COMMISSION
OF THE EUROPEAN
COMMUNITIES

Brussels, 04/04/93

CS/PM/2024

LR/lr

Brussels, 2 April 1993

PRACTICAL GUIDE N. 1

A PRACTICAL GUIDE FOR USERS OF EEC DIRECTIVES ON MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS

(preliminary draft updated to 2 April 1993)

This document, which is now available only in English, is a very preliminary and incomplete working document. Before consulting this document, read carefully the preface. Any suggestions about how to improve this document are welcome.

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COMMISSION
OF THE EUROPEAN
COMMUNITIES

Directorate-General
Internal Market and Industrial Affairs

Brussels, 02/05/93

CS/PM/2024 add 1

SUPPLEMENT N.1 TO PRACTICAL GUIDE N.1

1. CORRIGENDUM N. 1 TO *SOME* COPIES OF "PRACTICAL GUIDE N. 1"

In ***some copies*** of "Practical Guide N.1" (CS/PM/2024) diffused before the 1st May 1993 the following corrections shall be made:

1.1 **on p. 18, point 4.2, 4th line**

change "..them are listed" into "..them are **not** listed",

1.2 **on p.58, NOTA BENE N. 3**

change "0.5 micron" into "**500** micron";

1.3 **on p. 103, 2 comma, first line and third indent (last line)**

change "0.025 mg/kg" into "0.025 mg/kg **bw** "

2. INTERPRETATION

The Commission services was asked whether the guidelines for obtaining migration data appearing in "Practical Guide N.1" (see p. 58 and following) are also applicable when checking the compliance of an article with the EEC Directives.

According the Commission services, the answer is yes. But, please, read carefully the conditions to be fulfilled in order to use conditions other than those fixed in the EEC Directives.

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TABLE OF CONTENTS

Nota bene: This preliminary version contains only the preface and annexes. The other sections are indicated as remainders. They will be written later.

1. PREFACE

This "Practical Guide" is addressed to all persons concerned with the application of Directives on materials and articles intended to come into contact with foodstuffs.

This document has no legally binding value and is intended to provide:

a) **information on the current status of the Community and national legislation as well as other Community and non Community documents which are not legally binding;**

b) **guidelines for a correct application of Community and national legislation;**

c) **guidelines for the application of general principles or rules for which the legislation does not give the needed details;**

d) **guidelines for all cases where either there is no yet a legal solution (e.g. regulation on dyestuffs or catalysts for plastics) or the matter does not lend itself to a legal solution (e.g. modification of organoleptic characters);**

e) **guidelines for checking the compliance of the material and article, particularly where the Directive does not give instructions (e.g. where the check of global migration for plastics fails for technical reasons);**

f) **guidelines for the procedures to be followed and data to be submitted for authorisation of a new substance on the Community lists or for the re-evaluation of an existing substance;**

g) **indications of future Community legislation.**

It is recognised that this " Practical guide " is largely incomplete and that it will subject to numerous integrations and amendments, particularly as regards the format. However this guide has been circulated outside the Commission, even though it is in an incomplete form, to give the best possible current guidance since all the EEC Directives adopted before 1st January 1993 are now in effect.

This "Practical Guide" has been drafted by the "Foodstuffs" Division of the General Directorate "Internal Market and Industrial Affairs", after consultation of working group "Packaging" of the Scientific Committee for Food (SCF) and the assistance of a task group of governmental and professional experts. However further consultation with the above mentioned groups and other different bodies (e.g. Consultative Committee for Foodstuffs) is planned in order to obtain a larger consensus.

In principle, this document intends to answer, as much as possible, the relevant questions or comments raised in letters/faxes, particularly as regards problems of impurities, of mixture, of the data to be submitted to the SCF, of the use of polymers used as additives, of the request about the evaluation of the SCF. Moreover, this document takes into account all the proposal

of changes to the previous version of this document, transmitted by European professional associations or by individuals. However, not all the suggestions have been accepted by the Commission services, because some of them differ from the SCF or Commission services point of view. All the above mentioned associations and individuals, if not fully satisfied, may write again to the "Commission of the European Communities, DG III (for the attention to Mr. L. Rossi, 200 rue de la Loi, B-1049 Brussels)", referring to the previous correspondence and **enclosing a copy of it and a label with its address**. It should be stressed that some questions relating to scientific field, mainly toxicology, oblige the Commission services to ask the opinion of other bodies i.e. the SCF and, therefore, a long delay in answering should be considered as normal.

Copies of this document as well as "Synoptic 6" can be obtained by application to the addresses given below.

If you are affiliated, send a request to the following of European professional organisation (in alphabetical order):

APME, Avenue van Nieuwenhuise, 4 -bte 10, B-1160 Brussels
BLIC, Avenue des Arts, 2 -B-1040 Brussels
CEFIC, Avenue van Nieuwenhuise, 4 - Bte 10 - B-1160 - Brussels
CEPE, Avenue van Nieuwenhuise, 4 -bte 10, B-1160 Brussels
CEPI, Avenue Louise, 306 -B-1050 Brussels
CIIA, rue de la Loi, 74 -Bte 9, B-1040 Brussels
CITPA, Arndstrasse, 47 -D-6000 Frankfurt/Main
EAA, Avenue de Broqueville 12 -B-1150 Brussels
EFPA, rue de la Presse, 4 -B-1000 Bruxelles
EUPC, Avenue Cortemberg, 66, B-1040 Brussels
EUROMETAUX, Rue Montoyer, 47 -B-1040 Brussels
FABRIMETAL, Rue des Drapiers, 21, B-1050 Brussels
FEC, rue de Louvre, 58 -F-75002 Paris
PRO-CARTON, Whitfield Street, 67-GB-London W1A 4PU
SEFEL (see Fabrimetal)

If you are not affiliated to the above mentioned organisations send a request to your national authorities ("Focal points")

BELGIQUE: (for the attention of Mr D'Adesky) Ministère de la Santé Publique (Inspection des denrées alimentaires), Cité Administrative de l'Etat, Quartier Vésale B-1010 BRUXELLES
DANMARK: (for the attention of Mr Berg) Levnedsmiddelstyrelsen, Morkoj Bygade, 19 DK-2860 SOBORG
BUNDESREPUBLIK DEUTSCHLAND:(for the attention of Mr Evers) Bundesministerium für Jugend, Familie, Frauen und Gesundheit Deutschherrenstrasse, 87 D-5300 BONN 2
HELLAS: (for the attention of Mr Spyropoulos) Ministère des Finances, Laboratoire Général d'Etat, Rue Anastassion Tsoha, 16, 115.21 ATHENES
ESPAÑA:(for the attention of Mrs Carretero Baeza) Ministerio de Sanidad y Consumo - Direccion General de Salud Alimentaria y Proteccion de los Consumidores Paseo del

Prado, 18 -ES-28014 MADRID

FRANCE: (for the attention of Mrs Motisi) Ministère de l'Economie, des Finances, Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes , Boulevard Vincent Auriol n. 59, 75703 Paris Cedex 13

IRLANDE: (for the attention of Mr Lanvin) EOLAS (The Irish Science & Technology Agency) Glasnevin IRL-DUBLIN 9

ITALIA: (for the attention of Mr Porcelli) Ministero della Sanità Piazza Marconi, 25 I-00144 ROMA

LUXEMBOURG: (for the attention of Mr Arendt) Ministère de la Santé, Division de l'Inspection Sanitaire, Rue de Prague, 5a L-2348-LUXEMBOURG

NEDERLAND: (for the attention of Mr Roelfzema) Ministerie van WVC, Directie VVP Postbus 5406 NL-2280 HK RIJSWIJK

PORTUGAL: (for the attention of Mr Lopes Costa), Instituto de Qualidade Alimentar Rua Alexandre Herculano, 6 P-1100 LISBOA

UNITED KINGDOM: (for the attention of Mr Watson), Food Safety Division Ministry of Agriculture, Fisheries and Food Ergon House c/o Nobel House Smith Square, 17 GB-LONDON SW1P 3JR

These 2 documents are available also to the national Authorities of the AELE countries and some Institutes or Offices as (in alphabetical order)

ASSOGOMMA (Mr Zerilli), Via S. Vittore 36, I- MILANO, ITALIA

CENAM (Mr Sanchez Saez), Carretera de Majadahonda a Pozuelo, Km 2 E-28220 MADRID -SPAIN

CEN (Mr Jeanson) Rue de Stassart, 36, B-1050 BRUXELLES -BELGIQUE

CIVO-TNO (Dr Rijk): Utrechtseweg, 48 Postbus 360, NL3700 AJ ZEIST

CITIP (Casilla de Correo 157, 1650-San Martin, BUENOS AIRES, ARGENTINA

EURO-DATA ANALYSTS .P.O. Box 13, Dorking, Surrey RH 5 4YL, UK.

FEDERCHIMICA (Sig. Terraneo), Viale Accademia, 33 I-20131 MILANO, ITALIA

FDA (Ms Schwartz P.) 200 C Street, S.W. 20204 WASHINGTON DC -USA.

FINNISH PACKAGING ASSOCIATION, (Mr HMLINEN Jorma). Ritarikatu 3b A SF - 00170 HELSINKI 17 -FINLAND

FINNISH PULP AND PAPER RESEARCH INSTITUTE, PO BOX 136 SF-00101 HELSINKI, FINLAND

FRAUNHOFER INSTITUT (Mr Piringer), Fraunhofer-Institut for Lebensmitteln Technology und Verpackung, Schragenhofstrasse, 35 D-8000 MUNCHEN

INRA (Mr. Feigenbaum) F-78352 JOUY-en-JOSAS Cedex FRANCE

HECKMAN Jerome, Keller and Heckman, 1150 17th Street N.W. WASHINGTON D.C. 20036 -USA

INSTITUT D'HYGIENE ET D'EPIDEMIOLOGIE (Mr Gosselé), Rue J. Witsman, 14 B-1050 BRUXELLES -BELGIQUE

INTERNATIONAL PACKAGING CLUB (Mr. LOUIS Pierre), Avenue des Versailles, 42 -75016 PARIS -FRANCE

ISTITUTO SUPERIORE DI SANITÀ (Ms Gramiccioni), Viale Regina Elena 299 ROMA

LNE (Mr. Camus) Rue Gaston Boissier F-75015 PARIS FRANCE

NORWEGIAN FOOD RESEARCH INSTITUTE Osloveien 1, N-1430 AS NORWAY

ORTEP (Mr Jonker), PO Box 70 4380 4B Vlissingen NEDERLAND

PACKFORSK (Ms Salmen),Torshamnsgatan, 24 BOX 9 S-164 93 KISTA -SWEDEN

INSTITUT NAT. RECH. AGRON. (Mr. Pascal) F-78350 JOUY-EN-JOSAS -FRANCE

RCC (Mr Wietscorke R), CH-4452 ITINGEN - BASEL

ANNEX 1

GUIDELINES ON THE COMMMUNITY POSITIVE LISTS FOR PLASTICS

GUIDELINES ON THE COMMUNITY POSITIVE LISTS FOR PLASTICS

1. POSITIVE LISTS

In this chapter the concept of positive list for plastics and its application are discussed. However it has to be stressed that the "Synoptic 6" is now only a provisional list of substances and not yet a positive list.

The Directive 89/109/EEC provides in article 3 that, for certain groups of materials and articles, the specific Directives may include "a list of the substances the use of which is authorized to the exclusion of all others (positive list)". The Directive 90/128/EEC has already established a positive list, although it is restricted to monomers and other starting substances for certain types of plastics.

It is recognized that the aim of a positive list is to protect the consumer against the risks for health from exposure to substances migrating into the food. Therefore, theoretically, the positive list could contain only those substances which may migrate into foodstuffs (see also the introduction of the "SCF Guidelines"", pag. 47).

However, unless one applies a system which authorizes individually every possible finished material and article, it is, practically impossible to know "a priori" the migration of a substance in all the possible situations. For the same reasons, it is also difficult to establish, as an alternative, a positive list of all the substances which could be present in the finished material or article.

Therefore, the Commission of the European Communities (Commission), in accordance with the opinion of the SCF and with the principle on which the "national" positive lists have been based, has chosen from the beginning, the usual system of the **list of all the substances deliberately used in the manufacture of the finished material and article, hereinafter called "positive list"**. These substances should therefore be requested for authorization (application).

As a consequence of this decision, the Community list does not contain substances, not intentionally added, but which may be present in the finished product such as:

- impurities in the components used;
- reaction intermediates (e.g. oligomers);
- decomposition products.

This is, in fact, clearly set out in Annex 2, paragraph 3 of the Directive 90/128/EEC. However it shall be stressed that information on the mentioned substances shall be contained in the technical dossier accompanying a request for authorization, according to the "SCF Guidelines" (pag 47).

2. COMMUNITY POSITIVE LISTS

The Commission services are preparing a positive list concerning the following products:

a) plastics;
b) surface coatings obtained from resinous or polymerized products in liquid, powder or dispersion form, such as varnishes (epoxyresins included), lacquers, paints, etc..

Silicones, ion exchange resins, adhesives and printing inks are not yet covered by these lists. These products will be considered later.

According the present intentions of the Commission services, the Community positive list for plastics and varnishes will be established by Commission Directive(s) and it will be enforced from 1 January 1997. A first positive list of monomers for some types of plastics has already been adopted (Directive 90/129/EEC) and it will be progressivelly extended to the additives and will be applied to all the types of plastics and varnishes. In view of this extension, the Commission services prepared a working, non binding, document called "Synoptic 6" in which all the monomers and additives (see the explanation of the terms in paragraphs 2.1 and 2.2) authorized or used at national level have been included, applying the criteria described in the Appendix (pag. 21)

Future "possible" rules concerning, for example, catalysts, colorants, inks and adhesives will be considered later. At this stage, the Commission services are unable to specify whether the list will be extended to these products. Therefore any extrapolation of the list to these products is gratuitous. Moreover the Commission services can only add that the rules to be applied to these products will be examined only after that the positive list for monomers and additives is officially adopted and that they are unable to specify any date. Please, do not ask for further information on this matter.

However, questions may arise out of the application of the sentence "substances deliberately used in the manufacture of the finished material and article" when it is applied to the possible Community lists. The following paragraphs 2.1 and 2.2 should help the reader in clarifying these questions.

2.1 Positive list of monomers and other starting substances

2.1.1. Generalities

Monomer and other starting substance" means any substance used in the manufacture of a macromolecule, which constitutes the repeating unit of a polymer chain or polymer network of any substance used in the manufacture of a plastic for food contact application. It includes also the substances used to modify existing natural or synthetic macromolecular substances. According to Directive 90/128/EEC, Annex 2, paragraph 1, the following substances are included in this definition:

"- substances undergoing polymerization, which include polycondensation, polyaddition or any other similar process, to manufacture macromolecules;
- natural or synthetic macromolecular substances used in the manufacture of modified macromolecules, if the monomers or the other starting substances required to synthesize them are not included in the list;
- substances used to modify existing natural or synthetic macromolecular substances."

Although the definition and the examples seem very precise, some difficulties arise in the identification of the "monomers and other starting substances" in practice.

2.1.2. Monomers and other starting substances for thermoplastics.

In this case the definition is clear by itself. The applicants should present applications for all the substances added deliberately as "monomer or starting substance" to a polymerization medium to obtain a polymer. The only permitted exceptions provided by Directive 90/128/EEC, Annex 2, paragraph 3 are:

- "the oligomers and natural or synthetic macromolecular substances as well as their mixtures, if the monomers or starting substances required to synthesize them are included in the list.
- the mixtures of the authorized substances."

Therefore also the esters deriving from an acid and an alcohol contained in the Section A of the positive list of monomers shall be subject to an application. In fact, the SCF believes that the esters may have different biological effects from the acids and alcohols from which they are derived. However, in this case, the technical dossier accompanying the application, need not contain the toxicological data, if it is shown that the esters hydrolyse completely.

2.1.3 Monomers and other starting substances for thermosets.

The definition given in the paragraph 2.1.1 needs further explanation. The thermosets are produced in a different manner depending on the various types of thermosets. However the complete process of polymerization can be summarized in the following phases:

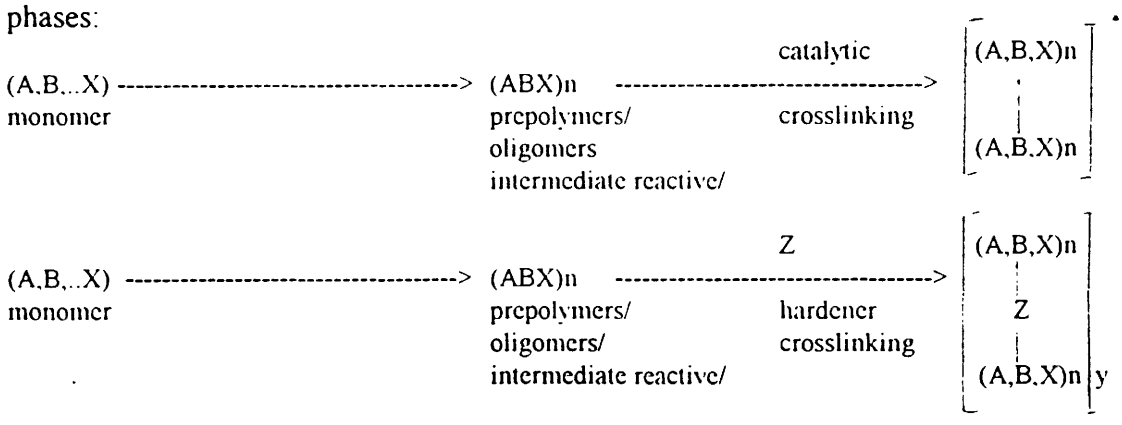

Figure 1

The phases I, II and III could be considered all "polymerization process" and therefore all the substances appearing in figure 1, (A, B..X), (ABX)n could be considered "monomers and other starting substances", and, therefore, they could be individually appear in the positive list. However, it has to be noted that:

- the phases I, II and III could each be carried out in a different manner and not always by the same producers;

- that the number of the possible intermediate substances, the so called "prepolymers", could be very large.

Therefore it would not be "practical" to require the application and the listing of all the above mentioned substances. Moreover, taking into account that the risk for the consumer may derive, mainly, from the presence in the finished product of the monomers or starting substances in figure, the choice of listing only these "monomers and starting substances" seems the more appropriate.

In conclusion, the Commission services, after consulting the SCF, require that only the so called "monomers and starting substances" (see figure 1, pag. 9) should be requested for an authorization according to "SCF Guidelines".

In view of this decision the prepolymers (ABX)n should be considered as reaction intermediates, and, therefore, need not be listed. Information on these reaction intermediates as well as on decomposition products or impurities of the "monomers and starting substances" should be contained in the technical dossier which accompanies any substance to be authorized, according to the "SCF Guidelines" (see points 1 and 2 on pag. 49 and 50).

2.2. Positive list of additives

"Additive" means any substance which is added either to polymers ("Category I") or to the polymerization medium ("Category II") in order to achieve a technical effect.

