A FLEXIBLE MODEL FOR THE DEVELOPMENT AND VALIDATION OF MULTIANALYTE METHODS FOR THE DETERMINATION OF MIGRANTS FROM FOOD CONTACT MATERIALS

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Abstract – Several thousands of chemical substances which are used in the production of food contact materials and articles have the potential to migrate into foods. It needs high analytical experience, hard work and high level instrumentation to determine the level of their migration into foods or food simulants. Development of multi-analyte methods is necessary in order to cope with the huge number of chemical compounds which should be determined. Application for the official control necessitates validation for each combination of analyte/substrate/simulant/migration condition.

A very promising approach is based on the design and development of a structured flexible model for the establishment of modular analytical process which will incorporate the standard migration methods, different substrates in combination with various analytes and will include procedures for samples' preparation and instrumental analysis. The model foresees the extension to additional migrating compounds and food substrates followed by the necessary minimum validation actions in order to achieve a reliable result at the shortest time. The philosophy of this approach focuses on the breakdown of the analytical process into fully documented individual, independent and clearly defined stages (modules) which can be combined together to give the appropriate analytical process according to the target analyte(s) and simulants or food substrates. The implementation of this model provides a continuously expanding measurement capability of the laboratory with simultaneous satisfaction of the requirements for reliable, traceable and comparable results.

This model is successfully applied to plastics' starting substances and additives, focusing on incorporation of the analysis of new plasticizers like diethylhexyl terephthalate using GC-FID and GC-MS instrumentation.

Keywords: flexible, multianayte, food contact materials (FCM)

1. INTRODUCTION

Food contact materials comprise a wide range of material types and successively several thousands of compounds which are used for their production. These compounds include monomers, additives and production aids. Apart from them, during the production of polymers, oligomers and reaction/breakdown products – known as non intentional added substances are produced. All these substances may migrate into foods which are in contact with these materials. Furthermore, new substances are continuously produced and authorized for use in FCM [1].

A laboratory performing FCM control needs to cover various substrates in combination with various analytes and due to new emerging substances a fast analytical response along with

reliability are required demanding continuous design, development and validation of methods. On the other hand substantial number of substrates and anlytes could be analyzed applying similar techniques e.g. GC, LC, MS. This leads to a new approach which applies a flexible analytical process by constructing a core process consisting of individual modules corresponding to each possible analytical step. New analytes are determined through extension of the application by combination of the appropriate modules.

One category of additives which are used in FCM are plasticizers including various compounds like phthalates. Phthalates are used in polyvinylchloride (PVC) polymers, organosol lacquers, adhesives and elastomers, for food contact articles, toys, and other consumer products as buildings and construction materials, cables, floorings, cars, inks e.t.c., [2,3,4]. However phthalates are considered as endocrine disruptors and have been accused for adverse effects on reproductive systems in humans and other animals. Therefore restrictions in their use have been stated by the legislation and general demand. One substitute of these plasticizers are terephthalates which do not present this high toxicological concern but have a legislative limit for migration, for example di-ethylexyl-terephthalate has an SML of 60 mg/kg. Therefore the determination of these additive can be achieved applying the following model.

2. EXPERIMENTAL

2.1. Flexible models - Requirements

In case of ? quantitative? analytical processes two flexible models are proposed [5].

A. Same analytical technique (e.g. GC, HPLC, Head Space GC, MSD, e.t.c.) used for the analysis of groups of analytes in groups of substrates. In this case one or more instruments can be included but the instrumental analysis is based on one technique type. This is a technique based approach.

B. Similar analyte groups in groups of substrates or specific substrates (e.g. analysis of pharmaceuticals). In this case different analytical techniques such as spectroscopy, spectrometry, liquid chromatography e.t.c. can be involved. This is analyte based approach.

In both cases the fundamental philosophy of the proposed approach focuses on the breakdown of the overall analytical process into individual independent clearly defined steps – modules, fully documented, which can be combined in order to result to the appropriate analytical process case by case. The analytical process can be divided in individual steps as follows:

Sampling

Several parameters should be taken into account for the development, validation and implementation of a sampling plan for chosing, as well as handling, sampling and dividing a product portion in order to achieve a representative sample. Examples are the type of testing (counting or measuring), the number of samples required, the way of sampling, the size and the number of potential subsamples, the sample identification and the relation between control results and the decision which will be taken on the lot (acceptance or rejection).

Sample preparation

Substrates are grouped in categories with similar behaviour, interferences, pre-treatment e.t.c. and the step of sample preparation is validated in one substrate at least per group of analytes. The laboratory needs to have and implement a standard procedure of validation (with defined validation requirements) for extension of the scope of the method in new substrate groups (case A). Validation should examine the substrate effect on recovery and repeatability. Validation data is not necessary to be new but various old studies performed by the laboratory and/or scientific literature can be combined. Sample preparation can be further described by individual steps in order to accommodate for the cases where different treatment per substrate group is required.

Instrumental analysis and equipment

Detailed system suitability checks should be designed, performed and documented. Appropriate records of maintenance and calibration should be kept and traceability should be designed in order to cover the worst case.

Reagents, standards and reference materials

Specific protocol for the used reagents, critical reagents, internal and external standards along with purity requirements and relevant certificates, certified reference materials (CRMs) should be

developed and implemented. Standards to be used in system suitability checks should be designated. In case CRMs are available their use in validation is preferable in order to estimate trueness and repeatability or to calibrate working materials for the internal quality control.

