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Validacija in interpretacija analitskih metod, migracijsko preskušanje in analitski podatki za materiale in predmete v stiku z živili – 1. del: Splošne ugotovitve

Validation and interpretation of analytical methods, migration testing and analytical data for materials and articles in contact with food - Part 1: General considerations

Validierung und Interpretation analytischer Verfahren, Migrationsprüfung und analytischer Daten von Werkstoffen und Bedarfsgegenständen in Kontakt mit Lebensmitteln - Teil 1: Allgemeine Betrachtungen

Validation et interprétation des méthodes d'analyse, essais de migrations et données analytiques des matériaux et objets en contact avec les denrées alimentaires - Partie 1 : Considérations générales

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This Technical Report was approved by CEN on 16 January 2006. It has been drawn up by the Technical Committee CEN/TC 194.

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Foreword

This document (CEN/TR 15356-1:2006) has been prepared by CEN /TC 194, "Utensils in contact with food", the secretariat of which is held by BSI.

Introduction

0.1 Requirement for validation of analytical methods for enforcement of Directives

Regulation (EC) No. 1935/2004[1] has laid down the requirements that may be included in specific Directives to protect human health. It allows for specific Directives to set overall migration limits and specific limits on the migration of certain constituents or groups of constituents into foodstuffs.

Commission Directive 90/128/EEC[2] and its subsequent amendments (e.g.[3]) introduced specific migration limits for more than 300 substances. A consolidation of these directives has since been issued as Commission Directive 2002/72/EC[4]. In addition, some substances are subject to a maximum permitted quantity of the residual substance in the material or article. Some substances are subject to group limits. Continuously, additional substances are being evaluated and added to the Directive.

New technical dossiers are being prepared for substances which could eventually be listed in future amendments to Directive 2002/72/EC. Methods of control will be required for the majority of the abovementioned substances.

The two Food Control Directives (European Council Directive 89/397/EEC[5] and Council Directive 93/99/EEC[6]) require that methods used for control purposes must be correctly and fully validated. So far only the methods developed by CEN as parts of EN 13130 have been so validated. Methods developed in the project sponsored by DG Research (SM&T project, MAT1-CT92-0006, "Development of Methods of Analysis for Monomers") have only been validated by two competent laboratories. Most methods from technical dossiers have only limited validation data at best.

This Technical Report considers the background to whether or not acceptable validation of analytical methods could be achieved faster and at less cost. The Technical Report also considers the need for validation of the whole test procedure for enforcement purposes, for compliance purposes, and for the creation of data for risk assessment purposes. It should be noted that the considerations apply to both overall as well as specific migration.

The list of current legislation currently adopted by the Commission is given in Annex A.

The list of current methods adopted by CEN/TC 194/SC 1 is given in Annex B.

0.2 Variability in the migration contact stage

The determination of migration from plastics is quite unlike other measurement tasks in ensuring food safety and quality. Reliable measurements depend upon more than simply having validated analytical methods for measuring chemical concentrations in foods. The Directives allows that, as an alternative to the analysis of foodstuff itself, migration testing can be carried out with food simulants applied under conditions which simulate actual use of the plastic material or article with food. This introduces many potential sources of variability in the final migration value. These are discussed in Clause 8.

0.3 Quality of data submitted for risk assessment purposes

Migration data is usually an important part of the petition submitted for a risk assessment carried out by the Scientific Committee on Food (since 2003, by the European Food Safety Authority, EFSA). For new substances it is unlikely that a fully validated method in food simulants will exist. A single laboratory (in-house) system of validation is required as part of the demonstration that the data submitted is of adequate quality. For example, validation of a method's intended use, the determination of accuracy and precision, usually involves replicate analyses of appropriate matrices

spiked with known amounts of the additive at concentrations similar to those encountered in the migration studies and determination of the percentage recovery of the spiked additive.

Where data are supplied to other authorities, e.g. the US-FDA, the data has to be applicable and acceptable to those authorities.

Even when a validated method exists there is still the need for the laboratory carrying out the test to ensure the migration testing carried out within the laboratory does not suffer from excessive error. The possibility of error may be reduced by taking part in proficiency testing schemes. Proficiency testing schemes aim to assess the competence of laboratories to carry out migration testing. At present there is at least one scheme which is known to operate in this area. This is the Food Analysis Performance Assessment Scheme (FAPAS) operated by the FAPAS Secretariat, Central Science Laboratory, Sand Hutton, York (UK).