In order to assist the applicants in the request for an authorization, the Commission services have prepared, as an example, the following list of usual categories of substances covered by all the new definition of the term "additive":

"Category I"

- antifoaming agents
- antiskinning agents
- antioxidants
- antistatic agents
- dryers
- emulsifiers
- fillers

- flame retardants
- foaming agents
- hardening agents
- impact modifiers
- lubricants
- miscellaneous additives
- optical brighteners
- plasticizers
- preservatives
- protective colloids
- reinforcements
- release agents
- solvents
- stabilizers
- thickeners
- UV absorbers

"Category II"

- anti-foam reagents/degassing agents
- blowing agents
- buffering agents
- build-up suppressants
- dispersing aids
- emulsifiers
- flow control agents
- nucleating agents
- pH regulators
- solvents
- surfactants
- suspension agents
- stabilizers
- thickening agents
- water treatment reagents

NOTA BENE:
The following substances "Substances which directly influence the formation of polymers" are excluded from the "additive list". They include, for example:

- accelerators
- catalysts
- catalyst deactivators
- catalyst supports
- catalyst modifiers
- chain scission reagents
- chain transfer or extending agents
- chain stop reagents
- cross-linking agents
- initiators and promoters

- molecular weight regulators
- polymerization inhibitors
- redox agents

3. IMPURITIES AND MIXTURES

Although the Directive 90/128/EEC does not define these two terms, some practical guidelines are given below in order to try to avoid misunderstanding about the use of these two terms in the "Food packaging" documents of the Commission of the European Communities.

The main differences between impurities and constituents of mixtures are summarized below.

Substance	Impurity	Constituent of mixtures
Presence is deliberate	no	yes
It has a technological function	no	yes
It requires an authorization	no*	yes
It is specified on the positive list	no*	yes

*) In some exceptional cases an impurity may appear in general purity criteria (to be established later) or in the positive list itself.

3.1 Informations on the impurities

The Directive 90/128/EEC specifies clearly in Annex II, point 3 that the impurities of the authorized substances should not be listed and, therefore, do not require specific authorization.

- If impurities are substances which are listed in the positive list, it is the responsibility of the manufacturer that the migrations of these impurities must stay within the specific migration limitations or restrictions indicated in the Directive 90/128/EEC and following;

- if impurities are substances which are not listed in the positive list, it remains the responsibility of the manufacturer of the finished material and article that "the materials and articles which contain impurities shall comply with the requirements stated in Article 2 of Directive 89/109/EEC" i.e. they do not transfer these impurities to foodstuffs "in quantities which could

  - endanger human health,

  - bring about an unacceptable change in the composition of the foodstuffs or a deterioration in the organoleptic characteristics thereof."

Moreover, in the "SCF Guidelines" (see pag. 47) it is stated that the applicant should give in the technical dossier accompanying any application, the information requested in point 1.1.4 (pag.49) and point 2.3 (pag.50). If necessary, the SCF may decide to put

some restrictions on the presence of the impurities.

NOTA BENE N. 1: Data base on substances authorized

A data base is being prepared for all monomers listed in Section A of the Directive 90/128/EEC and it will be extended to include all the substances appearing in future EEC Directives. The data base will include purity data, physical properties and spectra for commercial samples of every substance. This should give a clear indication if a particular substance has a purity problem and could form the basis of a monomer specification. Further information on the availability of this data bank and how it can be obtained may be addressed to:

MAFF Food Science Laboratory
("Program: Reference substance for food packaging")
Colney Lane
Norwich NR4 7UQ
UNITED KINGDOM

Phone: (0603)259350
Fax: (0603)501123

NOTA BENE N. 2 :Impurities in fats and fatty acids derived from natural raw materials

It is generally recognized that the presence of minor amounts of certain fatty acids in natural oils e.g. fatty acids with odd numbers of carbon atoms should be dealt with as impurities of the natural oil and therefore form part of the specification of the individually listed major components. In this way it would not be necessary that all these "rare" acids appear in the positive list.

3.2 Informations on the mixtures

The objective of this section is to help industry to foresee the number of tests which will be required by the SCF for the evaluation of a mixture.

"Mixture" means any physical combination of substances, where each constituent keeps its chemical identity. Therefore the mixture where chemical reactions occur between the individuals are not covered by this definition.

3.2.1 Synthetic mixtures

"Synthetic mixture" means any mixture made by intentionally mixing up the individual constituents.

The applicant should present a separate application for any component deliberately used in making up a mixture independently of its proportion in the mixture. In fact it would not be logical not to request an application for a substance added deliberately as a component of a mixture, when, at the same time, an application is requested for

additives, even if these are added in very low quantity.

3.2.2 Possible procedures for authorization of mixtures other than synthetic mixtures

"Mixture other than synthetic mixture" means any mixture arising from natural sources ("mixture from natural sources") or from the production process ("process mixture).

a) Mixtures from natural sources

In principle, the applicant should present a application for the mixtures from natural sources (see later, procedure A"). In fact, for the mixtures derived from natural sources there are many factors such as origin of source, climate, chemical treatment, which make it impossible to give exact descriptions of the components of mixtures. Technical processes like distillation, ethoxylation, hydrogenation, create an artificial distribution of the components, thus forming a huge number of individual components. In many cases it is therefore impossible to list all the components for authorization and the mixture with the best available specification should be submitted for authorization.

b) Process mixtures

"Process mixture" means a mixture arising from a production process. For instance, "diisononylphthalate" is not really a single compound but a mixture of differents compounds. For producing diisonylphthalate (DINP) some industries use a mixture of C9-alcohols consisting mainly of mono-methyl substituted octanols and dimethyl substituted heptanols (derived from mono-, di-, and tri-methyl branched olefins commercially produced). Some C8 and C10 alcohols are also present. Therefore the DINP should be considered as a mixture of all the possible isomers of C8-C10 alcohols.

The applicant has three options:

a) he may present an application for each component of the mixture (Procedure A)

b) he may present an application for the mixture (Procedure B);

c) may present an application for the mixture giving the toxicological data for one or several representative components of the mixture (Procedure C).

The advantages and disadvantages of the possible procedures are summarized below.

Procedure A.

The applicant introduces an application for those individual components of the mixture which are not yet included in the Community positive lists. In this case the toxicological tests should be carried out on possible samples of the individual component, which should be as pure as possible.

The advantages are:

- that future applications for mixtures having the same qualitative composition but "different" quantitative composition are avoided;

- that the need for a precise and therefore complicated description of the mixture and the problem of the formulation of the restriction, if any, are avoided;

The disadvantage (but a very expensive disadvantage for the applicant) consists of the need to supply the toxicological data for every listed component.

Procedure B.

The applicant introduces an application for the mixture as produced commercially, giving the information requested in paragraph 1 of the "SCF Guidelines"(pag. 49) as well as the results of the toxicological tests carried out on the commercial mixture.

The advantage (for the applicant) is the limiting of the toxicological tests to the commercial mixture.

The disadvantages are:

- that authorization will be given only to the requested mixture and for the other mixtures corresponding to the declared composition. Therefore:

  (i) the legislator should describe exactly the mixture authorized;

  (ii) mixtures having the same qualitative composition but "different" quantitative composition need to be authorized separately;

  (iii) the SCF and the legislator should find a way to express the restrictions, if any, based on the results of toxicity tests. For example, if a t-TDI less than 1 mg/kg has been allocated to the mixture, it will be difficult to enforce the corresponding SML because, generally, the mixtures are not determinable analytically.

  One of the possible solutions for this problem (expression of a

quantitative restriction) is indicated hereinafter.

If the mixture comprises mainly substances of similar structure and similar molecular weight (e.g. isomers, C8-C10 alkyl mixtures), then it may be assumed that each component migrates to approximately the same extent - i.e. the composition of the migrated substance will be approximately the same as that of the original product.

Thus, if it is not feasible to determine the mixture as a whole (e.g. be derivatizing to a common substance or by summing peak areas), then it should be possible to measure the migration of one specific component of the mixture only (e.g. the major component) and to calculate the total migration of the mixture from this figure i.e. if the substance determined is contained in X% in the mixture and its migrated level is Y mg/kg, then the calculated migration of the mixture is (Y/X) x 100

Procedure C

The applicant introduces an application for the mixture but will present toxicological and migration data only for one or more components, selected as representatives of the mixture. For example, if all the components of the mixture are homologous compounds, it can be envisaged that the evaluation is made on the basis of the following information:

- a set of toxicity data on one or on a few components of the mixture;
- scientific evidence (e.g. structure-activity correlation) showing how the toxic properties of the other components are related to those of the previous compound.

This procedure combines the advantages of the previous procedures but avoids the disadvantages. However, it should be emphasized that it remains the responsibility of the SCF to decide whether the available data are acceptable and whether additional tests on another compound would be needed.

The SCF suggested the "Procedure A" because it avoids any difficulty in the examination of the technical dossier of the "process mixtures" and in fixing the consequent restrictions, if any. However the SCF, aware of the possible difficulties in applying strictly "Procedure A", recognized that "a general rule" cannot be established and that it will decide "case by case".

Therefore, the Commission recommends to applicants to follow Procedure A or to introduce the application accompanied by a technical dossier containing only the data of the paragraph 1 of the "SCF Guidelines" (see pag. 49) and a possible strategy to obtain toxicological data. For example. if the applicant intends to follow Procedure C, he should present the scientific data showing how the toxic behaviour(s) of the other components are related to that (those)

of the previous compound(s). The SCF, after examination of the technical dossier, will inform the applicant whether the chosen strategy is acceptable or whether other alternatives should be followed.

3.2.3. Recommended procedure for the evaluation of a mixture

1st step: The applicant transmits a technical dossier describing the mixture and communicating its choice of the procedure (A, B or C).

2nd step The SCF examines the dossier and decides on the procedure to be followed by the applicant.

3rd step The applicant carries out the toxicity and migration tests.

4th step Final evaluation by SCF.

3.2.4. Other questions on mixtures and on the individual components on mixture

Some other questions have been raised. They are discussed below with the corresponding answer and explanation.

A. If a mixture A+B+C (where A, B, C mean the individual components of a natural or synthetic mixture) appears in the Community positive lists, are the individual components automatically authorized?

No, not always because the toxicity of a substance depends on the dose of substance ingested by the animals under examination in the toxicological test. Therefore the data obtained on a certain % of the substance cannot always be extrapolated to a 100 % of a substance.

B. If the various components of a mixture appear listed individually in the positive list, all the mixtures are automatically authorized?

Yes.

4. POLYMERS USED AS STARTING SUBSTANCES OR AS ADDITIVES

A certain number of questions have been raised as to the necessity of presenting an application for the oligomers or polymers and their allocation in SCF lists. Therefore, it is useful to examine in detail the meaning of these substances and their status in the monomer and additive list and to search for a possible solution of the problems raised.

4.1. Explanation of some important terms

In the Directive 90/128/EEC the definition of the different terms does not appear. However the Commission services, after consulting with the SCF, for the application of the Community Directives use the terms according to the meanings which are reported below.

"Monomer and other starting substance" means any substance used in the manufacture of a macromolecule, which constitutes the repeating unit of a polymer chain or of a polymer network of any substance used for the manufacture of a plastic for food contact application. It also includes the substances used to modify existing natural or synthetic macromolecular substances.

"Oligomer" means any substance consisting of a few repeating units of the monomer or starting substance, e.g. approximately from C_2 to C_{20} repeating units.

"Polymer" means any macromolecular compound obtained by polymerization (polyaddition, polycondensation or any other similar process) of monomers and other starting substances.

"Polymeric additive" means any polymer that cannot be used as such for the manufacture of finished materials and articles and which may be added to plastics in order to achieve a technical effect.

"Prepolymer" means any reactive polymer with only a few repeating units, e.g. approximately from C_2 to C_{20} repeating units, which has been prepared deliberately for use as a monomer or starting substance.

"Plastic" means any polymer to which additives may have been added and which is used as such for the manufacture of finished materials and articles.

"Blend" means any mixture of polymers and/or plastics in the same physical state, each of which can be used for the manufacture of finished materials and articles.

4.2. Status of oligomers and polymers used as "monomers or starting substances"

The Directive 90/128/EEC in Annex 2 establishes that the list of monomers and other starting substances includes natural or synthetic macromolecular substances used in the manufacture of modified macromolecules, if the monomers or the other starting substances required to synthesize them are **not** listed (e.g. polyvinylalcohol as vinylalcohol is non existent). Moreover this list does not include the following substances although they may be present:

- oligomers and natural or synthetic macromolecular substances as well as their mixtures, if the monomers or starting substances required to synthesize them are included in the list.

- mixtures of the authorized substances.

It must be stressed that the "blends of the approved polymers used as starting substances" are automatically authorized and, therefore, should not be listed.

4.3 Status of oligomers and polymers used as "additives"

The future list of additives (see the document "Synoptic 6") lists:

- oligomers and natural or synthetic macromolecular substances as well as their mixtures, if the monomers or starting substances required to synthesize them are not included in the list (same as monomer list);

- oligomers and natural or synthetic macromolecular substances as well as their mixtures, although the monomers or starting substances required to synthesize them are included in the list (contrarily to the monomer list);

4.4 Why this difference in the treatment of oligomers and polymers used as starting substances and used as additives?

The reason for this is that, if oligomers and polymers are used as "monomer or starting substances", the end result of polymerisation would be a much higher molecular weight polymer which would be less likely to migrate that the starting substance. That does not happen when the oligomers and the polymers are used as polymeric additives. They should remain unchanged and, in principle, they may migrate, if the molecular weight is not so high. Therefore, in principle, they should be listed. In fact these substances have a different toxicity from the monomers required to synthesize them.

4.5. A practical approach for the polymers used as "additives"

All the polymers used as additives shall be listed and an application made following the "Note for guidance" (see pag. 23), accompanied by a technical dossier, shall be transmitted. However the technical dossier can be limited first only to the data requested in paragraph 1.4 of the "SCF Guidelines" (see pag. 50). According to the SCF, they will be divided in two categories:

a) Polymers used as additives with a molecular weight distribution, the lower end of which is greater than 1.000 daltons (1 dalton is equivalent to $1.66\ 10^{-24}$ grams

   - They are toxicologically acceptable and classified in list 3 with the indication "polymer" without specific individual evaluation, if their

monomers or starting substances are on lists 0, 1, 2, 3 and 4.

- They need an individual evaluation. Technological and toxicological data on the monomers shall be supplied according to "SCF Guidelines" (see pag. 47), if their monomers or starting substances are on lists 6, 7, 8, 9 or not yet evaluated.

b) Polymers used as additives with part of their molecular weight distribution below or equal to 1.000 daltons.

the interested persons should first provide the information requested in the point 1.4 of the "SCF Guidelines"". Depending on this information, the SCF will decide whether it is necessary to provide toxicity data according to the "SCF Guidelines"".

5. Threshold of regulation

Currently, "Threshold of regulation" means a level of quantity of a substance ingested (or, alternatively, a level of migration), below which the substance is not considered by the legislation (i.e. there is not a need to introduce a application). This concept is now under discussion in USA and the hypothetical level is around 0.5 - 1 ppb in the diet. However some exceptions could be provided.

The Commission services, after consultation with the SCF, are not yet in favour of this concept, because it rules out the advantage of a positive list (mainly, to avoid the authorization of very dangerous substances). They noted that the "SCF Guidelines" allowed the applicant to deviate from the guidelines, if the reason for this deviation is indicated. ***Therefore, if an applicant believes that for its application the risk connected with the use of a "new" substance is not significant, he may introduce an application with a limited information explaining why he retains the remaining information. The SCF will examine the technical dossier and request other data, if necessary.***

6. Chemical recycling

Recently new procedures for obtaining monomers have been introduced eg. by depolymerization of the finished articles already used. The Commission services consider that these monomers can be used as starting substances for the manufacture of plastics intended to come into contact with foodstuffs, if they comply with the applicable EEC Directives. As regards of the purity criteria of the mentioned monomers, see paragraphe 3.1 on pag. 12.

CRITERIA USED BY THE COMMISSION FOR PREPARING THE DRAFT OF THE COMMUNITY POSITIVE LISTS CONTAINED IN "SYNOPTIC 6"

N.B. The development of the synoptic documents is so complex, that it is impossible to summarize all the decisions taken in the last ten years on this matter. In some cases the decisions on the introduction/deletion/modification of a substance have been taken after consultation with the competent authorities and have been based on "practical" criteria. Therefore the criteria summarized below, although they reflect the past situation of the lists, should be considered in a more flexible manner and the Commission services are not obliged to follow them. In any case, the presence of a substance in "Synoptic 6" is not a guarantee for its presence in the future positive list, because only the substances classified by SCF into lists 0-4 before 31 December 1993 or, in any case, before the drafting of the proposal of Directive (on varnishes and on additives) will be included in that list.

Recently, the Commission services had not accepted any application for a new notified substances unless it was accompanied by the technical dossier requested by the SCF in its guidelines and it was transmitted according to the instructions given in the EEC document "Note for guidance" (see pag. 23).

In principle, the Commission included in the draft all the substances which, according to the definitions of "monomers and other substances" and "additives" given in this document, are enumerated in the national lists of the following countries:

a) Belgium
b) Federal Republic of Germany (see later)
c) France (see later)
d) Italy
e) Netherlands
f) Spain

As regards the United Kingdom, the Commission services accepted in the past a British national list of the following substances, if they were requested officially by the government:

a) substances included in the "Code of practice" of the British Plastics Federation

b) some substances included in the Food and Drug Administration list.

- before 31 December 1988 for the monomers and other starting substances;
- before 31 December 1990 for the additives.

As regards the Federal Republic of Germany the Commission, at the specific request of the governmental authorities, has considered as the German list for surface coatings the substances included in the current BGA recommandations on coatings (chapter XIV and XL) as well as the draft revision of recommendation XL, with the exception of those substances not contained in "Synoptic 2" or in at least one of the existing national lists

As regards the other Member States which do not have a positive list (including France*), the Commission, in the past, has accepted to introduce some substances (really only a few) if these have been requested specifically.

As regards the epoxyresins, for which there are no positive lists at national level, the Commission introduced all the substances requested officially by the European professional organization (CEFIC). These substances have been included in the coating lists, which has been added to the lists appearing in the "Synoptic 6".

(*) France does not have a list of monomers and other starting substances.

ANNEX 2

NOTE FOR GUIDANCE

PRESENTATION OF A REQUEST FOR ASSESSMENT OF A SUBSTANCE TO BE USED IN PLASTICS MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS

CONTENTS

WARNING TO THE APPLICANTS

PROVIDE THE DATA REQUESTED BY SCF AS SOON AS POSSIBLE, OTHERWISE YOUR SUBSTANCE MAY NOT APPEAR IN THE FUTURE COMMUNITY LIST.

YOUR APPLICATION MAY NOT BE EXAMINED, IF YOU DO NOT FOLLOW COMMISSION SERVICES GUIDELINES CORRECTLY.

