judgment or otherwise.

[3] Note that the use of bioassays is not mandatory but can be used as tool assisting in the final risk assessment.

[4] HI+ and HI- (hazard identification 'yes' or 'no') are respectively a positive or negative conclusion based on the outcome of a genotoxicity assay.

[5] I.e. substances with different phys./chem. characteristics as methods used will not be detected. These substances can however induce an effect in a biological assay.

CHART 2 – OLIGOMER FLOWCHART.



5. TIMESCALES

It is estimated that the length of time to carry out screening tests (extraction and/or migration) for each coating is approximately three weeks.

However, if identification and quantification of substances is required then this could initially take several months for each coating, depending upon the level above which identification is required, but it will depend upon the complexity and number of substances detected in the screening.

As knowledge and experience of types of NIAS present in different coatings types is gained it is expected that the length of time to carry out a complete NIAS/Risk assessment will reduce.

It is recognised that this approach to NIAS will be an evolving one over time as science and technology advances.

Some coatings manufacturers have in-house analytical knowledge and equipment whereas others will need to rely on external testing laboratories.

Although there are some commercially available tests they may not fulfil all of the requirements of this protocol. It should be noted that although the protocol can be standardised, the analytical results and subsequent evaluation could vary widely.

6. PROCESS OPTIMISATION

Due to the number of different coatings which are in use, it is not possible to fully risk assess all coatings immediately.

Therefore it makes sense to use a family approach, whereby coatings are evaluated which are representative of a family of coatings. The definition of what constitutes a family of products is to be decided at business level and should be justified as part of the risk assessment.

7. OUTLOOK

It is recognised that the comprehensiveness of the risk assessment of NIAS may fall short of the expectations of some members of the supply chain in the early stages of the implementation of this guideline, resulting in more reliance on risk management.

Reducing the perceived gaps in the risk assessment could be achieved through measures such as;

- Reducing the number and level of detectable migrants
- Improved identification and quantification of NIAS
- Availability of bio-assays

The supply chain for coatings intended for rigid metal packaging is committed to continually improve risk assessments as knowledge grows and analytical techniques are developed. To facilitate this a new activity will be initiated.

8. GLOSSARY

FACET – flavour, additives (food) contact exposure tool

FCM – food contact materials

GC-FID - Gas chromatography with flame ionisation detection

GC-MS – Gas chromatography with mass spectroscopy detection

HS-GC-MS - Head space gas chromatography with mass spectroscopy detection

LC-MS – Liquid chromatography with mass spectroscopy detection

LOI – Level of interest

NIAS – non-intentionally added substance(s)

RA – Risk Assessment

TTC – Threshold of toxicological concern

9. REFERENCES

1. ILSI Europe Report Series. Guidance on Best Practices on the Risk Assessment of Non Intentionally Added Substances (NIAS) in Food Contact Materials and Articles. July 2015.

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4. EFSA CEF Panel. Scientific opinion on recent developments in the risk assessment of chemicals in food and their potential impact on the safety assessment used in food contact materials. s.l. : EFSA Journal, 2016. Vol. 14(1), 4357. 1831-4732.

5. Dutch Packaging and Utensils Decree. 14th March 2014.

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