Results

Procedures for the description of measurement and expression of results – square leasts, bracketing, molecules with similar extinction coefficient e.t.c. - should be documented in individual protocols. It should be mentioned that it is possible to determine analytes from a standard of another anlayte which has similar behavior with regard the physical property which is measured (e.g. absorption, emission, absorption e.t.c.). In this protocol the form of the final result could be specified.

Traceability

Specific procedure for satisfaction of traceability requirements, if necessary, apart from the general procedures applied in the laboratory, should be developed and implemented. It is proposed that laboratories applying flexible methodologies have more strict policy on traceability.

Quality control

Specific protocol describing the requirements for the choice of representative analytes and substrates should be designed. In case A it should include documented procedures for the required internal quality control when a method is intended to new groups of analytes.

Estimation of uncertainty

Case A. Combined uncertainty is estimated for the analytical process for each specific group of analytes. In case of extension to new substrates or analytes the uncertainty of the general process corresponding to the closest already existing group could be used.

Case B. Combined uncertainty is estimated for each substrate group in relation to the corresponding group of analytes.

Extension – minimum validation requirements

A fundamental individual module in the flexible process is the procedure which describes the extension in new substrates and analytes. It is necessary to specify the minimum criteria which should be examined during validation of the extension, obligatory including precision, trueness and limits of detection and quantification. Furthermore, the necessity to check robustness, specificity, selectivity e.t.c. should be examined.

2.2. Application to a multianalyte method for FCM

A flexible model was designed, developed and implemented for the identification and determination of FCM monomers, additives, production aids and NIAS in plastics, food simulants and foods, which provides continuous extension of the method's scope in new substrates and analytes. This flexible model is based on the combination of different analytical procedures as independent modules in order to apply the appropriate combination on a case by case basis to succeed the extension of the scope. A diagrammatic description is provided in figure 1.

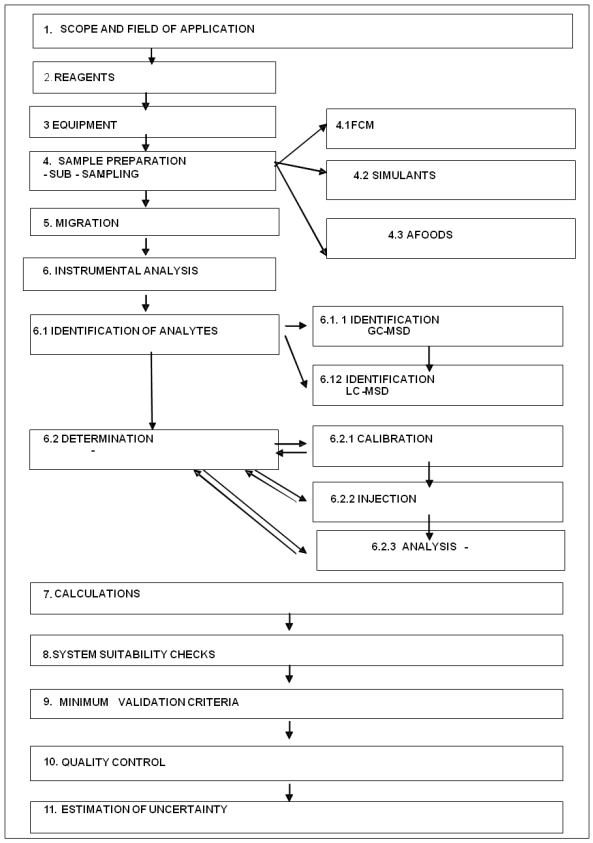

Figure 1. Flexible analytical process for multianalysis of FCM based on combination of independent steps

Each step should be developed in depth in order to ensure that possible deviations are avoided. For example, in sample preparation, composition, chemical properties, interaction between simulants and FCM, chemical affinity of analytes to foods e.t.c. should be taken into account.

3. RESULTS AND DISCUSSION

Flexible approach was applied for the determination of the migration of di-ethylexyl-terephthalate (DEHTP) from FCM into olive oil. It is an extension of the scope of the validated methods for specific migration with GC-FID using BBP as internal standard and GC-MSD using the d4-isotopes as internal standards (isotopic dilution). Due to the similarity in chemical properties and lipophilicity with isophthalic esters which are already validated, robustness, specificity and selectivity were not investigated. Linearity, limits of detection and quantification, precision, recovery and uncertainty were studied and determined. Linearity was checked at two concentration levels 0.8-8.0 μg g^{-1} and 0.02-0.32 mg g^{-1} with correlation coefficients (R^2) at 0.9999. LOD and LOQ were at the level of 10 ng g^{-1} and 50 ng g^{-1} correspondingly for the GC-MS analysis using isotopic dilution and at the level of 0.2 μg g^{-1} and 0.6 μg g^{-1} for GC-FID analysis. The precision is around 10% according to the concentration level.

4. CONCLUSIONS

The present study points out, that a flexible approach for the extension of a multi-analyte method for the determination of migrants from FCM can be successfully applied. This provides a useful tool in laboratories in order to cope with demand to analyze continuously increasing number of migrants from FCM with reliability.

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