AVOID MAKING ONE OF THE FOLLOWING MOST COMMON MISTAKES, IF YOU WANT YOUR APPLICATION TO BE EXAMINED.

THE TEN RULES
FOR FOOD PACKAGING APPLICATIONS

1. READ CAREFULLY AND FOLLOW STRICTLY THE "NOTE FOR GUIDANCE" IN THE PREPARATION OF ANY APPLICATION AND BEFORE ANY REQUEST OF INFORMATION.

2. CONTACT EUROPEAN PROFESSIONAL ASSOCIATIONS OR NATIONAL AUTHORITIES, IF YOU NEED FURTHER EXPLANATION.

3. CONTACT THE COMMISSION SERVICES ONLY IF YOU ARE LOCATED OUTSIDE OF THE EUROPEAN COMMUNITIES OR IF, BY APPLYING THE RULES N.1 AND N.2, YOU DID NOT RECEIVE A SATISFACTORY ANSWER.

4. SEND A SINGLE APPLICATION FOR ANY SINGLE SUBSTANCE.

5. USE ONLY THE MODEL OF LETTERS PROVIDED IN THE "NOTE FOR GUIDANCE" AND ENCLOSE ALL THE MENTIONED DOCUMENTS AND SEND THEM TO ALL INDICATED PERSONS.

6. DO NOT SEND AN INCOMPLETE TECHNICAL DOSSIERS, BECAUSE THE SCF WILL REFUSE TO EXAMINE IT, UNLESS YOU ARE ABLE TO GIVE AN EXPLANATION IN THE "SUMMARY DATA SHEET".

7. REMEMBER a) TO ALWAYS FILL OUT A "SUMMARY DATA SHEET", INCLUDING THE SUMMARIES OF MIGRATION DATA AND OF TOXICOLOGICAL DATA AND b) TO SEND THE ORIGINAL DATA (AND NOT ONLY REFERENCES).

8. CONSULT EUROPEAN PROFESSIONAL ORGANIZATIONS OR NATIONAL AUTHORITIES BEFORE TRANSMITTING A TECHNICAL DOSSIER TO THE COMMISSION SERVICES, IN ORDER TO BE SURE THAT THERE IS NO CHANGE IN THE NOTE FOR GUIDANCE.

9. SEND LETTERS ONLY. DO NOT SEND FAXES OR FAXES FOLLOWED BY LETTERS

10. INCLUDE AN ADDRESS LABEL WITH YOUR LETTER, IF YOU WISH TO RECEIVE A QUICK ANSWER. ALWAYS ADD A COPY OF THE PREVIOUS CORRESPONDENCE, IF YOU REFERS TO IT IN YOUR LETTER

THE SEVEN MAIN COMMON MISTAKES IN THE APPLICATIONS

1. NOT USING THE APPROPRIATE MODEL LETTER

2. NOT SENDING FULL DOSSIER TO COMMISSION AND RIVM

3. SENDING AN *INCOMPLETE* TECHNICAL DOSSIER OR A DOSSIER DEVIATING FROM GUIDELINES WITHOUT ANY EXPLANATION

4. NOT SENDING REQUESTED DATA OR SENDING DATA NO REQUESTED

5. NOT SENDING THE "SUMMARY DATA SHEET" OR SENDING THE "SUMMARY DATA SHEET" WITHOUT THE APPROPRIATE SUMMARY OF THE MIGRATION DATA OR TOXICOLOGICAL DATA.

6. PUTTING REFERENCES OR SUMMARIES IN THE TECHNICAL DOSSIER WITHOUT SENDING THE ORIGINAL DATA.

7. SENDING A SINGLE APPLICATION FOR MORE THAN ONE SUBTANCE.

NOTE FOR GUIDANCE

1. INTRODUCTION

The aim of this note is to provide:

a) guidelines for requesting addition of new substances to the "Synoptic 6" and/or to the national positive lists;

b) guidelines for requesting re-evaluation of substances included in the "Synoptic 6";

c) guidelines for submission of technical dossiers accompanying the requests.

In order to facilitate the examination of the technical dossiers and to avoid delays, the applicant is invited to follow strictly these guidelines.

2. ADDITION OF A NEW SUBSTANCE

In order to obtain the addition of a new substance in "Synoptic 6" and later in Directives eg in Directive 90/128/EEC and future extensions, any person concerned is invited to submit an official request to the Commission of the European Communities using model letter 1 (see pag. 32) and enclosing the documentation requested.

3. RE-EVALUATION OF A SUBSTANCE

A number of substances have been classified by the SCF in lists 6 to 8 in "Synoptic 6". This means that the SCF has yet not been able to deliver a final opinion on these substances because of a lack or insufficiency of technical (mainly toxicological) information. The SCF expects the necessary information on these substances to be provided, so that they can be re-evaluated. Moreover a substance classified in lists 0-5, may be re-evaluated, if the applicant provides new documentation.

In order to have a substance re-evaluated, the person concerned is invited to submit a request to the Commission, using model letter 2 (see pag. 33) and enclosing the documentation requested.

4. SPECIFIC CASES

4.1. Addition of a new substance to the national positive lists

In order to have a new substance added to the national positive list waiting for a Community Directive (this situation applies to the monomers for varnishes and for additives for plastics and varnishes), the applicant is invited:

a) to submit a request to the national authority, using model letter 3 (see pag. 34)

and enclosing the documentation requested;

b) to submit an official request to the Commission of the European Communities using model letter 1 (see pag. 32) and enclosing the same documentation transmitted to the national authorities. The request will be accompanied by a copy of the request transmitted to the national authorities.

In principle, the Commission services will evaluate the substance through the SCF and will add the substance to "Synoptic 6" establishing the appropriate restrictions. The Member State should take into account the evaluation of the SCF and the restriction suggested by the Commission services.

4.2. Submission to the SCF of specifications for substances in list 9.

In order to move a substance from list 9 into another list, the person concerned is invited to submit a request to the Commission, using model letter 4 (see pag. 35) and enclosing the data requested in paragraph 1 of "SCF Guidelines"(see pag. 49)

4.3. Submission to the SCF of additional documentation

During the evaluation or the re-evaluation of a substance any interested person obtaining new information on this substance is invited to submit immediately this information to the Commission, using a model letter 5 (see pag. 36) and enclosing the new documentation.

5. SUBMISSION OF TECHNICAL DOSSIERS

Before submitting a request to the Commission or to the national authorities, as appropriate, the applicant is invited to consult the European professional organizations (see pag. 4) or national authorities (see pag. 88) to check whether the technical documentation is drawn up conforming with this note for guidance and, mainly, in order to be sure that no change has been made to this note for guidance.

It could be, moreover, that in the course of evaluation of the dossier by the SCF it is considered necessary to have additional tests carried out in order to confirm the significance of effects already found or to have additional information. It is expected that such tests will be presented, as far as possible, in the same format as the initial studies.

The number of copies of technical dossiers to be submitted to the various authorities and experts is listed in appendix 2 (pag. 45). You should contact directly national authorities, if you cannot provide the requested copies. See appendix 4 (pag. 88) for the addresses of the national authorities and appendix 5 (pag. 91) for the addresses of the members of the working group "Packaging Materials" of the SCF.

6. CONFIRMATION OF RECEIPT OF AN APPLICATION BY THE COMMISSION

As from 1 January 1993, the Commission services have made it a rule to send a letter to the Applicants in which receipt of the request is acknowledged (see model letters 6 (pag. 37) and 7 (pag. 39)). In this letter the reference number attached by the Commission services to the request is given, and it is recommended that in future correspondence between applicant and Commission this reference number be used. The letter will also state whether or not the request is in compliance with the instructions set out in this Note for Guidance. If the request does not comply with the instructions, the applicant will be informed that the request should be modified to bring it into line with the instructions.

7. ESTIMATED TIME FOR EXAMINATION OF THE TECHNICAL DOSSIER

The working group "Packaging Materials" of the SCF (SCF-WG) will examine the technical documentation as soon as possible but, in principle, not before the second planned meeting after receipt of the request. The SCF will examine the proposal of the classification of the working group as soon as possible but not later, in principle, than the second planned SCF meeting after the opinion of the working group has been available. It is noted that in principle the working group and the SCF will have a meeting every 3 months. These estimated times could obviously be shortened or extended depending on the number of technical dossiers submitted to the Commission, to the commitments of the SCF in other areas and, of course, to the quality of the data submitted. At the end of the SCF's (and not of the working group!) evaluation, the Commission will inform the applicant by letter of the evaluation of the SCF according to model letters 8 (pag.41) and 9 (pag. 43). As regards the inclusion of a new monomer in the EEC approved positive list or other amendment the Annexes of Directive 90/128/EEC and following, it is the intention of the Commission to propose each year a Directive amending 90/128/EEC.

8. MODEL LETTERS

Then formats and the contents of model letters contained in Appendix 1 have been agreed by the national authorities and by the Commission, although other formats may also be used.

APPENDIX 1

MODEL LETTERS: LEGENDA

The numbers between brackets in model letters 1 to 7 have the following meaning:

(1) submit a separate request for every substance

(2) put X in the right case

(3) specify name, address, telephone and fax of applicant firm

(4) specify the chemical name, main chemical synonyms and trade names

(5) specify name, address, telephone and fax of the person responsible for the technical dossier

(6) see pag. 46

(7) see pag. 88

(8) see pag. 91

MODEL LETTER 1

REQUEST FOR ADDITION OF A NEW SUBSTANCE (1)

COMMISSION OF THE EUROPEAN COMMUNITIES
DIRECTORATE GENERAL FOR INDUSTRIAL
AFFAIRS AND INTERNAL MARKET
(For the attention of Mr. Rossi L.)
200, RUE DE LA LOI
B-1049 BRUSSELS

Our reference:..... Date:.....

Subject: Request for addition of a new monomer ☐/additive ☐ (2) to the "Synoptic 6".

The undersigned.....(3).....
.....
requests addition of the following new substance to the "Synoptic 6":
.....(4).....
CAS N.....

Responsible for answering detailed questions on the technical dossier is:
.....(5).....
.....

Enclosed are the following:

1. the technical dossier (6)/the technical dossier will be sent by separate cover.
2. the summary data sheet of the technical dossier (7)
3. a computer diskette containing the summary data sheet (if possible, use Word for Windows or Wordperfect).

One paper copy of the documentation under 1 and 2 and the mentioned diskette has also been sent to the RIVM (for the attention of Ms van Apeldoorn (8)). Another paper copy of the documentation under 1 and 2 and the mentioned diskette without the toxicological data has been sent to the CIVO-TNO (for the attention of Mr Rijk (8)). The other members of the working group included Mr L. Rossi (8), have been provided only with one copy (for Mr Rossi, however two copies) of the documents mentioned under 2. Additionally, a complete set of documentation under 1 and 2 and diskette will be held available for the Commission and sent to the person indicated by the Commission on request.

Yours sincerely

.....

Enclosures.
1. technical dossier/technical dossier sent by separate cover
2. summary data sheet of the technical dossier
3. diskette for computer containing the summary data sheet.

MODEL LETTER 2

REQUEST FOR RE-EVALUATION OF A SUBSTANCE (1)

COMMISSION OF THE EUROPEAN COMMUNITIES
DIRECTORATE GENERAL FOR INDUSTRIAL
AFFAIRS AND INTERNAL MARKET
(For the attention of Mr Rossi L.)
200, RUE DE LA LOI
B-1049 BRUSSELS

Our reference:..... Date.....

Subject: Request for re-evaluation of a monomer ☐/additive ☐ (2) PM/REF.N.....
The undersigned.....(3).....
requests re-evaluation of the following substance:
.....(4).....
CAS N.....

Responsible for answering detailed questions on the technical dossier is:
.....(5).....
.....

Enclosed are the following:

1. the technical dossier (6)/the technical dossier will be sent by separate cover.
2. the summary data sheet of the technical dossier (7)
3. a computer diskette containing the summary data sheet (if possible, use Word for Windows or WordPerfect).

One paper copy of the documentation under 1 and 2 and the mentioned diskette has also been sent to the RIVM (for the attention of Ms van Apeldoorn (8)). Another paper copy of the documentation under 1 and 2 and the mentioned diskette without the toxicological data has been sent to the CIVO-TNO (for the attention of Mr Rijk (8)). The other members of the working group included Mr L. Rossi (8), have been provided only with one copy (for Mr Rossi, however two copies) of the documents mentioned under 2. Additionally, a complete set of documentation under 1 and 2 and diskette will be held available for the Commission and sent to the person indicated by the Commission on request.

Yours sincerely

.....

Enclosures.
1. technical dossier/technical dossier sent by separate cover
2. summary data sheet of the technical dossier
3. diskette for computer containing the summary data sheet.

MODEL LETTER 3

REQUEST FOR ADDITION OF A NEW SUBSTANCE TO THE NATIONAL LIST (1)

-----> NATIONAL AUTHORITY (8)
copy to: Commission of the European Communities

Our reference:..... Date:.....

Subject Request for addition of a new monomer ☐/additive ☐ (2) to the National positive list of substances . PM/REF_N.....

The undersigned.....(3).....
requests addition of the following new substance to the national positive list:
substance.....(4).....
.....CAS.N.....

Responsible for answering detailed questions on the technical dossier is:
.....(5).....
.....

Enclosed are the copies (according to Practical Guide N.1 (pag. 45) of the following:

1. the technical dossier (6)/the technical dossier will be sent by separate cover.
2. the summary data sheet of the technical dossier (7)
3. a computer diskette containing the summary data sheet (if possible, use Word for Windows or WordPerfect).

Yours sincerely

.....

Enclosures.
1. technical dossier/technical dossier sent by separate cover
2. summary data sheet of the technical dossier
3. diskette for computer containing the summary data sheet

MODEL LETTER 4

TRANSMISSION OF SPECIFICATION FOR A SUBSTANCE IN LIST 9 (1)
(see explanation on pag.98)

COMMISSION OF THE EUROPEAN COMMUNITIES
DIRECTORATE GENERAL FOR INDUSTRIAL
AFFAIRS AND INTERNAL MARKET
(For the attention of Mr Rossi L.)
200, RUE DE LA LOI
B-1049 BRUSSELS

Our reference:.....Date:.....

Subject: Specification for a monomer ☐/additive ☐ (2) classified in SCF list 9. PM/REF_N.....

The undersigned.....(3).....provide the specifications requested for the substance.....(4).....
.....CAS N.....

Responsible for answering detailed questions on the technical dossier is:
.....(5).....
Enclosed are the following:

1. the technical dossier (6)/the technical dossier will be sent by separate cover.
2. the summary data sheet of the technical dossier (7)
3. a computer diskette containing the summary data sheet (if possible, use Word for Windows or WordPerfect).

One paper copy of the documentation under 1 and 2 and the mentioned diskette has also been sent to the RIVM (for the attention of Ms van Apeldoorn (8)). Another paper copy of the documentation under 1 and 2 and the mentioned diskette without the toxicological data has been sent to the CIVO-TNO (for the attention of Mr Rijk (8)). The other members of the working group included Mr L. Rossi (8), have been provided only with one copy (for Mr Rossi, however two copies) of the documents mentioned under 2. Additionally, a complete set of documentation under 1 and 2 and diskette will be held available for the Commission and sent to the person indicated by the Commission on request

Yours sincerely

.....

Enclosures. 1. technical dossier/technical dossier sent by separate cover
2. summary data sheet of the technical dossier
3. diskette for computer containing the summary data sheet.

MODEL LETTER 5

SUBMISSION OF ADDITIONAL DOCUMENTATION (1)

Use model letter 2 (pag. 33), because this case corresponds to a re-evaluation of the substance.

MODEL LETTER 6

RECEIPT OF AN APPLICATION BY COMMISSION: FIRST CASE APPLICATION ACCEPTED

Commission
of the European Communities

Scientific Committee for Food

Brussels,.....

Mr/Ms.....
.....
.....
.....

Dear Mr/Ms

Ref:.....

On behalf of the Commission Services, I acknowledge receipt of the documentation referred to above which you have sent for submission to the Scientific Committee for Food.

Your documentation has been classified under reference number CS/PM/.....
In all future correspondence referring to this documentation, please quote this number.

After evaluation by the Scientific Committee for Food (SCF) (see addendum), the Commission will write to inform you of the SCF's opinion.

I should inform you that as a general rule, the scientific basis for the Committee's opinions and in particular the analytical method for the determination of the substance may be made available to the Member States' competent authorities, should they so request. This general rule will be applicable in the case of your submission unless we hear to the contrary within 40 days from the date of this letter.

Yours sincerely

Secretariat of the SCF

Addendum to model letter 6

ESTIMATED TIME FOR EXAMINATION OF THE TECHNICAL DOSSIER

The working group "Packaging Materials" of the SCF will examine the technical documentation as soon as possible but, in principle, not before the second planned meeting after receipt of the request. The SCF will examine the proposal of the classification of the working group as soon as possible but not later, in principle, than the second planned SCF meeting after the opinion of the working group has been available. It is noted that in principle the working group and the SCF will have a meeting every 3 months. These estimated times could obviously be shortened or extended depending on the number of technical dossiers submitted to the Commission, to the commitments of the SCF in other areas and, of course, to the quality of the data submitted. At the end of the SCF's (and not of the working group!) evaluation, the Commission will inform the applicant by letter of the evaluation of the SCF according to model letters 8 or 9. As regards the inclusion of a new monomer in the EEC approved positive list or other amendment the Annexes of Directive 90/128/EEC and following, it is intention of the Commission to propose each year a Directive amending the 90/128/EEC.

MODEL OF LETTER 7

RECEIPT OF AN APPLICATION BY COMMISSION : SECOND CASE APPLICATION REFUSED

Commission
of the European Communities

Scientific Committee for Food

Brussels,.....

Mr/Ms.....
.....
.....
.....

Dear Mr/Ms

Ref:.....

On behalf of the Commission Services, I acknowledge receipt of the documentation referred to above which you have sent for submission to the Scientific Committee for Food.

Your documentation has been classified under reference number CS/PM/.....
In all future correspondence referring to this documentation, please quote this number.

Unfortunately your request does not comply with the guidelines described in the document "Note for Guidance" included in "Practical Guide N.1" for the reasons indicated in the addendum.

Therefore, I regret to inform you that your request cannot be examined until the technical dossier is completed or presented in the specified format set out in the above mentioned document, a copy of which is enclosed for your information. If you cannot conform to the guidelines, the reasons should be given. For further clarification, you are invited to consult your European Professional Association or your National focal point.

Yours sincerely

Secretariat of the SCF

REASONS FOR NON COMPLIANCE

The sign X indicates the reason of the non compliance with the "Note for Guidance". Read carefully the indicated pages of "Note for Guidance" in order to correct the mistake(s).