Laboratories carrying out these methods will also be able to demonstrate their general competence by being accredited to EN ISO/IEC 17025:2005, which is administered by the appropriate Accreditation Agencies in the European Countries. For overall migration testing, samples of plastics with known overall migration values are available from the IRMM, Geel, Belgium. Spectra and a table of physical properties of the monomers and additives listed in Directives have been published to assist ensuring that substances used for calibration are of adequate and known purity [7], [8].

1 Scope

This Technical Report gives guidance in support of Directives adopted by the European Union in the Food Contact Materials Sector and is intended to aid Food Control Authorities and industry enforce and comply with those Directives.

2 Form of regulations

2.1 General

The EU Directives on food contact plastics, provide for various types of quantitative restrictions i.e. specific migration limits (SML, expressed as mg (of substance) /kg of food), overall migration limit (OML, expressed as mg/kg of food or mg/dm^2 of surface) and maximal quantity of the substance in the finished plastic article referred either to the quantity of article (QM, expressed as mg/kg of article) or to area of the surface in contact with the foodstuffs (QMA, expressed as mg/dm² of surface). The determination of these quantities implies various procedural steps e.g. sampling, migration tests with different experimental conditions (OML, SML) or extraction (QM, QMA) as well the usual multi-step analytical determination. Each of these steps is subject to a certain variability and an overall variability will affect the value found by one laboratory (repeatability) or by more than one laboratories (reproducibility). In the past at the level of the Standing Committee for Foodstuffs a discussion took place on the method of analysis for vinyl chloride. The Commission proposed then that the variability should be expressed as "Reproducibility" but the majority of Member States were in favour of the "Repeatability". Therefore the Commission services decided to avoid any further scientific discussion on this issue and decided to propose a new term, "Analytical Tolerance" which shall comprise the variability due to all the above-mentioned procedural steps. Until now no Member States objected to this choice and no fundamental problems were raised from its application. Three options have been chosen by the Commission services as regards the various existing quantitative restrictions:

a) restrictions affected by a specified analytical tolerance,

b) restrictions affected by an unspecified analytical tolerance, and

c) restrictions not affected by any analytical tolerance.

The three options and their background are explained in 2.2, 2.3 and 2.4.

2.2 Restriction and specified analytical tolerance

This case applies to the overall migration limit, where the value of the OML in fatty simulants (60 mg/kg (ppm) or 10 mg/dm^2) is accompanied by an analytical tolerance of 20 mg/kg (ppm) (or 3 mg/dm^2). In this case the variability should be added to the limit value and, only if the value found is greater than 80 mg/kg (ppm) (=60+20) or 13 mg/dm^2 (=10+3), the article is considered not in compliance with the Directive. The choice to increase the OML by the value of the tolerance was due to the variability of the analysis.

NOTE This approach has the disadvantage that as the variability of sampling and analytical procedures becomes less, the overall limit becomes, effectively greater. However it is possible to change the value of the analytical tolerance by an amendment of the Plastics Directive. For example, as practical experience was gained and as both standardised methods and certified reference materials became available it became clear that many laboratories struggled to meet the analytical tolerance value of 1 mg/dm^2 set for tests using volatile simulants. Consequently, Commission Directive 2001/62/EC was issued which, based on expert judgement rather than any statistical evaluation of the available results, raised this tolerance figure to 2 mg/dm^2. The same problem would exist if an EN rather than a Directive establishes the value of the variability. If no value is specified, this issue is no longer harmonised and this should also be considered as disadvantage. The Member States and professional organisations requested, at unanimity, that an analytical tolerance should be fixed.

2.3 SML restriction which includes non specified analytical tolerance

This case applies to the substances, which are classified by EFSA into EFSA list 4 (carcinogens or high toxic substances) and, therefore, in principle should not be detectable in foodstuffs. For these substances a detection limit value (= DL) is fixed. Because there is also a variability in determining the detection limit, an analytical tolerance was considered also in this case. Therefore the Directive includes a sentence "Not detectable (Detection Limit = 20 µg/kg (ppb) analytical tolerance included). This choice, although not scientifically correct, was adopted pending the validation of the specific methods of analysis for the substances.

NOTE this approach suffers from the same disadvantage as above, except that the variabilities have not been quantified. However, it may also be argued that this is an advantage. For the analyst the lack of a specified variability could be a disadvantage and considered scientifically incorrect. But for a jury, a responsible of the production or enforcement laboratory is a great advantage, from the point of view of the juridical certainty, to know the limit which cannot be exceeded in any situation. It has also to be considered that the level chosen is so high that it is quite difficult to raise analytical difficulties in its enforcement and, at the same time, so low that the protection of the health is fully ensured. In fact the limit is expressed as concentration of the migrant in the food and not as exposure, which generally is lower, taking into account the current assumptions of the system that 1 kg of food is eaten by a person every day and this food is all in contact with a material that contains the substance and releases the substance at a concentration is equal to its SML. Moreover a limit expressed in these terms ("not detectability") avoids the criticism of some organisations, which are not in favour of establishing a limit for carcinogenic substances.