1.	Not using the appropriate model letter	☐
2.	Not sending full dossier to Commission and RIVM	☐
3.	Sending an *incomplete* technical dossier without any explanation	☐
4.	Not sending requested data or sending the data no requested	☐
5.	Not sending the "summary data sheet" or sending the "Summary data sheet" without an *appropriate* summary of the migration data or toxicological data.	☐
6.	Putting references or summaries in the technical dossier without sending the original data.	☐
7.	Sending a single application for more than one substance.	☐

MODEL LETTER 8

LETTER OF INFORMATION ON A SUBSTANCE CLASSIFIED IN LISTS 0-5

Commission
of the European Communities

Scientific Committee for Food

Brussels,.....

Mr/Ms.....
.....

Dear Mr/Ms

Ref:..... .....

On behalf of the Commission Services, I have a pleasure to inform you on the evaluation given by the Scientific Committee for Food on the substance(s) referred to above.
The Committee classified the substance(s) as follows (see definition of the list in appendix:)

List 0 ..... ☐

List 1..... ☐
ADI= .....
.....
.....

List 2..... ☐
TDI= .....
.....
.....

List 3..... ☐
.....

List 4..... ☐
.....

List 5..... ☐
.....

Yours sincerely

Secretariat of the SCF

DEFINITION OF SCF LISTS 0-5

List 0
Substances, e.g. foods, which may be used in the production of plastic materials and articles, e.g. food ingredients and certain substances known from the intermediate metabolism in man and for which an ADI need not be established for this purpose.

LIST 1
Substances, e.g. food additives, for which an ADI, a temporary ADI (t-ADI), a MTDI, a PMTDI, a PTWI or the classification "acceptable" has been established by this Committee or by JECFA.

LIST 2
Substances for which a TDI or t-TDI has been established by this Committee.

LIST 3
Substances for which an ADI or TDI could not be established, but where the present use could be accepted.

LIST 4

Section A (for monomers)
Substances for which an ADI or TDI could not be established, but which could be used if the substance migrating into foods or in food simulants is not detectable by an agreed sensitive method.

Section B (only for monomers)
Substances for which an ADI or TDI could not be established, but which could be used if the levels of monomer residues in materials and articles intended to come into contact with foodstuffs are reduced as much as possible.

LIST 4 (for additives)
Substances for which an ADI or TDI could not be established, but which could be used if the substance migrating into foods or in food simulants is not detectable by an agreed sensitive method.

LIST 5
Substances which should not be used.

NOTA BENE: for certain substances a double classification appear in the Column SCF_L because there are two parts of the molecule which are toxicologically active.

LETTER OF INFORMATION ON EVALUATION GIVEN BY THE SCF ON A SUBSTANCE CLASSIFIED IN LISTS 6A, 6B, 7, 8, 9 AND WAITING LIST

Commission
of the European Communities

Scientific Committee for Food

Mr/Ms.....

.....

Dear Mr/Ms.....

Ref.....

On behalf of the Commission Services, I am informing you about the evaluation given by the Scientific Committee for Food (SCF) on the substance(s) referred to above. The SCF classified the substance(s) as follows (see definition of the list in appendix:):

List 6A..... ☐

List 6B..... ☐

.....

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List 7..... ☐

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List 8..... ☐

List 9..... ☐

.....

List W..... ☐

.....

The Commission services will therefore not be able to propose the inclusion/retention of your substance in a Community positive list. In order to enable the Commission to deal with your substance and to include in/transfer to Section A of the Directive 90/128/EEC or in "Synoptic 6", you should provide the data requested by the SCF as set out in document "Data requested for substances in lists 6-9 (extract from "Practical Guide N. 1) here enclosed ☐/in your possession already ☐.

Yours sincerely

Secretariat of the SCF

Enclosure:"Data requested for substances in lists 6-9 (extract from "Practical Guide N.1")

DEFINITION OF SCF LISTS 6-9 and List W

List 6

Substances for which there exist suspicions about their toxicity and for which data are lacking or are insufficient. The allocations of substances to this list are mainly based upon similarity of structure of chemical substances already evaluated or known to have functional groups that indicate carcinogenic or other severe toxic properties.

Section A

Substances suspected to have carcinogenic properties. These substances should not be detectable in foods or in food simulants by an appropriate sensitive method for each substance.

Section B

Substances suspected to have toxic properties (other than carcinogenic). Restrictions may be indicated.

List 7

Substances for which some toxicological data exist, but for which an ADI or TDI could not be established. The required additional information should be furnished.

List 8

Substances for which no or only scanty and inadequate data were available.

List 9

Substances and groups of substances which could not be evaluated due to lack of specifications (substances) or to lack of adequate description (groups of substances).
Groups of substances should be replaced, where possible, by individual substances actually in use. Polymers for which the data on identity specified in "SCF Guidelines" are not available.

List W

"Waiting list". Substances not yet included in the existing positive lists of Member States. Although these substances appear in the Synoptic documents, they are not susceptible to be included in the Community lists, lacking the data requested by the Committee.

NOTA BENE: for certain substances a double classification appear in the Column SCF_L because there are two parts of the molecule which are toxicologically active.

APPENDIX 2

NUMBER OF COPIES OF TECHNICAL DOSSIER

The following number of copies of full technical dossier and summary data sheet have to be submitted, according to the indications given in the model letters, to the Commission of the European Communities and/or to the national authorities and/or to the members of the working group "Packaging Materials" of the Scientific Committee for Food (SCF-WG) in case of a request for amendment of the community and/or national positive lists of plastics materials and articles intended to come into contact with foodstuffs:

Country	Full dossier	Summary data sheet
Belgium	3	5
Federal Republic of Germany	3	5
Denmark	3	5
France	3	5
Greece	3	5
Italy	3	5
Ireland	3	5
Luxembourg	3	5
Netherlands	3	5
Portugal	3	5
United Kingdom	3	5
Commission	4*	9**

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*) one full copy addressed **officially** to the Commission ("Commission of the European Communities, (for the attention to Mr. L. Rossi, rue de la Loi, 200, B-1049 Brussels), the second full copy for RIVM, the third full copy (but, without toxicological data) for CIVO-TNO and the fourth full copy made available to the Commission services (on the request)

) one copy of summary data sheet (see pag. 83) for each member of the SCF-WG and ***two (please, remember two!)* copies **directly** addressed to Mr Rossi ("Mr. Luigi Rossi, Commission of the European Communities, DGIII, Rue de la Loi, 200 -B-1049 Brussels)(see pag. 91).

APPENDIX 3

TECHNICAL DOSSIER

1. **Technical dossier, submitted to the Commission of the European Communities or to the national authorities, should include the data hereinafter indicated.**

2. New substances

   For obtaining authorization for the use of a new substance as a constituent of food contact materials, the applicant is invited to submit to the Commission the data requested in the "SCF Guidelines" (see pag.47).

3. Substances already evaluated by the SCF

   For re-evaluation of a substance for use as a constituent of food contact materials, that has already been examined but not evaluated by the SCF because of lack or insufficiency of technical (mainly toxicological) data, the applicant is invited to submit to the Commission the data reported in Annex 3 (see pag. 92).

4. It will be noted that the "SCF Guidelines" are written in general terms and do not describe detailed methods. Guidance on methodology can be obtained from published sources (EEC or OECD) and it may be necessary to consult experts in the relevant areas (analysis, migration, toxicology) to obtain further advice on the tests to be carried out.

5. However without prejudice to paragraph 4, and emphasising that the choice of the test is the responsibility of the applicant, some guidance is given by the Commission services, following consultation of the SCF.
   For instance, in the addenda of this appendix, guidelines on certain subjects are given:

   - type of mutagenicity tests recommended;
   - procedure for obtaining hydrolysis data;
   - conditions for obtaining adequate migration data,
   - description of the analytical methods used in migration tests;
   - format of the summary data sheet.

NOTA BENE

The document reported in paragraph 6 "SCF Guidelines"(pag. 47) differs in some details from the same document published in the SCF Report, Series N. 26 (1992). The applicant is invited to follow strictly the document reported below.

6 SCF GUIDELINES

"Guidelines for presentation of data for toxicological evaluation of a substance to be used in materials and articles intended to come into contact with foodstuffs"

INTRODUCTION

These guidelines are written for plastic materials and articles, but they are also largely applicable to any material in contact with foodstuffs for which a list of authorized substances (positive list) is provided. Food utensils and any surface intended to come into contact with foodstuffs are also covered in this document by the term "packaging materials".

Packaging materials can contain substances that are capable of migrating into the packaged food. These toxicological guidelines are designed to assess potential hazards to consumers resulting from oral exposure due to migration of packaging substances into food.

Substances persisting in the environment can have harmful effects on the environment and/or can accumulate in food chains. There is currently no requirement for supplying information on the persistence of a substance in the environment or on its ecotoxicological impact to the Scientific Committee for Food. This information may have to be supplied to the appropriate competent authority. The fate of substances in the finished material or article after it has been submitted to waste disposal treatment is also considered by other competent authorities.

The safety in use of a substance in packaging materials depends on many factors, for example:

a. the biological properties of the substance (see later, point 6);

b. the maximum quantity of the substance likely to be consumed per day, which depends on:

i the types of packaging materials which contain the substance;

ii. the fraction of each packaging material which contains the substance and quantities of the substance incorporated;

iii. the length of contact of the foods with the materials, the unit weight of food in relation to the surface area of packaging and temperatures encountered while food is in contact with the material;

iv. the extent of migration of the substance or of its breakdown products into each type of food and its possible reactions with food components;

v. the types of food packaged;

vi the proportion of each type of food which is packaged in each type of packaging material;

vii. the quantities of foods consumed which have been in contact with each of the packaging materials containing the substance,

c. the frequency with which food containing the substance or its breakdown products or its reaction products with food is consumed;

d. the period over which food containing the substance is consumed. This is related to the period over which the substance is actually used in the manufacture of packaging materials intended for food contact. Technological advances have produced increasingly sophisticated types of packaging materials and many substances have been used in packaging formulations for limited periods, to be superseded by others. Some substances however have been in use for more than 20 years.

Substances migrating into food are not necessarily identical with substances used in the production of the packaging. Therefore, in assessing the safety of packaging materials, it is the toxicity of the substance which migrates that has to be assessed, since it is only this substance to which the consumer of the food is exposed.

In order to assess any risks to public health from using a substance in the production of food packaging materials, it is necessary to determine the identity of the chemical or chemicals which actually migrate into food, the quantities (in average and in extreme cases) which migrate into the total daily diet, and the toxicological profile of each chemical.

These guidelines set out the minimum data required to achieve the above objectives when approval of a new substance is being sought.

INFORMATION TO BE SUPPLIED FOR THE EVALUATION OF A SUBSTANCE TO BE USED IN MATERIALS AND ARTICLES IN CONTACT WITH FOOD

Reports submitted must contain sufficient details for evaluation. They should be structured in the order given below under 1-6. Justification for any deviation from the following guidelines must be given in the summary data sheet (see pag. 83). Any reference to published information offered in support of an application should be accompanied by reprints or photocopies of such references. A summary data sheet must also be prepared.

1. IDENTITY OF THE SUBSTANCE

NOTA BENE: In order to enable the preparation of a bank of reference substances and a handbook containing characteristic spectra and other physico-chemical data, a sample of 250 grams of the substance should be supplied to the following laboratory which is collaborating with the Commission of the European Communities - Community Bureau of Reference:

MAFF Food Science Laboratory
("Program: Reference substance for food packaging")
Colney Lane
Norwich NR4 7UQ
UNITED KINGDOM
Phone : (0603)259350
Fax: (0603)501123

If the substance is a gas at room temperature, a solution of the substance should be supplied at an appropriate concentration and in an appropriate solvent. In the case of difficulties in preparing the sample to be supplied, the applicant is instructed to contact the above mentioned laboratory.

1.1. In the case of an individual, well-defined substance give:

1.1.1. Chemical names (IUPAC and some synonyms such as common name, CAS name and trade name).
1.1.2. CAS number.
1.1.3. Molecular and structural formulae; molecular weight.
1.1.4. Degree of purity; methods for determination of purity; qualitative and quantitative data concerning impurities.
1.1.5. Spectroscopic data; supply data which allow identification and characterization of the substance, e.g. infrared and/or mass spectrometry.

1.2. Mixtures which can be defined.

a) Mixtures arising from natural sources.
These mixtures shall be submitted accompanied by toxicological data referring to the whole mixture (see point 6) with description of each component in accordance with points 1.1.1. - 1.1.5 and the proportion of each component.

b) Synthetic mixtures.
Each component of a synthetic mixture shall be submitted separately.

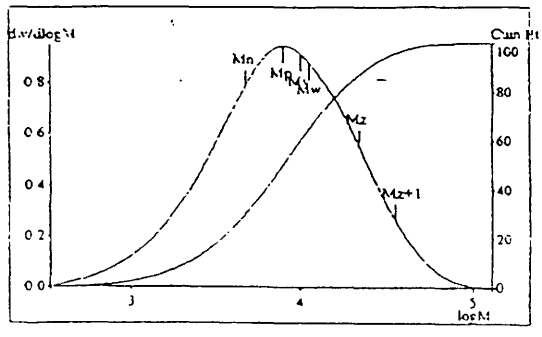
1.3. Mixtures which cannot be defined.

A description as complete as possible should be supplied, including:

1.3.1. the compounds or raw materials used in preparing the mixture;
1.3.2. the production process, production control and reproducibility of the process;
1.3.3. the method used to purify the product;
1.3.4. the substances formed during the process (by-products).

1.4. Polymer used as additive

1.4.1. CAS. N°
1.4.2. structure
1.4.3. starting substances and other substances present (e.g. impurities, additives) as well as their relative amounts
1.4.4. average molecular weight (in ponderal terms)
1.4.5. curve of the distribution of the molecular weights (ordinate weight % of molecules having a certain MW, abscissa the MW)(see figure below).
N.B. It was suggested that a calibration curve should be supplied including among the standards in the linear correlation two standards with MW of about 1000: a) a polystyrene standard, b) another standard whose structure should be as close as possible to that of the polymeric additive. However this suggestion is not yet discussed.
1.4.6 any relevant toxicological data, if they are available, because they may help accelerate evaluation.



2. PROPERTIES OF THE SUBSTANCE

2.1. Physical: give physical data like melting point, boiling point, decomposition temperature, flash point, vapour pressure and solubility in relevant solvents.
2.2 Chemical: give data e.g. nature of the substance i.e. whether is acidic, basic, or neutral, on reactivity, on stability to light, air, ionising radiation, heat, simulants in the condition of contact (use a concentration approximately 10 times the detection limi), on hydrolysis.
2.3. Information on any decomposition or transformation which the substance may undergo while the material or article is being manufactured; an indication of the decomposition or transformation products which may be formed in the finished material or article during production;
2.4. The maximum temperature reached in the manufacturing process.
2.5. If available, information on possible chemical reactions of the migrating substance with food components.

3. USE

3.1. Technological function of the substance.
3.2. All types of material in which the substance is intended to be used.
3.3. Any particular use of the material (e.g. microwave)
3.4. Maximum percentage in the formulation.
3.5. Maximum percentage which may remain in the material or article, when the amount given under 3.3 is reduced by chemical reactions and by processes such as washing, purification, evaporation, etc. The applicant should provide extraction data and details of the analysis carried out (see also point 5.5. on pag. 52).
3.6. Mention any restrictions for use, e.g. type of foodstuffs, type of material, contact conditions, temperature, etc.

4. INFORMATION ON AUTHORISATION GIVEN BY COUNTRIES AND ON EVALUATION BY INTERNATIONAL ORGANISATIONS

State in which countries and under what conditions the substance is authorised for use in contact with food. Include reference to the official publication concerning the authorisation.

State by which international organisations evaluations have been made and enclose copies of relevant documents.

5. MIGRATION DATA

Ideally, in order to permit estimation of the daily intake of the substance, data should be provided on the extent of migration of the substance, its breakdown and reaction products (specific migration) from each of its formulations into each of the food types packaged under all foreseeable conditions of storage and use. In practice, detection and analysis of low concentrations of substances and breakdown and reaction products migrating into food is often difficult. Thus the only way to determine potential migration into food may be to use food simulants.

When food simulants are used, the provisions concerning the specific and overall migration established in EEC directives (see relevant references referring to this subject on pag. 55) or guidelines (see addendum 3 to appendix 3 on pag. 65) have to be followed.

If the substance is largely transformed during the processes and/or if potentially toxic reaction products are suspected, then data on the specific migration of the reaction products should be supplied.

Migration tests should be carried out with all the materials described in 3.2 (e.g. all types of plastic); in each instance with the maximum percentage of the substance defined in section 3.3 and the largest thickness intended to be used.

Details of migration tests must be reported, particularly the following:

5.1. Detailed composition of sample used, including initial concentration of any identified migrant, obtained by solvent extraction of the sample (see point 5.4).

5.2. Food or food simulant(s) used.

5.3. Conditions of contact such as time, temperature, ratio surface/volume or weight of food or food simulant, type of migration cell used or any other parameter which can influence the level of migration.

5.4. Describe in detail the analytical method(s) and procedure(s) used for the quantitative determination of the substance(s) or its/their decomposition or transformation products. In cases where a specific migration limit is likely to be established, a method of analysis should be proposed and described according to the guidelines provided on pag. 65 and following. It should be a method which is suitable for food packaging control and which can be applied with consistent results by any properly equipped and trained laboratory personnel.

5.5 Results of migration data in mg/dm^2 and/or mg/kg (see point 5.5. on pag. 87).

5.6. Relationship between QM and SML in the worst estimated situation.

6. TOXICOLOGICAL DATA

6.1. The general requirements for toxicological studies which have to be supplied for substances in packaging materials are set out below.

In carrying out toxicological tests, the aim should be to obtain the maximum amount of relevant information using a minimum number of animals (5).

In deciding on the choice of studies, it should be recognised that not all chemicals used in the manufacture of a packaging material will migrate into food. Many will form a stable part of a polymer, some will migrate only in minute quantities, if at all, others will disappear during production, while yet others will decompose completely to yield either no or insignificant residues.

While many substances migrate in the same chemical form in which they were incorporated into packaging materials, others will migrate partially or totally in another chemical form (see point 5). In such cases the toxicological requirements may also apply to transformation or reaction products.

6.2. The essential core set of tests which has to be carried out comprises:

- a 90-day oral study
- 3 mutagenicity studies.
  - i) a test for gene mutations in bacteria;
  - ii) a test for chromosomal aberrations in cultured mammalian cells,
  - iii) a test for gene mutations in cultured mammalian cells; under special

circumstances another validated eukaryotic test detecting gene-mutations may be acceptable;

- studies on absorption, distribution, metabolism and excretion;
- data on reproduction;
- data on teratogenicity;
- data on long-term toxicity/carcinogenicity.

These studies should be carried out according to EEC Directives (6)(7) and/or OECD guidelines, including "Good Laboratory Practice" (8)(9)(10)(11). The test substances should be of the same specification as described in point 1 (see pag. 49).

If the above mentioned studies or prior knowledge indicate that relevant biological effects may occur, additional studies may be required.

At present no validated methods are available for studies in laboratory animals which would allow assessment of a substance's potential to cause intolerance and/or allergic reactions in susceptible individuals following oral exposure. However, studies on dermal or inhalation sensitization may give information relevant to possible hazards from occupational exposure and could be helpful in assessing consumer safety.

Observations in man as provided by health records of people employed in manufacture of the substance and, if relevant, of the polymer, would be regarded as useful ancillary information.

6.3. As a general principle, the greater the extent of migration into food, the more toxicological information will be required.

6.3.1. In cases where migration is above 5 mg/kg of food/food simulant, all the studies on the core list should be carried out. If any test is omitted this must be justified by providing appropriate reasons.

6.3.2. Under certain circumstances not all the core tests may be required, but at least the following should be carried out:

In cases where migration is in the range of 0.05 - 5 mg/kg of food/food simulant:

- demonstrate the absence of potential for bioaccumulation in animals (e.g. octanol/water partition coefficient),
- demonstrate the absence of mutagenic potential by the 3 mutagenicity tests listed above;
- supply a 90-day oral toxicity study.

6.3.3. In cases where migration is lower than 0.05 mg/kg of food/food simulant:

- demonstrate the absence of mutagenic potential by the 3 mutagenicity tests listed above;

6.3.4. As an alternative to determining the migration values mentioned in points 6.3.1, 6.3.2 and 6.3.3, it is possible to calculate the maximum level of migration by assuming that 100% of the substance in question migrates from the packaging material into food/food simulants.

6.3.5. In some cases results of hydrolysis studies may justify a reduction in toxicological testing. This may arise when the chemical structure suggests ready hydrolysis into substances which are toxicologically acceptable (e.g. stearic acid, ethyl ester, which may hydrolyse into a fatty acid and ethyl alcohol). Demonstration of hydrolysis may be carried out in foods or food simulants, representing the range of foods with which the substance may come into contact. Alternatively, or in cases where hydrolysis in food does not occur, hydrolysis can be evaluated in simulated saliva and/or gastrointestinal fluids.

BIBLIOGRAPHY

1) Council Directive 82/711/EEC of 18 October 1982.
(O.J. N. L 297 of 23.10.1982, p. 26).

2) Council Directive 85/572/EEC of 19 December 1985
(O.J. N. L 372 of 31.12.1985, p. 14).

3) Commission Directive 90/128/EEC of 23 February 1990
(O.J. N. L. 349 of 13.12.1990, p. 20).

4) Commission Directive amending Council Directive 82/711/EEC
(under press)

5) Council Directive 86/609/EEC of 24 November 1986
(O.J. N. L. 358 of 18.12.1986, p. 1).

6) Commission Directive 84/449/EEC of 25 April 1984
(O.J. N. L 251 of 19.09.1984).

7) Commission Directive 87/302/EEC of 18 November 1987
(O.J. N. L 133 of 30.05.1988, p. 1).

8) Council Directive 87/18/EEC of 18 December 1986
(O.J. N. L 15 of 17.01.1987, p. 29)

9) Council Directive 88/320/EEC of 9 June 1988
(O.J. N. 145 of 11.06.1988, p. 35)

10) Council Decision 89/569/EEC of 28 July 1989
(O.J. N. L. 315 of 28.10.1989, p. 1).

11) Commission Directive 90/18/EEC of 18 December 1989
(O.J. N. L. 11 of 13.01.1990, p. 37).

Addendum 1 to appendix 3

PRACTICAL GUIDELINES FOR MUTAGENICITY TESTING

The following mutagenicity test are recommended.

1.1. A test for gene mutation in bacteria

1.1.1. In S. typhimurium.

1.1.2. If S. typhimurium is not appropriate, the test may be performed with E Coli (WP2 reverse mutation assay).

1.2. A test for chromosomal aberrations in cultured mammalian cells

In vitro mammalian cytogenetics test (CHO or V79 or human lymphocytes)

1.3. A test for gene mutations in cultured mammalian cells

1.3.1. In vitro mammalian cell gene mutation assay (HGPRT or TK+/-) in CHO or V79 or mouse lymphoma L5178Y cells)

1.3.2. Under special circumstances another validated eukaryotic test detecting gene mutations may be acceptable (e.g. Drosophila).

Addendum 2 to appendix 3

PRACTICAL GUIDELINES FOR HYDROLYSIS TESTS

2.1. Preparation of simulants

2.1.1 Simulated saliva

Dissolve 4.2 g of sodium bicarbonate (NaHC03), 0.5 g of sodium chloride (NaCl), and 0.2 g of potassium carbonate (K_2C03) in 1 litre of distilled water or water of equivalent quality. The solution should be approximately pH 9.

2.1.2. Simulated gastric fluid

HCl 0.07 M (pH 1.15)

2.1.3. Simulated intestinal fluid

Dissolve 6.8 g of KH_2P04 in 250 ml of water and add 190 ml of 0.2 M NaOH and 400 ml of water. Add 10.0 g of pancreatin, mix, and adjust the resulting solution with 0.2 M NaOH to a pH of 7.5 + 0.1. Dilute with water to 1000 ml.

2.2. Procedure

Simulants should be in contact with the test substances at a temperature of 37°C for 1, 2 and 4 hours with shaking. The concentration of the test substance used should not be lower than maximum likely human intake predicted from migration studies. The hydrolysates should be examined by quantitative methods for both parent compound and breakdown products.

N.B. Non-water soluble substances.

The Commission services recently funded experimental research, the aim of which was to find a solvent dispersion method for non-water soluble substances. Although the study is not yet finished, it could be useful for the applicants to know how th contractor be solved the problem. This suggestion is reported below and , at this stage, cannot be considered a suggestion of the SCF - which has not yet been consulted - or of the Commission services.

For those test substances which are not fully soluble in the simulants at the concentrations selected, satisfactory dispersion in the simulants can usually be achieved by first dissolving the test substance in a small quantity of a water miscible solvent and then adding the solution to the simulant. Care must however be taken to ensure that during the hydrolysis test period the dispersedance is not isolated onto the walls of the vessel used for the hydrolysis studies and removed from contact with the simulant."

Addendum 3 to appendix 3

GUIDELINES FOR THE OBTAINING AND DESCRIBING MIGRATION DATA

1. The applicant should follow the general criteria given in the "SCF Guidelines"(see point 5 on pag. 51). As it is specified here, the migration data should be obtained applying the conditions established in EEC directives (see references on pag. 55).

   It is also recommended to follow the guidance given in the following CEN documents:
   - "Guide to the selection of conditions and test methods for overall migration" (ENV..., under press);
   - "Guide to the selection of conditions and test methods for specific migration and determination of substances in plastics" (ENV...., under press).

N.B.
1. Send a letter to CEN (Mr. Jeanson), rue Stassart 36, B-1050 Brussels (fax: (02)5196819 -phone (02)5196819) for obtaining a copy of the above mentioned documents.
2. Read carefully and apply (see * at pag. 86 of this document) the paragraph "Assessment of results". of the mentioned CEN documents.
3. Remember that in the total immersion test, only for the samples having a thickness greater than **500 micron**, it is allowed to divide for both the surfaces.

However, in order facilitate the applicant, a summary of the main conditions contained in these Directives is given in the addendum as well some practical guidelines in some specific cases.

2. The applicant should avoid submitting data obtained in conditions, e.g. FDA conditions, other than those here specified ("different conditions"). Only if the applicant can indicate that the data obtained in "different conditions" is equivalent or more stringent to that obtained applying these guidelines, then the SCF, exceptionally and case by case, may consider this data as being equivalent. In these cases, however, the applicant should provide supporting documents or convincing arguments, otherwise the migration data cannot be considered appropriate.

3. The Commission services also stress that the applicant should, in principle, use the methods of analysis "validated" at Community level. For the purpose of this document the term "validated" is taken to mean a method which is recognized by one of the following organizations:

   1) European Communities;
   2) CEN
   3) other organizations, generally recognized qualified in this matter (e.g. ISO, ASTM, AOAC).

   If such a method does not currently exist, an analytical method with appropriate performance characteristics (accuracy and precision) at the specified limit may be used.

4. The Commission services also stress that the applicant should, in principle, describe the methods of analysis as indicated in pag. 65. This is particularly important, if the method is not described in the scientific literature or for the new substances.

Annex 1 to addendum 3 of appendix 3

(Extract from Directive 93/../EEC, under press)

"BASIC RULES FOR TESTING MIGRATION IN FOOD SIMULANTS

The determination of migration in food simulants shall be carried out using the food simulants laid down in Chapter I of Annex and under the test conditions specified in Chapter II of Annex. However the determination of migration shall be restricted to the food simulant(s) and to the condition(s) of test which, in the specific case under examination, may be considered to be the most severe on the basis of experience.

CHAPTER I

FOOD SIMULANTS

1. GENERAL CASE: PLASTIC MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH FOODSTUFFS OF ALL TYPES*

The tests shall be carried out using the food simulants mentioned below, taking a fresh sample of the plastic material or article for each simulant:

- distilled water or water of equivalent quality (= simulant A),
- 3% acetic acid (w/v) in aqueous solution (= simulant B),
- 15% ethanol (v/v) in aqueous solution (= simulant C),
- rectified olive oil (4)(= simulant D); if for technical reasons connected with the method of analysis it is necessary to use different food simulants, olive oil shall be replaced by a mixture of synthetic triglycerides (5) or by sunflower oil. If all the food simulants provided in this indent are inappropriate, other food simulants and conditions of time and temperature may be used.

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* *Reduction factors which appear in the list of simulants (85/572/EEC) shall not be used in this case.*

(4) Characteristics of rectified olive oil:

- iodine index (Wijs) = 80 to 88,
- refraction index at 25°C = 1.4665 to 1.4679,
- acidity (expressed in % of oleic acid) = 0.5% maximum
- peroxide index (expressed in milli-equivalents of oxygen per kg of oil) = 10 maximum.

(5) Characteristics of the standard synthetic triglycerides mixture as described in K. Figge's article, "Food Cosmet. Toxicol. 10(1972) 81.5

However, the simulant A shall be used only in the cases mentioned specifically in the Table of this annex (see pag. 62).

2. **SPECIAL CASE: PLASTIC MATERIALS AND ARTICLES INTENDED TO COME INTO CONTACT WITH A SINGLE FOODSTUFF OR A SPECIFIC GROUP OF FOODSTUFFS**

The tests shall be carried out:

- using only the food simulant(s) specified as appropriate for the foodstuff or group of foodstuffs in the Directive 85/572/EEC (6),

- where the foodstuff or group of foodstuffs is not included in the list referred to in the first indent, selecting the food simulant(s) prescribed in Section 1 which correspond most closely to the extractive capacity of the foodstuff or group of foodstuffs.

CHAPTER II

TEST CONDITIONS (TIMES AND TEMPERATURES)

1. The migration tests are to be carried out, selecting from the times and temperatures specified in the table those which correspond most closely to, but are not less than, the normal or foreseeable conditions of contact for the plastic materials or articles being studied.

2. Where a material or article passes a test at a given time and temperature, it need not be tested for a shorter time at the same temperature, nor for the same time at a lower temperature.

3. However if a plastic material or article is intended for a food contact application covered by two or more combinations of time and temperature taken from the Table, migration will be determined by subjecting that material or article successively to all the applicable test conditions, using the same aliquot of food simulant*

4. If a plastic material or article is intended to come into contact with foodstuffs at any condition of time, the conditions for testing will be the following:

   a) where the plastic material or article may in actual use be employed at any temperature up to and including 70 °C and that is indicated by an appropriate labelling or instructions, only the 10 day test(s) at 40 °C shall be carried out*;

   b) where a plastic material or article may in actual use be employed at a temperature above 70 °C.

      i) where no labelling or instructions are given to indicate temperature expected in real use, simulants B and C shall be used at reflux temperature, if possible, or at 2 hours test(s) at 100 °C and simulant D shall be used for 2 hours at 175 °C*;

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(6) O.J. N. L. 372, 31.12.85, p. 14.

ii) where labelling or instructions are given to indicate conditions expected in real use, times and temperatures from the Table shall be selected*.

5. By derogation from the conditions provided in the table and in paragraph 2, if the plastic material or article may in actual use be employed for periods of less than 15 minutes at temperatures between 70°C and 100 °C and that is indicated by an appropriate labelling or instructions, only the 2 hours test at 70°C and the 10 day test at 40 °C shall be carried out. These tests shall be carried out separately taking different samples. For each of these two types of test, use a new sample of the same material or article to be examined.

6. If it is found that carrying out the tests under the conditions specified in the table causes physical or other changes in the plastic material or article which do not occur under normal or foreseeable conditions of use of that material or article, the migration tests shall be carried out under conditions more appropriate to the specific case.

7. For materials and articles intended for use in microwave ovens, migration testing shall use a conventional oven and appropriate time and temperature conditions selected from the Table.

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*) If a plastic material or article is intended to come into contact with foodstuffs at any condition of time and therefore also at two or more combinations of time and temperature taken from the Table, what conditions described in paragraphs 3 or 4 shall be applied?

Although the legal interpretation of the Directives is on the responsability of the Court of Justice, according to the Commission services these materials should be subject only to the rule of the paragraph 4.

TABLE

Conditions of contact in actual use	Test condition
Contact time	**Test time**
t ≤ 0.5 hours	0.5 hours
0.5h < t ≤ 1 hour	1 hour
1h < t ≤ 2 hours	2 hours
2h < t ≤ 24 hours	24 hours
t > 24 hours	10 days
contact temperature	**test temperature**
T ≤ 5° C	5° °C
5°C < T ≤ 20° C	20 °C
20°C < T ≤ 40° C	40 °C
40°C < T ≤ 70° C	70 °C
70°C < T ≤ 100°C	100 °C or reflux temperature
100°C < T ≤ 121°C	121 °C (*)
121°C < T ≤ 130°C	130 °C (*)
130°C < T ≤ 150°C	150 °C (**)
T > 150°C	175 °C (**)

(*) Use simulant C at reflux temperature.

(**) Use simulant D at 150°C or 175°C, in addition to simulants A, B and C used as appropriate at 100°C or at reflux temperature, .

EXCEPTIONS TO THE EEC TEST CONDITIONS FOR MIGRATION

Hereinafter some special cases are reported as examples of possible derogations from the EEC test conditions for migration (food simulants, time and temperature) in accordance with paragraphe 5 (pag. 61).

1. If there is conclusive experimental proof that the detection limit in the simulant D is greater than 0.05 mg/kg and therefore, it would be impossible to present a "reduced" dossier as provided in point 6.3.3 (pag. 53) of "SCF Guidelines", the applicant may replace the simulant D by one of the following "alternative EEC fat food simulants":

   - isooctane
   - ethanol 50% or 95%

   In that case it should be demonstrated that the substance under examination is sufficiently soluble in the alternative food simulant.

2. In the case of isooctane the test conditions to be used are indicated in the following table in correspondence with the test conditions used for the "Fat test":

Test condition with olive oil	Test conditions with iso-octane
10 d - 5 °C	0.5 h - 5 °C
10 d - 20 °C	1 h - 20 °C
10 d - 40 °C	2 d - 20 °C
2 h - 70 °C	0.5 h - 40 °C
1 h - 100 °C	0.5 h - 60 °C
0.5 h - 121 °C	1 h - 60 °C *
0.5 h - 130 °C	1 h - 60 °C *
2 h - 150 °C	2 h - 60 °C *
2 h - 175 °C	3 h - 60 °C *

(*) Before submitting a sample of the material to the test using isooctane ascertain that the material can withstand contact with oilve oil at elevated temperature by submerging a sample in olive oil under relevant t-T conditions taken from the table.

3. In the case of ethanol, the test for 10 d at 40 °C is replaced by a test using 1, 2, 4 and 10 days at 40°C at the following concentrations:

   (i) 50% (e.g. for PVC/PETP/PS)
   (ii) 95% (e.g. polyolefins)

4. If there is conclusive proof that the test for the determination of the migration in simulant D is inadequate from a technical standpoint, the applicant may replace the simulant D as indicated in paragraph 1.

5. The fat test for global migration need not to be necessarily carried out, if it is shown that the extraction by a solvent, carried out with a validated procedure, gives an extract higher than one obtained in the migration test according to the Directives.

   Solvents to be used should have low boiling points (B.P. < 100°C) and should be capable of causing swelling of the polymer. As a general rule, non polar polymers, e.g. polyolefines should be treated with non polar solvents e.g. heptane, iso-octane and polar polymers, e.g. polyamide should be treated with polar solvents, e.g. methanol, ethanol. Medium polar materials, such as polyesters can be treated with e.g. ethyl acetate, dichloromethane.

Question: Shall the reduction factors to be used in the case of replacement of olive oil by other simulants?

Answer : Yes.

Annex 3 to addendum 3 of appendix 3

GUIDELINES TO BE FOLLOWED FOR THE DESCRIPTION OF THE METHOD OF ANALYSIS OF A SUBSTANCE

As stated in the point 5.4 (see pag. 52 of the "SCF Guidelines"), a method of analysis must be included in the technical dossier. In order to help the applicant, some general indications are given below. However it is recommended to follow, as much as possible, the format recently adopted at CEN level, which is also reported later (see pag. 68).

Methods should be capable of either quantification of the substance in the material or article itself or quantification in appropriate food simulants (or foods) respectively.

Method of analysis should comply with the following format (specimen examples may be seen in Methods EN XXX) :

1. Scope
2. Principle
3. Sampling
4. Reagents (Safety precautions)
5. Apparatus
6. Procedure
7. Confirmation
8. Precision
9. Test report

1. SCOPE

Statement of types of materials and articles for which the method is applicable. Statement of food simulants (or foods) for which the method is suitable. Statement of the limit for which the method is capable of quantitative determination of the substance in the material and article or food simulant (or food).

2. PRINCIPLE

Statement of the principle that is employed for the determination (for example headspace GC, extraction followed by HPLC, extraction followed by colorimetric determination).

3. REAGENTS

Statement of safety requirements and any special precautions in handling reagents. Statement of purity requirements of substance (obtainable from BCR Reference collection), internal standard and any special requirements for solvent or reagent purity. Statement of primary and diluted calibrant solutions which should have a concentration range to span the QM or SML limit.

4. APPARATUS

Normal laboratory apparatus can be assumed but any instrument or special piece of apparatus or particular specification should be stated.

The minimum performance of chromatographic methods should be stated in terms of the resolution of the substance to be determined from internal standard, solvent or other components. Examples of columns found to be suitable should be given.

5. SAMPLES

Statement of requirements for taking of representative samples of materials and articles for analysis. For testing with simulants the guide to the selection of conditions and methods of test is stipulated in CEN Method Part 1 (EN XXX).

6. PROCEDURE

Statement in sufficient detail of how to carry out procedure which should include the manner of preparation of calibration curves, evaluation of data, and final determination graphically or by calculation.

As quantitative extraction from materials and articles can never be fully demonstrated the method of standard addition should always be employed for calibration. For determinations of substances in food simulants an internal standard should always be employed for chromatographic procedures and calibration should be against blank food simulant fortified with the substance in question.