2.4 SML Restriction without any reference to analytical tolerance

This case applies to the substances affected by an SML of 50 µg/kg (ppb) or greater or to the substances affected by QM or QMA restrictions. In all three cases there is no indication of the variability. This choice was justified by the following considerations:

a) variability at this level is not so great,

b) lack of real technical obstacles to the trade, and

c) lack of human and financial resources.

NOTE This is the normal approach for legal limits, but can lead to inconsistencies if the approaches used by different control authorities are not standardised. In principle, any quantitative limit should be accompanied by a validated method of analysis establishing the analytical variability. This is the reason why the Commission has given a mandate to the CEN to validate some methods of analysis for global and specific migration. However the reality is that this approach requires too much time and human and financial resources. Therefore it is necessary to decide on a case by case basis if a validation is necessary or not. When the value of SML is high, the importance of the determination of variability is questionable or, in any case, not a priority. The Commission's proposal is to restrict the validation process only to those substances, economically very important and/or for which the restriction is very low (e.g. not detectable or very low concentration).

3 Terms and definitions

For the purposes of this Technical Report, the following terms and definitions apply.

3.1
plastics
organic macromolecular compounds obtained by polymerisation, polycondensation, polyaddition or any similar process from molecules with a lower molecular weight or by chemical alteration of natural molecules

NOTE Other substances or matter may be added to such compounds.

3.2
final material and article
materials or article in its ready-for-use state or as sold

3.3
sample
material or article under investigation

3.4
test specimen
portion of the sample on which a test is performed

3.5
test piece
portion of the test specimen

3.6
conventional oven
oven where the air within the oven is heated and this heat is then transferred to the food through the plastic as opposed to a microwave oven where the food itself is heated directly by microwave irradiation

3.7
food simulant
medium intended to simulate ('mimic' or 'model') the essential characteristics of a foodstuff

3.8
overall migration
mass of material transferred to the food simulant or test media as determined by the relevant test method

3.9
specific migration
mass of the substance transferred to the food/simulant as determined in the test method

3.10
residual content
mass of the substance present in the final material or article

3.11
specific migration limit (SML)
maximum permitted level of a named substance migrating from the final material or article into food or food simulants

3.12
SML(T)
maximum permitted level of a group of named substances migrating from the final material or article into food or food simulants, expressed as total of chemical moiety or substance(s) indicated

3.13
compositional limit (QM)
maximum permitted amount of the named substance in the material or article

3.14
QM(T)
maximum permitted amount of a group of named substances, in the material or article, expressed as total of chemical moiety or substance(s) indicated

3.15
quantity per surface area (QMA)
maximum permitted amount of residual monomer, additive or substance in the material or article expressed on an area-related basis as mg/6 dm^2

3.16
reduction factor
factors in the range 2 to 5 which may be applied to the result of the migration tests relevant to certain types of fatty foodstuffs and which are conventionally used to take account of the greater extractive capacity of the simulant for such foodstuffs

3.17
migration test
test for the determination of specific migration of a substance, using food simulant under conventional test conditions

3.18
substitute fat test
test carried out which uses test media under conventional substitute test conditions when the use of a migration test into fatty food simulant(s) is not feasible

3.19
test media
substances used in "substitute tests", isooctane, 95 % ethanol in aqueous solution and modified polyphenylene oxide (MPPO)

3.20
alternative fat test
tests, with volatile test media, that may be used instead of migration tests with fatty food simulants

3.21
'volatile' test media
volatile substances used in alternative fat tests

3.22
extraction tests
tests in which media having strong extraction properties under very severe test conditions are used

3.23
dissolution test
tests in which the specimen is dissolved to liberate the substance from the plastics test specimen

3.24
pouch
receptacle of known dimensions manufactured from plastics film/sheet to be tested, which when filled with food simulant or test medium exposes only the food contact side of the film/sheet to the food simulant or test medium

3.25
reverse pouch
pouch which is fabricated such that the plastics surface intended to come into contact with foodstuff is the outer surface

NOTE All of its edges are sealed to prevent the inner surfaces coming into contact with the food simulant or test medium during the test period. The reverse pouch is intended to be totally immersed in the food simulant or test medium, exposing only the outer and not the inner surface.