7. CONFIRMATION

The method of analysis must include details for confirmation of test results to be used in cases where the measured QM or SML values have been found to exceed the limits specified in Directive 90/128/EEC and subsequent amendments.

The principle behind the confirmation step is that the technique used is sufficiently different from that first used, that it confers additional assurance of identity and level of putative substance. Thus for example :

For volatile substances where GC is employed then confirmation by GV/MS (scanning or selected ion monitoring) is appropriate polarity or derivative formation. For non-volatile substances using HPLC, confirmation can be carried out by GC/MS after formation of a suitable volatile derivative or by using at least one other HPLC column with differing separation characteristics and a different solvent system, and/or stopped-flow scanning UV or fluorescence studies.

8. PRECISION

Statement of the detection limit of the method of analysis and the limit of

quantification. The analytical tolerance that will be applied to QM or SML limits will depend on the performance of the method and the calculation of a critical difference value that can only be obtained by inter-laboratory collaborative trial. However, the method should include a statement of the within-laboratory "repeatability" of the method obtained by the proposer of the method or similar laboratory.

9. TEST REPORT

The test report should give the relevant information on the method used (see pag. 73).

(extract from CEN document, final version - 18 March 1992)

STANDARD FORMAT FOR DRAFTING OF CEN METHODS FOR DETERMINATION OF PLASTICS CONSTITUENTS IN FOODSTUFFS, FOOD SIMULANTS AND MATERIALS AND ARTICLES

PART 0. EXPLANATORY NOTE

This Standard Format has been prepared by Task Group 4 of Working Group 5 of CEN TC194 'Utensils in contact with food' as a template for drafting analytical methods of test for plastics materials and articles destined to come into contact with foodstuffs.

The analytical methods of test are concerned with the determination of specific migration of plastics constituents into foodstuffs and food simulants and with the determination of residual constituents in plastics materials and articles.

The Standard Format consists of two parts:
Part 1. STANDARD FORMAT sets out the minimum requirement of items to be covered in the description of an analytical method of test. The items are given in a very general way only.

Part 2. GUIDELINE FOR COMPLETION OF STANDARD FORMAT sets out in what way the items in Part 1. can be elaborated in a particular case in order to obtain the full description of the method.

Therefore Part 1 should be read in direct conjunction with Part 2.

1. **STANDARD FORMAT**

TC194/[PM/REF-Y] [ISSUED]

MATERIALS AND ARTICLES IN CONTACT WITH FOODSTUFFS

PLASTICS

PART [X]. DETERMINATION OF [ANALYTE] IN [MATRIX]

WARNING: [SET OUT]

Contents

FOREWORD

This part of European Standard EN [XXX] has been prepared by Working Group 5 of TC194 'Utensils in contact with food' as one of a series of analytical methods of test for plastics materials and articles intended to come into contact with foodstuffs.

The methods of test are concerned with the determination of overall and specific migration of plastics constituents into foodstuffs or food simulants and with the determination of residual content of plastics constituents in the finished plastics product.

[ANNEX]

This part should be read in conjunction with PART 1 of EN [XXX].

0. INTRODUCTION

ANALYTE, FORM], [PM/REF] is a [CONSTITUENT] used in the manufacture of certain plastics materials and articles intended to come into contact with foodstuffs.

After the manufacture residual [ANALYTE] can remain in the finished product and may migrate into foodstuffs coming into contact with that product.

The method described in this European standard allows of the determination of [ANALYTE] in [MATRIX]. The method is to be used in conjunction with Part 1 of EN [XXX] which describes the procedures required prior to the determination of [ANALYTE] in [MATRIX].

The method has been validated by collaborative trial using [MATRIX] (see 8).

1. SCOPE

This part of EN [XXX] describes a method for the determination of [ANALYTE] in [MATRIX].

The method is appropriate for the quantitative determination of [ANALYTE] in approximate analyte concentration range of [RANGE] [MASS]/kg [MATRIX].

2. PRINCIPLE

The level of [ANALYTE] in [MATRIX] is determined by [TECHNIQUE]. Quantification is achieved using [STANDARD].

[CONFIRM].

3. REAGENTS

Reagents and solvents shall be of analytical quality.

3.1 [ANALYTE ST, FORM]
(PURITY)

3.2 [STANDARD, FORM]
(PURITY)

3.3 [REAGENTS]
(PURITY)

3.4 [SOLUTIONS]
(INSTRUCTIONS)
(CONDITIONS)

4. APPARATUS

NOTE An instrument or item of apparatus is listed only where it is special or made to a particular specification, usual laboratory glassware and equipment being assumed to be available.

4.1 [SPECIAL]

5. SAMPLES

The laboratory samples of [MATRIX] to be analysed are obtained as described in PART 1 of EN [XXX]. Analyte-free samples of [MATRIX] of the same type as those to be analysed are also required for use for calibration purposes.

(CONDITIONS)

5.1 Test sample preparation

(DESCRIPTION)

5.2 Calibration sample preparation

(DESCRIPTION)

5.3 Blank sample preparation

(DESCRIPTION)

6. PROCEDURE

6.1 [TECHNIQUE] parameters

(DESCRIPTION)

6.2 Optimisation of instrumentation

(DESCRIPTION)

6.3 Calibration

(DESCRIPTION)

6.4 Execution of determination

(DESCRIPTION)

6.5 Evaluation of data

NOTE The following calculations assume that for all measurements exactly the same weight or volume of [MATRIX] has been used and, for the internal standard, that invariably the same volume of internal standard solution has been added.

6.5.1 [TECHNIQUE] interferences

(DESCRIPTION)

6.5.2 Calculation of analyte level

(DESCRIPTION)

7. CONFIRMATION

In cases where [SML or QM] of [ANALYTE], calculated according to the procedure given in Part 1 of EN [XXX] from the analyte level calculated according to Section 6.5 exceeds the restriction criterion set in Commission Directive 90/128/EEC (SML or QM), the result of the determination shall be confirmed. The confirmation is qualitative in the sense that it should demonstrate the correct identity of the measured analyte and the absence of interferences. For the purposes of quantitation the result as calculated according to Section 6.5 shall be taken as the true value.

(DESCRIPTION)

8. PRECISION

Method performance has been evaluated by carrying out a precision experiment according to ISO 5725-1990 'Accuracy (Trueness and Precision) of Measurement Methods and Results', Parts 1-6.

8.1 Validation *(N.B. For the applicant this item may be omitted).*

For validation of this method a precision experiment was conducted in [YEAR], involving [NUMBER] laboratories. Each participant in this experiment obtained [NUMBER] samples of [ANALYTE]-free [MATRIX] together with sets of [NUMBER] samples of [MATRIX] fortified with [ANALYTE] at levels of approx. [LEVEL] [MASS]/kg respectively.

Calibration solutions were prepared with comparable concentrations so that the calibration samples could be corrected.

8.2 Repeatability and reproducibility

Evaluation of the results of the precision experiment at a concentration of

[LEVEL] [MASS] [ANALYTE]/kg [MATRIX] for the 95% probability level yielded the following performance characteristics:

Repeatability: r = [LEVEL][MASS][ANALYTE]/kg

Reproducibility:R=[LEVEL][MASS][ANALYTE]/kg *(N.B. For the applicant this item may be omitted).*

There was no influence of the calibration method using [STANDARD] on the numerical values of r and R.

8.3 [LIMIT]

The [LIMIT] of [ANALYTE] - measured as equal to the mean content of representative [BLANK] (n _ 20) plus three times the standard deviation of the mean - was found to be in the range of [RANGE] [MASS] [ANALYTE]/kg [MATRIX].
Thus the method is capable of quantitative determination of [ANALYTE] at a minimum level of [LEVEL] [MASS]/kg [MATRIX].

8.4 Critical [ANALYTE] level

The question whether there is a significant difference for the 95% probability level between the restriction for [ANALYTE] - i.e. [RESTRICTION] - and [SML or QM], calculated from the analyte concentration in [MATRIX] determined by this method, can be decided by means of the critical difference CrD_{95}.

If the determined [ANALYTE] level in [MATRIX] exceeds the limit value calculated from the [RESTRICTION] by more than CrD_{95}, [SML or QM] of [ANALYTE] must be considered to exceed the [RESTRICTION].

So, if analyte level and CrD_{95} are expressed in mg/kg [MATRIX]:

Critical [ANALYTE] level = [RESTRICTION] + CrD_{95} mg/kg [MATRIX].

Evaluation of the results obtained in a precision experiment involving [NUMBER] laboratories resulted in:

CrD_{95} = [LEVEL] [MASS]/kg [MATRIX]

9. TEST REPORT

The test report shall contain, as a minimum, the following:

- an identification
- name of laboratory
- name of person responsible for analysis

- date of report
- date of analysis
- analyte
- a reference to this method
- performance characteristics of the method
- sample details, such as:

    - type of food/food simulant/material/article
    - origin and denotation of the sample
    - date and method of obtaining the laboratory sample
    - storage conditions

- results expressed in [MASS] [ANALYTE]/kg [MATRIX]. Results should be reported as the average value from two or more determinations satisfying the repeatability criterion of Section 8.2
- details of confirmation procedure, if any
- reasons for modifications introduced into the test method, if any.

2. GUIDELINE FOR COMPLETION OF STANDARD FORMAT

Expressions between brackets in PART 1. STANDARD FORMAT should be completed as follows:

Method No.:

[PM/REF-Y] = set out EEC PM/REF No. of analyte and Y = version no. of method.

Date of issue:

[ISSUED] = set out month (abbreviated) and year of issue, e.g. 'Feb. 1993'.

PART No.:

[X] = set out part no. of method in European Standard [XXX].

PAGE No.:

[page p of q] = set out p = sequential number of page and q = total number of pages of method description.

Throughout PART 1. STANDARD FORMAT:

[XXX] = number of European Standard
[ANALYTE] = set out food contact material constituent to be determined
[MATRIX] = set out foods and/or food simulants in which food contact material constituent can be determined by this method.

WARNING:

[SET OUT] = set out whether analyte or any other chemical involved in the procedure is hazardous or harmful to health and what precautions must be taken before or during application of the method.

Contents:

[ANNEX] = set out annexes, if any

FOREWORD:

[ANNEX], if any = set out 'Annex to this standard is normative, where applicable'.

0 INTRODUCTION:

[ANALYTE, FORM] = set out analyte to be determined, bruto formula inclusive
[PM/REF] = set out EEC PM/REF No. of analyte

[CONSTITUENT] = set out 'monomer' or 'additive' or 'aid to polymerisation'.

1. SCOPE:

[RANGE] = set out numerical values of analyte concentration range
[MASS] = set out 'µg' or 'mg'.

2. PRINCIPLE:

[TECHNIQUE] = set out principle of method used to determine analyte in matrix, e.g. 'headspace gas chromatography' or 'solvent extraction, then gas chromatography' or 'high performance liquid chromatography', etc.

[STANDARD] = set out whether an internal standard or an external standard is used or whether standard addition is applied.

Note 1: An internal standard should be used whenever possible and an explanation should be offered for not using one.

[CONFIRM] = set out what confirmation procedure is used.

3. REAGENTS:

3.1 [ANALYTE ST, FORM]= set out analyte standard used for calibration, bruto formula inclusive

(PURITY) = set out purity requirements, if any, of analyte standard.

3.2 [STANDARD, FORM]= set out internal or external standard, bruto formula inclusive

(PURITY) = set out purity requirements, if any, of internal standard, if any.

Note 2: In general the internal standard should contain no impurity at > 1% by peak area or peak height which will elute at the same retention time as that of the analyte.

3.3 [REAGENTS] = set out chemicals, other than analyte standard and internal standard or external standard and solvents involved in the procedure

(PURITY) = set out purity requirements, if any, of reagents and solvents, or set out 'all reagents shall be of analytical quality'.

3.4 [SOLUTIONS]= set out solutions, concentration inclusive, involved in the procedure, such as:

- primary solution of analyte standard
- dilute solution(s) of analyte standard
- solution(s) of internal or external standard
- mobile phase
- reagent solutions
- etc.

(INSTRUCTIONS) = set out detailed instructions for preparation of solutions.

Note 3: Two primary solutions of analyte standard should be prepared and checked against one another with one dilution only. If there is agreement within 5% then further dilute standards are made from only one of the primary standards.

Note 4: Avoid weights of analyte and internal standard larger than 150 mg and also avoid volumes of solvent greater than 100 ml.

(CONDITIONS)= set out conditions of storage and maximum storage time for solutions, as obtained from stability tests.

4. APPARATUS:

4.1 [SPECIAL] = set out special equipment e.g.:

- gas chromatograph, equipped with:
  - automatic headspace sampler
  - alkali flame-ionisation detector
- chromatographic column
- etc.

Note 5: set out column requirements, such as:

- the column must exhibit reasonable peak shape with respect to half-width and asymmetry and must permit the separation of analyte and internal standard

- the column must exhibit minimum overlap of peaks of analyte and internal standard and other substances. A check should be specifically carried out on interference with the internal standard.

- etc.

Note 6: set out examples of columns that have been found suitable for analyte determination - include details of type, dimensions, column flow, temperature etc.

5. SAMPLES:

(CONDITIONS) = set out conditions of storage of samples

Note 7: Analytical determinations should be carried out on duplicate samples, these being duplicate portions of [MATRIX], with at least duplicate measurements (injections) of the final extract.

5.1 Test sample preparation:

(DESCRIPTION) = set out test sample preparation.

5.2 Calibration sample preparation:

(DESCRIPTION) = set out calibration sample preparation.

5.3 Blank sample preparation:

(DESCRIPTION) = set out blank sample preparation.

6. PROCEDURE:

6.1 [TECHNIQUE] parameters:

[TECHNIQUE] = set out 'GC' or 'HSGC' or 'HPLC', etc.

(DESCRIPTION)= set out established parameters or guidance parameters, e.g. injector/column/detector temperature, carrier gas and flow rate, etc.

6.2 Optimisation of instrumentation:

(DESCRIPTION) = set out optimisation of instrumentation.

Note 8: For methods involving GC or HPLC, optimisation will be required in terms of demonstrating adequate specificity and sensitivity. The satisfactory choice of column should be demonstrated, and optimum instrumental parameters should be established, such as:

- injector temperature
- column temperature
- detector voltage/wavelength
- detector temperature
- detector gas flow rate(s)
- carrier gas/elution solvent
- carrier gas flow rate/elution solvent flow rate
- etc.

Some indication should be given of the minimum requirement in terms of detector performance, e.g.: should be able to detect 20 pg on-column of analyte at a signal to noise ratio of 5:1.

6.3 Calibration:

(DESCRIPTION) = set out in what way calibration is achieved.

i. By calibration graph using an internal or external standard:

- the calibration graph shall be constructed from at least five measurements

- concentration range of analyte calibration solutions shall span from x 0.1 specific migration limit (SML) or x 0.1 residual content limit (QM) to x 2.0 SML or x 2.0 QM
- the calibration graph shall be rectilinear
- the correlation coefficient shall be 0.996 or better.

Set out construction of calibration graph.

ii. By calibration graph employing standard addition:

- the sample with no addition of analyte standard solution shall be analysed in triplicate
- addition of analyte standard shall be at three levels, i.e. at sample level, at double and at thrice the sample level
- analyses shall be carried out with at least duplicate measurements (injections) of the final extracts
- the standard addition graph shall be rectilinear
- the standard error on the intercept shall not exceed a coefficient of variation of 10% of the mean value.

Set out construction of calibration graph.

iii. Where recovery experiments are appropriate (e.g. with methods involving extraction, without standardisation and not using standard addition) they shall be carried out in duplicate, using at least three different analyte concentrations. Where correction for recovery is appropriate recovery shall be 70% or better.

Set out recovery experiments.

6.4 Execution of determination:

(DESCRIPTION) = set out execution of the determination.

6.5 Evaluation of data:

6.5.1 [TECHNIQUE] interferences:

[TECHNIQUE] = set out 'GC' or 'HSGC' or 'HPLC', etc.
(DESCRIPTION) = set out possible interferences and set out instructions to solve the problems.

6.5.2 Calculation of analyte level:

(DESCRIPTION) = set out in what manner analyte level in the matrix is calculated.

Note 9: Either a mathematical or a graphical method may be applied to calculate analyte level in the matrix.

7. CONFIRMATION:

[SM or QM] = set out 'specific migration' or 'residual content'

(DESCRIPTION) = set out in what way confirmation is achieved, e.g.:

i. For volatile substances, determined before by a GC-procedure:

i.1 Using gas chromatography/mass spectrometry (GC/MS):

Note 10: If the SML or QM for the analyte and the method allow for more than 20 ng analyte/injection then full mass scanning should be carried out for the supposed analyte peak, looking for a correspondence in the analyte spectrum and in the spectrum of the analyte standard, in terms of presence and correspondence of relative intensities of specified characteristic ions.

If the analyte mass is estimated to be less than 20 ng/injection then the selected ion monitoring (SIM) mode should be used. Confirmation is now achieved by observance of the presence of two characteristic ions - one of those for preference being the molecular ion - at the retention time of the analyte, which in relative abundances agree to ± 10%.

NOTA BENE: SIM conditions could also be stated for quantitative confirmation.

Set out in what way confirmation of determination is carried out.

i.2 Using at least one other column with a different polarity.

Note 11: A peak must be found at the correct retention time for analyte ± 3%, and when measured the quantitative result for the two columns must agree to within ± 10%, or - if within less than 10% - within ± the critical difference CrD_{95} for the method.

Set out in what way confirmation of determination is carried out.

ii. For non-volatile substances, determined before by an HPLC-procedure:

ii.1 By formation of a volatile derivative.

Note 12: qualitative confirmation may be obtained by formation of a volatile derivative which subsequently is examined by GC/MS as described in Section i.1.

Set out in what way confirmation of determination is carried out.

ii.2 By formation of a non-volatile derivative:

Note 13: Qualitative confirmation may be obtained by formation of a non-volatile derivative which subsequently is subjected to HPLC examination. The shift in retention time as compared to that of the analyte must be found to correspond to within ± 3% with the shift in retention time obtained for the analyte standard.

Set out in what way confirmation of determination is carried out.

ii.3 Using at least one other column with differing separation characteristics and a different solvent system:

Note 14: A peak must be found at the correct retention time for analyte ± 3%, and when measured the quantitative result for the two columns must agree to within ± 10%, or - if within less than 10% - to within ± the critical difference CrD_{95} of the determination.

Set out in what way confirmation of determination is carried out.

ii.4 Using a UV or diode array detector:

Note 15: When using a UV detector, absorbance values for analyte at three separate wavelenghts should agree to within ± 3% with that of the analyte standard. When using a diode array detector, correspondence of spectra of analyte and analyte standard should be obtained.

Set out in what way confirmation of determination is carried out.

8. PRECISION:

8.1 Validation *(N.B. For the applicant this item may be omitted)*.

[YEAR]	=	set out year in which precision experiment was performed
[NUMBER]	=	set out number of laboratories or number of samples
[LEVEL]	=	set out numerical values of levels of analyte
[MASS]	=	set out 'µg' or 'mg'.

8.2 Repeatability and reproducibility *(N.B. For the applicant the reprodicibility may be omitted)*.

[LEVEL]	=	set out numerical value of level of analyte
[MASS]	=	set out 'µg' or 'mg
[STANDARD]	=	set out 'internal standard' or 'external standard' or 'standard addition'.

8.3 [LIMIT]:

[LIMIT]	=	set out 'detection limit' or 'determination limit'
[BLANK]	=	set out 'matrix blanks' or 'matrix blanks fortified with analyte at the level of x 0.1 SML' or 'matrix blanks fortified with analyte at the level of x 0.1 QM'
[RANGE]	=	set out numerical values of analyte concentration range
[MASS]	=	set out 'µg' or 'mg'
[LEVEL]	=	set out numerical value of level of analyte.

8.4 Critical [ANALYTE] level:

[RESTRICTION]=		set out 'SML' or 'QM' or a value derived from one of either of those
[SM or Q]	=	set out 'specific migration' or 'residual content'.
[LEVEL]	=	set out numerical value of level of analyte.
[MASS]	=	set out 'µg' or 'mg'.

9. TEST REPORT:

[MASS]	=	set out 'µg' or 'mg'.

It is recommended that the applicant fill out the following summary data sheet.

SUMMARY DATA SHEET

SUBSTANCE (1).....

USE OF SUBSTANCE (2).....

PM/REF.N..(3).....

CAS.N.....

SOCIETY .....

PERSON RESPONSIBLE FOR THE TECHNICAL DOSSIER.....

ADDRESS OF THE RESPONSIBLE .....

.....

.....

PHONE.....FAX.....

Where the technical dossier does not contain all the requested data (see below) give relevant reasons:

.....

.....

.....

.....

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.....

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.....

(1) Indicate first the most common chemical name of the substance or, in the case, of a substance included in the Directive 90/128/EEC the name given in this Directive.

(2) Specify whether it is monomer either additive

(3) PM/REF. N = Plastic Material Reference Number. Indicate this number if it has been given to the substance under examination.

LIST OF DATA REQUESTED

1. IDENTITY OF THE SUBSTANCE

1.1. Individual compound:

1.1.1a. Chemical name:
1.1.1b Synonims:
1.1.1c Trade name(s):
1.1.2. CAS number:
1.1.3a. Molecular and structural formulae:
1.1.3b. Molecular weight:
1.1.4a. Purity (%):
1.1.4b. Major impurities (%):
1.1.5. Spectroscopic data:

1.2 Defined mixtures:

1.2.1a Chemical name:
1.2.1b Trade name(s)
1.2.2. CAS number:
1.2.3. Constituents:
1.2.4. Proportions in the mixture
1.2.5. Data on constituents
1.2.6. Other informations:

1.3. Non-defined mixtures

1.3.1a. Chemical name:
1.3.1b Trade name(s):
1.3.1c CAS number:
1.3.2a. Starting substances:
1.3.2b. Manufacturing details:
1.3.2c. Substances formed
1.3.3 Purification by:
1.3.4. By-products:
1.3.5. Spectroscopic data:
1.3.6 Other information:

1.4. Polymer used as additive:
1.4.1a. Trade name(s)
1.4.1b CAS. N°;
1.4.2. structure of polymer;
1.4.3a. starting substances and other substances present (e.g. impurities, additives) as well as their relative amounts;
1.4.3b residual monomers (mg/kg);
1.4.4. average molecular weight (in ponderal terms);

1.4.5. curve of the distribution of the molecular weights (ordinate weight % of molecules having a certain MW, abscissa the MW) (give a figure similar to the figure on pag. 50).

2. PROPERTIES OF THE SUBSTANCE

2.1. Physical

2.1.1. Melting point (°C):
2.1.2. Boiling point (°C):
2.1.3. Decomposition temperature (°C):
2.1.4. Solubility (g/l):
2.1.5. Other:

2.2. Chemical:

2.2.1. Nature: acid/base/neutral
2.2.2. Reactivity:
2.2.3. Stability (light/air/ionising radiation/heat/simulants):
2.2.4. Hydrolysis:

2.3. Decomposition

2.3.1 Decomposition or transformation during processing
2.3.2. Decomposition or transformation product(s):

2.4. Maximum process temperature (°C):

2.5. Other information:

3. USE

3.1. Technological function:
3.2. Type of plastics:
3.3. Particular use
3.4. Maximum percentage in formulation:
3.5. Residue in finished product and method of extraction:
3.6. Conditions of contact:
3.6.1 Type of foodstuffs
3.6.2. Time/temperature (°C):
3.6.3. Surface to volume ratio (dm^2/kg):
3.6.4. Other information on the conditions of contact:
3.7. Other information on use:

4. AUTHORIZATIONS

4.1. EEC Member States:
4.2 USA: yes/no

4.3. Other countries:

4.4 If the substance is considered as a "new substance" according to Directive 79/831/EEC, was it notified to the competent EEC authorities? Yes/No.

5. MIGRATION DATA

5.1. Food contact material sample
5.1a. Composition of sample (polymer, thickness, %).
5.1b. Treatment of sample prior to testing
5.1c. Other information:

5.2. Food or food simulants used
5.3. Conditions of contact:
5.3.1. Time, temperature
5.3.2. Surface to volume ratio:
5.3.3. Cell or apparatus:
5.4. Analytical method:
5.4.1. Principle of the method
5.4.2. Detection limit
5.4.3. Repeatability
5.4.4. Reproducibility
5.4.5. Other

5.5. Migration data results in the worst cases (give the results in a table):

Simulants	Time	Temperature (° C)	Results mg/dm^2	Results* (mg/kg of food)

**) the results shall be expressed following the guidelines appearing in the CEN documents "Guide to the selection of conditions and test methods for overall migration" (ENV..., under press) and "Guide to the selection of conditions and test methods for specific migration and determination of substances in plastics" (ENV...., under press). Specify clearly the calculations made (see N.B. on pag. 58)*

5.6. Relationship between QM (=quantity maximum in the polymer) and SML (=specific migration limit)

6. **TOXICOLOGICAL DATA**

. ***N.B. VERY IMPORTANT. READ AND FOLLOW STRICTLY.***

. ***A summary should be completed for each study reported in this section. The main findings should be summarized and a statement made on whether significant deviations from control and normal values occurred. The absence of summaries could be the reason for the SCF-WG refusing to examine an application.***

6.1. Genotoxicity
6.1.1. Gene mutation in bacteria:
6.1.2. Chromosomal aberrations in cultured mammalian cells:
6.1.3. Gene mutation in cultured mammalian cells:
6.1.4. Other information:

6.2. General toxicity
6.2.1. Acute (LD50):
6.2.2. Subacute (28 d):
6.2.3. Subchronic (90 d):
6.2.4. Long term and/or carcinogenicity:
6.2.5. Reproduction:
6.2.6. Teratogenicity:
6.2.7. Other information:

6.3. Miscellaneous:
6.3.1. Absorption:
6.3.2. Distribution:
6.3.4. Metabolism:
6.3.5. Excretion:
6.3.6. Dermal effects:
6.3.7. Inhalation effects:
6.3.8. Effects on the immune system:
6.3.9. Induction on peroxisome proliferation:
6.3.10. Other information

7. **SUMMARY OF ALL THE DATA PRESENTED, MAINLY OF TOXICOLOGICAL DATA.**

8. **REFERENCES**

Include the photocopies of the references (see note at the beginning of pag. 49)

Appendix 4

ADDRESSES OF NATIONAL AUTHORITIES AND OF COMMISSION

BELGIQUE

Inspection des denrées alimentaires
Ministère de la Santé Publique
Cité Administrative de l'Etat
Quartier Vésale
B-1010 BRUXELLES

Tel: (32-2) 2382820/2382823
Fax: (32-2) 2303862

DENMARK

Levnedsmiddelstyrelsen
Morkoj Bygade, 19
DK-2860 SOBORG

Tel: (45-39) 696600
Fax: (45-39) 660100

BUNDESREPUBLIK DEUTSCHLAND

Bundesministerium für Jugend, Familie, Frauen und Gesundheit
Deutschherrenstrasse, 87
D-5300 BONN 2

Tel: (49-228) 3083322
Fax: (49-228) 3082221

HELLAS

Ministère des Finances,
Laboratoire Général d'Etat
Rue Anastassion Tsoha, 16
115-21 ATHENES

Tel: (30-1) 6428-211
Fax: (30-1) 6465-123

ESPAÑA

Ministerio de Sanidad y Consumo
Direccion General de Salud Alimentaria y Proteccion de los Consumidores
Paseo del Prado, 18-20
ES-28014 MADRID

Tel: (34-1) 4203210
Fax (34-1) 4201549

FRANCE

Ministère de l'Economie, et des Finances
Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes
59, Boulevard Vincent Auriol
75703 PARIS CEDEX 13

Tel: (33-1)44871717
Fax: (33-1)44873043

IRLANDE

EOLAS (The Irish Science & Technology Agency)
Glasnevin
IRL-DUBLIN 9

Tel: (353-1) 370101
Fax: (353-1) 379620

ITALIA

Ministero della Sanità
Piazza Marconi, 25
I-00144 ROMA

Tel: (39-6) 5994 Extn 238
Fax (39-6) 5925936

LUXEMBOURG

Ministère de la Santé
Division de l'Inspection Sanitaire
Rue de Prague, 5a
L-2348-LUXEMBOURG

Tel: (35-2) 4785650
Fax (35-2)481349

NEDERLAND

Ministerie van WVC, Directie VVP
Postbus 3008
NL-2280 MK RIJSWIJK

Tel: (31-70) 3406965
Fax: (31-70) 3405177

PORTUGAL

Instituto de Qualidade Alimentar
Rua Alexandre Herculano, 6
P-1100 LISBOA

Tel: (351-1) 529186
Fax: (351-1) 549451

UNITED KINGDOM

Chemical Safety of Food Division
Ministry of Agriculture, Fisheries and Food
Ergon House
c/o Nobel House
Smith Square, 17
GB-LONDON SW1P 3JR

Tel: (44-71) 2386334/2386566
Fax: (44-71) 2386382/2386591

COMMISSION

Commission of the European Communities
Division III/C/1
(For the attention of Mr Rossi Luigi)
200, Rue de la Loi
B-1049 BRUXELLES

Tel: (32-2) 2956068/ 2956969
Fax: (32-2) 2960951/ 2951735

APPENDIX 5

LIST OF ADDRESSES OF THE MEMBERS OF THE WORKING GROUP "PACKAGING MATERIALS" OF THE SCIENTIFIC COMMITTEE FOR FOOD*

Miss S.M. BARLOW *
Department of Health
Hannibal House, Elephant and Castle
GB-LONDON EC4A 1AL

Mr Chr BOHME*
Max von Pettenkofer Institut,
Bundesgesundheitsamt
Postfach 330013-D-1000 BERLIN 33

Mr J. CARSTENSEN*
Novo Nordisk A/S
Novo Allé
DK-2880 BAGSVAERD

Mr P. ELIAS*
Bertha-von Suttner-strasse 3A
D-7500 KARLSRUHE WALDSTADT, 1
DEUTSCHLAND"

Mr A. FEIGENBAUM*
I.N.R.A
F-78352 JOUY-en-JOSAS Cedex

Ms A. KNAAP*
RIVM
P.O. Box 1
NL-3720 BA BILTHOVEN

Mr A. Preben NIELSEN*
Morkoj Bygade, 19
DK-2860 SOBORG
DENMARK

Mr Luigi ROSSI**
Commission of the European Communities
DG III
Rue de la Loi 200 -B-1049 BRUSSELS

****

*) send *one* copy of summary data sheet

) send *two* copy of summary data sheet (*remember: a full copy shall be send officially to the Commission and another full copy made available on the request of the Commission)***

NOTA BENE: Additional Institutes to which documentation shall be sent according to model of letters are (read carefully Appendix 1 on pag. 31):

RIVM (for the attention of Ms van Apeldoorn) P.O. Box 1,NL-3720 BA BILTHOVEN (one full technical dossier)

CIVO-TNO (for the attention of Mr Rijk) Utrechtseweg, 48, Postbus 360, NL3700 AJ ZEIST(one full technical dossier but without toxicological data!)

ANNEX 3

DATA REQUESTED FOR SUBSTANCES CLASSIFIED IN LISTS 6-9 AND IN LIST W

INTRODUCTION

1. The Commission services wish to emphasise that the applicant should read carefully Note for Guidance (see pag.23), particularly the "SCF Guidelines"(see pag. 47) in order to supply the correct data requested by the SCF for the evaluation of a substance.

2. The Commission services moreover wish to stress that the "SCF Guidelines" represent an attempt to specify as much as possible the data to be supplied in order to allow the SCF to evaluate the risk connected by the use of a substance in materials in contact with foodstuffs. However the SCF recognised, that the size of the data base, which might be required for evaluation, would depend on whether it is intended to submit a "full dossier" or a "reduced dossier". "Full" dossier containing the complete core set of toxicological data are essential, in principle, for an evaluation in terms of a TDI. However, even in these circumstances deviations from the core requirements could be made, provided an adequate justification for this approach and appropriate reasons are given for omitting any toxicological test. When it is not intended to request the establishment of a TDI, a "reduced" dossier would be acceptable as outlined in paragraphs 6.3.1 to 6.3.3. (pag. 53) of the "SCF Guidelines".

Definitively, it is strongly recommended to the applicant to specify clearly in the summary data sheets (see pag. 83) whether he wishes to deviate from the "SCF Guidelines" and the reasons of his deviation.

3. On the basis of the letter received in the last years, the Commission services think that the applicants have some difficulties to know which data should be supplied to the SCF for the substances allocated into lists 6-9 and list W. Therefore they decided to issue this specific document, where, for each list, the data requested by the SCF as well as the possible options and consequences are clearly specified

4. It must be stressed that the SCF considered the requests listed in "Sixth amendment - Dangerous substances) (79/831/EEC O.J. L. 259 of 15 October 1979) and the data base for the authorization of a substance by the FDA. The SCF conclusion was that both data, in principle, are inadequate to obtain a classification into lists 0-4, unless they are accompanied by a technical explanation in which the applicant has provided an adequate justification for this approach and gives the appropriate reasons for omitting any migration or toxicological test. Therefore the applicant is invited to comply with "SCF Guidelines" in order to obtain a complete evaluation a substance.

5. To facilitate the comprehension of this document, the definitions of the SCF lists 6-9 and list W are reported below:

LIST 6

Substances for which suspicions exist about their toxicity and for which data are lacking or are insufficient.

The allocations of substances to this list are mainly based upon similarity of structure of chemical substances already evaluated or known to have functional groups that indicate carcinogenic or other severe toxic properties.

Section A

Substances suspected to have carcinogenic properties. These substances should not be detectable in foods or in food simulants by an appropriate sensitive method for each substance.

Section B

Substances suspected to have toxic properties (other than carcinogenic). Restrictions may be indicated.

LIST 7

Substances for which some toxicological data exist, but for which an ADI or TDI could not be established. The required additional information should be furnished.

LIST 8

Substances for which no or only scanty and inadequate data were available.

LIST 9

Substances and groups of substances which could not be evaluated due to lack of specifications (substances) or to lack of adequate description (groups of substances). Groups of substances should be replaced, where possible, by individual substances actually in use.

Polymers for which the data on identity specified in "SCF Guidelines" are not available.

LIST W

"Waiting list". Substances not yet included in the existing positive lists of Member States. Although these substances appear in Synoptic documents, they are not susceptible to be included in the Community lists, lacking the data requested by the Committee.

SUMMARY OF ADDITIONAL DATA REQUESTED BY SCF FOR SUBSTANCES CLASSIFIED IN LISTS 6A, 6B, 7, 8, 9 AND W.

SUBSTANCES CLASSIFIED IN LIST 8 OR LIST 6A OR LIST 6B

If not yet transmitted, the applicant should provide data on:

- chemical properties and stability
- use
- migration (see pag.51) (N.B. The data shall be always provided except if they may be derived from calculation (see point 6.3.4 in "SCF Guidelines"", pag. 54);
- toxicology (see below)

Concerning the toxicological data to be submitted, these depend on the level of migration (M) obtained in the "worst" possible or foreseeable case. Three situations have been set out by the SCF in its guidelines (pag. 47) and these are hereinafter repeated:

"6.3.1. IF 5< M < 60 MG/KG OF FOOD OR FOOD SIMULANT

the applicant should provide the following "full dossier" containing:

- a 90-day oral study
- 3 mutagenicity studies (see for the details pag. 56)
  - i) a test for gene mutations in bacteria
  - ii) a test for chromosomal aberrations in cultured mammalian cells;
  - iii) a test for gene mutations in cultured mammalian cells; under special circumstances another validated eukaryotic test detecting gene-mutations may be acceptable;
- studies on absorption, distribution, metabolism and excretion;
- data on reproduction;
- data on teratogenicity;
- data on long-term toxicity/carcinogenicity.

These studies should be carried out according to the instructions in the EEC Directives and/or OECD guidelines, including "Good Laboratory Practice" (see bibliography, pag. 55).

"6.3.2. IF 0.05 < M < 5 MG/KG OF FOOD/FOOD SIMULANT:

the applicant should provide either the "full dossier" mentioned in 6.3.1. in order to obtain an allocation of a TDI or the "reduced dossier" containing at least the following data:

- data demonstrating the absence of potential bioaccumulation in animals (e.g. octanol/water partition coefficient);
- data demonstrating the absence of mutagenic potential by the 3 mutagenicity tests listed in 6.3.1;

- 90-day oral toxicity study."
- other additional tests, if they are specifically requested by SCF.

"In principle", if only a "reduced dossier" is available, the SCF will not allocate a TDI but will propose a restriction less or equal to 5 mg/kg of food or food simulant or some other equivalent restriction.

Only in some exceptional cases where other data are available, (i.e. studies on absorption, distribution, metabolism, excretion, reproduction, teratogenicity etc.), the SCF could establish a NOEL and consequently a TDI. Therefore the applicant is invited to summarize in the "Summary data sheet" accompanying the technical dossier the arguments on the basis of which he considers that a TDI could be established.

"6.3.3. IF M < 0.05 MG/KG OF FOOD OR FOOD SIMULANT

The applicant should provide either the "full dossier" mentioned in 6.3.1. in order to obtain an allocation of a TDI or the "reduced dossier" containing at least the migration data (they are necessary) and the data demonstrating the absence of mutagenic potential by the 3 mutagenicity tests listed under 6.3.1."

In principle, if only a "reduced dossier" is available, the SCF will not allocate a TDI but will propose a restriction less or equal to 0.05 mg/kg of food or food simulant or some other equivalent restriction. The SCF stressed that this restriction may be established, only if the migration data in the "worst conditions" are supplied.