3.26
cell
device in which a plastics film to be tested can be mounted and which when assembled and filled with food simulant or test medium, exposes only the food contact side of the film to the food simulant or test medium

3.27
repeatability value 'r'
value below which the absolute difference between two single test results obtained under repeatability conditions may be expected to lie with a probability of 95 %, as defined by ISO 5725

3.28
reproducibility value 'R'
value below which the absolute difference between two single test results obtained under reproducibility conditions may be expected to lie with a probability of 95 %, as defined by ISO 5725

3.29
repeatability conditions
conditions where mutually independent test results are obtained with the same method on identical test material in the same laboratory by the same operator using the same equipment within short intervals of time

3.30
reproducibility conditions
conditions where test results are obtained with the same method on identical test material in different laboratories with different operators using different equipment

4 Analytical tolerances

In the Food Contact Materials sector the present approach to variability is inconsistent. The three situations described in Clause 2 are not self-consistent. The normal approach within the EU is that food analysis limits are specified without any indication of analytical tolerances (i.e. the situation described in 2.3).

In quantitative chemical analysis many important decisions are based on the results obtained by a laboratory and so it is important that an indication of the quality of the results reported is available. Analytical chemists are now more than ever coming under pressure to be able to demonstrate the quality of their results by giving a measure of the confidence placed on a particular result to demonstrate its fitness for purpose. Users of the results of chemical analysis, particularly in those areas concerned with international trade, wish to minimise the replication of effort frequently expended in obtaining the results. Confidence in data obtained outside the user's own organisation is a prerequisite to meeting this objective. In many sectors of analytical chemistry it is now a formal (frequently legislative) requirement for laboratories to introduce quality assurance measures to ensure that they are capable of and are providing data of the required quality. Such measures include: the use of validated methods of analysis; the use of defined internal quality control procedures; participation in proficiency testing schemes; accreditation based on EN ISO/IEC 17025, and establishing traceability of the results of the measurements.

Whenever decisions are based on analytical results, it is important to have some indication of the quality of the results, that is, the extent to which they can be relied on for the purpose in hand. In analytical chemistry, there has been great emphasis on the precision of results obtained using a specified method, rather than on their traceability to a defined standard or SI unit. This has led the use of "official methods" to fulfil legislative and trading requirements. The use of official methods is not in itself a complete answer. To demonstrate fitness for purpose, irrespective of the analytical methods used, one useful indicator is measurement uncertainty. A number of ways are available for analysts to estimate their measurement uncertainty. These included:

— evaluation of the effect of the identified sources of uncertainty on the analytical result for a single method implemented as a defined measurement procedure in a single laboratory;

— results from defined internal quality control procedures in a single laboratory;

— results from collaborative trials used to validate methods of analysis in a number of competent laboratories;

— results from proficiency test schemes used to assess the analytical competency of laboratories.

A practical solution is needed in the short term, and for this a Horwitz equation[9] approach is often taken. Here the Horwitz value is derived from the Horwitz trumpet and equation, which states that for any method:

$RSD_R = 2^{(1-0,5\log C)}$

and that the value is independent of matrix/analyte.

RSD_R is the relative standard deviation of the reproducibility (S_R x 100/MEAN).

The major values are:

Concentration ratio	RSD_R
1 (100 %)	2
10^{-1}	2,8
10^{-2} (1 %)	4
10^{-3}	5,6
10^{-4}	8
10^{-5}	11
10^{-6} (ppm)	16
10^{-7}	23[a]
10^{-8}	32[a]
10^{-9} (ppb)	45[a]
[a] At levels below 120 µg/kg (ppb), the more usual value to be used is 22 % of the concentration[10].	

Horwitz derived the equation after assessing the results from many (ca. 3 000) collaborative trials. Although it represents the average RSD_R values and is an approximation of the possible precision that can be achieved, the data points from "acceptable" collaborative trials are less than twice the predicted RSD_R values at the concentrations of interest. This idealised smoothed curve was found to be independent of the nature of the analyte or of the analytical technique that was used to make the measurement. In general the values taken from this curve are indicative of the precision that is achievable and acceptable of an analytical method by different laboratories. Its use provides a satisfactory and simple means of assessing method precision acceptability.

A comparison of the RSD_R obtained in the method validation procedure and that predicted by the Horwitz equation is increasingly being used by organisations to assess the acceptability of the precision characteristics of their methods. If the ratio between the two is significantly greater than 2, then many organisations would deem the method to be unacceptable (too imprecise).