NOTA BENE.

a) If, by calculation, it is possible show that the level of migration of the substance (assuming that 100% of substance migrates) may not exceed the upper limits fixed in points 6.3.2 or 6.3.3, then the applicant can supply only the "reduced" dossier;

b) If the applicant believe that for an adequate evaluation of its substance, it is not necessary to supply all the requested data, he should give in the summary data sheet (see pag. 83) relevant reasons accompanied by supporting documents. **If the technical dossier does not contain a summary data sheet and the requested summaries , it would not be examined;**

c) As regards migration data, see pag. 58

SUBSTANCES CLASSIFIED IN LIST 7

The applicant should provide only the data specifically requested by the SCF.

However it should be noted that, frequently, these data represent only the minimal data requested to enable a first toxicological assessment to be made. These data would suffice for completion of a "reduced dossier", but would not be adequate for providing a "full dossier". In principle, if only a "reduced dossier" is available, the SCF would not allocate a TDI but will propose a restriction depending on the toxicological data available.

SUBSTANCES CLASSIFIED IN LIST 9

The SCF list 9 contains the following categories of substances which are listed below together with a summary of information required:

Category 1
Groups of substances inadequately described e.g. alkyl vinyl ethers; acids aliphatic (C6-C24); nonylphenol.

The applicant should specify, **as a first step**, the individual substances actually used (isomers included!) which are covered by this category, giving for each substance the details described in "SCF Guidelines", paragraph 1.1 and reported again in addendum 6 (see pag. 98)

Category 2
Substances, natural or synthetic, which need specifications (e.g. castor oil; polymers or copolymers).

The applicant should provide, **as a first step**, specifications for these substances according to "SCF Guidelines" paragraphs 1.2 or 1.3 for the mixtures and to paragraph 1.4. for polymers used as additives (see pag. 98 and also explanation on pag. 19). Particularly important is the reference to specifications given, for example, by JECFA, Codex Alimentarius, Food Chemicals Codex, European or US Pharmacopoeias. The SCF examine the dossier and decides which types of additional data should be transmitted by the applicant (e.g. migration and/or toxicological data). The applicant finally supplies the requested additional data.

Category 3
Mixtures, defined or not defined, and inadequately described for toxicological evaluation.

The applicant should provide, **as a first step**, full details of these mixtures, according to "SCF Guidelines" in paragraphs 1.2 and 1.3, set out again in pag. 98 and also explanation in pag. 13 and following of "Practical Guide N.1"). The SCF examines the dossier and decides which types of additional data should be transmitted by the applicant (e.g. migration and/or toxicological data). The applicant then supplies the requested additional data.

SUBSTANCES CLASSIFIED IN WAITING LIST

This case applies only to the "new" substances e.g. substances not yet included in the "official" Community list and never authorized at national level. It has to be underline that these "new" substances are evaluated and classified applying the same criteria used for the "old" substances (substances already authorized at national level). **However they will never be included in the official Community lists until they are classified in lists 0-4.** They are listed in the synoptic document only for information. If the substance is allocated in waiting list without any further indication ("W" in the column "SCF_L" of the synoptic document) or with the indication W8, the applicant should supply all the data depending on the level of migration obtained (see points 6.3.1-6.3.3, pag. 95$). If the substance is allocated into W7 or W9 supply the data respectively mentioned for the substances classified in lists 7 or 9.

Addendum 6

DATA REQUESTED BY SCF IN ORDER TO RECLASSIFY A SUBSTANCE TO LIST 9

1. IDENTITY

1.1. In the case of an individual, well-defined substance give:

1.1.1. Chemical names (IUPAC and some synonyms such as common name, CAS name and trade name).
1.1.2. CAS number.
1.1.3. Molecular and structural formulae; molecular weight.
1.1.4. Degree of purity; methods for determination of purity; qualitative and quantitative data concerning impurities.
1.1.5. Spectroscopic data; supply data which allow identification and characterisation of the substance, e.g. infrared and/or mass spectrometry.

1.2. Mixtures which can be defined.

a) Mixtures arising from natural sources.
These mixtures shall be submitted accompanied by toxicological data referring to the whole mixture (see para 6) with description of each component in accordance with paragraphs 1.1.1. - 1.1.5 and the proportion of each component.

b) Synthetic mixtures.
Each component of a synthetic mixture shall be submitted separately.

1.3. Mixtures which cannot be defined.
A description as complete as possible should be supplied, including:

a) the compounds or raw materials used in preparing the mixture;

b) the production process, production control and reproducibility of the process;

c) the method used to purify the product;

d) the substances formed during the process.

1.4. Polymer used as additive

1.4.1. CAS. N°
1.4.2. structure
1.4.3. starting substances and other substances present (e.g. impurities, additives) as well as their relative amounts
1.4.4. average molecular weight (in ponderal terms)
1.4.5. curve of the distribution of the molecular weights (ordinate weight % of molecules having a certain MW, abscissa the MW)(see figure pag. 50)

ANNEX 4

CRITERIA APPLIED BY SCF IN THE EVALUATION OF SUBSTANCES

CRITERIA APPLIED BY SCF IN THE EVALUATION OF SUBSTANCES

1. INTRODUCTION

1.1. On 20 April 1990 the SCF adopted the "Guidelines for presentation of data for toxicological evaluation of a substance to be used in packaging materials" ("SCF Guidelines")(SCF Series N.26, 1992). These guidelines apply to "new" substances (e.g. substances not yet included in the "official" Community list and never authorized at national level) as well as "old" substances (e.g. substances already authorized at national level). An updated version of the document appears in Appendix 3 (see pag. 47).

1.2. The "SCF Guidelines" do not specify sometimes explicitly the criteria followed by SCF in the evaluation of a substance and particularly the criteria used in setting out some quantitative restriction which appear in its reports. However in some cases the SCF in its reports on packaging or in minutes of meeting of "ad hoc" working group has clarified its opinion in this matter.

1.3 **The aim of this document is to summarize these criteria as much as possible in order to provide basic information to outside and, mainly as pro-memoria to avoid discrepancies in future evaluations.**

1.4. For further explanation on criteria applied, read the two following publications:

a) Barlow S. Lecture at Pira meeting, Amsterdam, May 1993, to appear in Food additiv. and contamin.., 1993;
b) Feigenbaum A, International Conference on Materials for Food Packaging, Gothemburg 10-11 March 1993.

which are enclosed as Appendix 1 and 2 to this Annex.

2. ALLOCATION INTO SCF LISTS.

2.1 The SCF in the last report on monomers, actually in press, classified the substances in ten lists, whose definitions are reported in pag. 42 (lists 0-5) and in pag. 44 (lists 6-9 and list W). In all of these definitions the general criteria applied for the allocation of the substances into these lists are already included in the report and therefore will not be repeated in this document. However it could be useful

1) to repeat some criteria of classification as a pro-memoria or underline some aspects of the allocation in lists 6 (6A and 6B), 7, 8 and 9, because recently some detailed criteria have been added for these lists and they are not yet widely known;

2) to explain better the criteria used by the SCF in establishing a TDI or other quantitative restrictions.

Both these requirements should be satisfied by the following text.

2.2. LIST 6

As indicated in the last report on monomers "the allocations of substances to this list are mainly based upon similarity of structure of chemical substances already evaluated or known to have functional groups that indicate carcinogenic or other severe toxic properties".

2.2.1 LIST 6A

The SCF recently expressed the opinion that the following compounds are "suspected to have carcinogenic properties":

- acrylamides and methacrylamides
- allyl compounds
- crotonyl compounds
- epoxy compounds
- hydrazides
- vinyl compounds

Therefore, in principle, all these compounds appear in list 6A accompanied by the notation that "these substances should not be detectable in foods or in food simulants by an appropriate sensitive method". In principle the Commission services established for these substances in the Directive 90/128/EEC and a SML (specific migration limit) equal to 0.05 mg/kg or a QM (maximum quantity in finished product) equal to 5 mg/kg. Only a few substances are classified in other lists. The general criteria used are described below.

General criteria for classification of acrylamides and methacrylamides, allyl, crotonyl, epoxy and hydrazide compounds

Substances with sufficient data to allocate a TDI List 2.
In principle, if mutagenicity data according to the guidelines and/or carcinogenicity data are missing, the TDI should be temporary.

- Generic terms
  List 9 (with the same restriction mentioned above).

- Polymers made from the substances mentioned above
  List 9.

- All other substances (except those listed in L4A)
  List 6A

General criteria for reclassification of vinyl compounds:

- Substances with sufficient data to allocate a TDI
  List 2.
  In principle, if mutagenicity data in compliance with the guidelines and/or carcinogenicity data are missing, the TDI should be temporary.

- Generic terms
  List 9 (with the same restriction mentioned above).

- Polymers made from the substances mentioned above
  List 9.

- All other substances
  List 6A except the compounds in L4A and the following substances:

  (i) vinyl ethers of those alcohols which are in lists 0, 1, 2, 3
  List 7 (with the same restriction mentioned above).
  Needed: hydrolysis data;

  (ii) vinyl ethers of those alcohols which are in lists 6, 7 and 8:
  List 7 (with the same restriction mentioned above).
  Needed: provided hydrolysis can be demonstrated, data on corresponding alcohol.

  (iii) vinyl esters of those monocarboxylic acids which are in lists 0,1,2 and 3:
  List 7 (with the same restriction mentioned above).
  Needed: hydrolysis data.

  (iv) monovinyl esters of those polycarboxylic acids which are in lists 0,1,2 and 3:
  List 7 (with the same restriction mentioned above).
  Needed: hydrolysis data

  (v) vinyl esters of those monocarboxylic acids which are in lists 6, 7 and 8:
  List 7 (with the same restriction mentioned above).
  Needed: provided hydrolysis can be demonstrated, data on corresponding acid.

  (vi) monovinyl esters of those polycarboxylic acids which are in lists 6, 7 and 8:
  List 7 (with the same restriction mentioned above)
  Needed: provided hydrolysis can be demonstrated, data on corresponding acid.

2.2.2 LIST 6B

The SCF recently decided that the following compounds are "suspected to have toxic properties (other than carcinogenic)":

Esters of:
- adipic
- azelaic

- citric
- phosphoric
- phosphorous
- phthalic
- sebacic
- trimellitic

Therefore, in principle, all these compounds appear in list 6B with exception of a few classified in list 2 (data are available for allocating a TDI), in list 7 (hydrolysis data can justify the assessment of hydrolysates, see later) or in list 9 (the SCF wishes always to know the precise identity of the substances before taking any decision). The allocation into list 6B has been accompanied by a group restriction of 0.025 mg/kg b.w. and by the request for peroxisome proliferation study (except for a few compounds) and one or more of the following data:

- reproduction and teratogenicity studies

- mutagenicity studies

- neurotoxicity studies

The attribution of a group restriction of **0.025 mg/kg bw** is based on the following considerations:

- these compounds are suspected to have "severe toxic effects" and therefore their "migration should be as low as possible";

- these compounds have often the same use (plasticizers) and are used as a mixture and therefore it is useful to put a restriction for all the group;

- the great majority of these additives are peroxisome proliferators and they are lacking data to evaluate their potency as peroxisome proliferators and to indicate whether they are more toxic than DEHP, which is considered the most potent peroxisome proliferator among these additives. Therefore the level of the restriction for all group may be fixed at the level of the TDI of DEHP (= **0.025 mg/kg bw**).

The reasons for the requests of other specific studies have been indicated and may be summarized as follows:

Mutagenicity studies

They are considered useful either as test for detect mutagenic properties or, mainly, as screening test for detect the substances "suspected to have carcinogenic properties".

In principle, the following three tests should be provided:

i) a test for gene-mutations in bacteria;

ii) a test for chromosomal aberrations in cultured mammalian cells;

iii) a test for gene-mutations in cultured mammalian cells; under special circumstances another validated eukaryotic test detecting gene-mutations may be acceptable.

For detection of chromosomal aberrations the Committee has chosen an in-vitro test with cultured mammalian cells only, despite the fact that for many chemicals the in-vivo micronucleus test will already have been performed. The reason is that the micronucleus test may be relatively insensitive in comparison with the in-vitro test with cultured mammalian cells.

Peroxisome proliferation study

A number of esters possess the potential of inducing proliferation of hepatic peroxisomes and increased enzyme activity when administered at high dietary levels to rodents. The rodents have also reacted with an increase in hepatic adenomas and/or hepatic carcinomas.

It is not known whether tumour development is causally related to peroxisome proliferation. However, peroxisome proliferation is one of the sensitive toxic responses to these compounds and is a marker for their hepatotoxicity.

These studies have been requested for all alkyl esters because there is evidence to indicate that both branched and unbranched esters of differing chain lengths may cause peroxisomal proliferation. These data have not been requested for cycloaliphatic or aromatic esters because there is no evidence to suggest that they cause peroxisomal proliferation. Where such studies have been requested they should be carried out in the rat and dosing should be a minimum of 14 days in duration. Enzyme activity measurements should include at least cyanide-insensitive palmitoyl CoA oxidase and lauric acid 12-hydroxylase. Of the various methods in use to assess these activities the SCF recommends that the following are used:

Palmitoyl-CoA oxidation
a spectrophotometric assay based on the methods of either Lazarow or Bronfman.

Lazarov P.B. and DeDuve C., Proceedings of the National Academy of Sciences 73(1976)2043-2046.

Lazarov P.B., Methods in Enzymology 72(1981)315-319;

Bronfman et al. Biochemical and Biophysical Research Communications 88(1979) 1030-1036;

Lauric acid 12-hydroxylase
a radiometric assay using radiolabelled substrate and HPLC to separate individual hydroxy metabolites from unmetabolised substrate.

Parker G.L. and Orton T.C. Biochemistry Biophysics and Regulation of Cytochrome P-450. Eds: Gustafasson J-A, Duke JC, Mode A & Rafter J. pp 373-377. Elsevier/North Holland; T.C.(1980);

Sharma, R Lake BG, Foster J. & Gibson GG (1988). Biochemical Pharmacology 37(1988)1193-1201.

Reproduction and teratogenicity studies

These studies have been requested for certain substances because there is evidence that a number of substances in the group have adverse effects on reproduction and/or are teratogenic. However, these data need only be provided if migration exceeds 5 mg/kg of food (see "SCF Guidelines", point 6.3.3 on pag. 53).

Neurotoxicity studies

Neurotoxicity studies have been requested for phosphoric and phosphorous acid esters because there is evidence that a number of substances in the group have neurotoxic properties. Tests in chickens or measurements of anticholinesterase activity would be appropriate. However, these data need only be provided if migration exceeds 0.05 mg/kg of food (see "SCF Guidelines", point 6.3.1 on pag. 53).

2.3. LIST 7

In principle the allocation to list 7 is based on the knowledge of certain data, often summarized in the reports. However they are not so complete or adequate to allow a classification into lists 0-4. Therefore the additional data specified in the notation "needed" should be furnished.

Hydrolysis data

In principle, the SCF requires this information with the objective of reducing the amount of toxicological testing. This may arise when the chemical structure of monoesters suggests ready hydrolysis into substances which are toxicologically acceptable and already in list 0, 1, 2 or 3. Therefore not for all esters are these hydrolysis data requested, but only for some specifically indicated compounds.

For instance the SCF required hydrolysis data only for acrylic and methacrylic esters of monohydric alcohols or monoesters of the same acids with polyalcohols, provided the alcohols are in lists 0,1,2 and 3. Therefore all other esters of acrylic and methacrylic acids follow the general rules for the allocation of the substances in SCF lists. The same criterion applies for the esters of adipic, azelaic, citric, phosphoric, phosphorous, phthalic, sebacic, trimellitic for which the hydrolysis data are requested only for those monoesters which may hydrolyse to substances which are already in lists 0, 1, 2 and 3.

Demonstration of hydrolysis may be carried out in foods or food simulants, representing the range of foods with which the substance may come into contact. Alternatively, or in cases where hydrolysis in food does not occur, hydrolysis can be evaluated in simulated saliva and/or gastrointestinal fluids.

The SCF underlined that when it requires hydrolysis data, this does not imply that all other toxicity data should not be provided. In some cases moreover other toxicity data may render the request for hydrolysis data superfluous.

2.4 LIST 8

The SCF allocated to this list "the substances for which no or only scanty and inadequate data are available".

The notation "inadequate data" which appears besides some compounds in List 8 (or other list too) should be correlated with the request made by the SCF in its guidelines. In these guidelines the SCF recommended to the applicants to provide:

a) only the data specified in "full" or "reduced" dossier (see "SCF Guidelines", points 6.2 on pag. 52 and 6.3 on pag. 53);

b) provide the data under a) according to EEC Directives and/or OECD guidelines, including "Good Laboratory Practice".

Therefore the term "inadequate" means that the data supplied (e.g. acute toxicity data, inhalation studies) are either not those specifically requested (e.g. subchronic or long term studies, oral studies) or are not in conformity with EEC/OECD guidelines (e.g. number of animals or biological parameters examined are insufficient).

2.5. LIST 9

The SCF classified in this list all the "substances and groups of substances which could not be evaluated due to lack of specifications (substances) or to lack of adequate description (groups of substances)." Also the polymers for which the data on identity specified in "SCF Guidelines"are not available. See pag. 96 for a detailed discussion of the various situations.

2.5.1 Groups of substances or mixtures

According to the SCF, the groups of substances or the mixtures should be replaced, where possible, by individual substances actually in use. If the applicant cannot specify the individual substances used, the SCF requires to know the reasons. In this case the SCF, in principle, will authorize only the mixture for which the applicant supplied technical data and, therefore, the applicant should give a precise description of the mixture.

Concerning the "mixtures" general criteria for their evaluation have not be established. The SCF decided to evaluate them case by case. For example, since phthalates, adipates and phosphates have been frequently requested as mixtures, for these substances a group restriction of 0.025 mg/kg has been fixed (see further explanation also pag. 13 and following).

2.5.2 Polymers

The SCF divided the polymers into 2 categories:

Cat. 1. Polymers and their mixtures ("blends") used as starting substances;

Cat. 2. Polymeric additives.

The reason for this distinction is that the polymeric additives may not necessarily have the same degree of polymerisation as the polymers of cat. 1.

For cat. 1) only data on the monomers are of interest and, therefore, in Directive 90/128/EEC it is provided that the "oligomers and natural or synthetic macromolecular substances as well as their mixtures, if the monomers or starting substances required to synthesize them are included in the list", have not be listed specifically.

For cat. 2) data requested in "SCF Guidelines", paragraph 1.4. (see pag. 50) should be provided for an evaluation, particularly the curve of distribution of the molecular weights.

According to the SCF:

a) Polymers used as additives with a molecular weight distribution, the lower end of which is greater than 1.000 daltons.

- They are toxicologically acceptable and classified in list 3 with the indication "polymer" without specific individual evaluation, if their monomers or starting substances are on lists 0, 1, 2, 3 and 4.
- They need an individual evaluation. Technological and toxicological data on monomers shall be supplied according to "SCF Guidelines" (see pag. 47) if their monomers or starting substances are on lists 6, 7 ,8, 9 or not yet evaluated.

b) Polymers used as additives with part of their molecular weight distribution below or equal to 1.000 daltons.

In the first phase the following data are needed:

1.4.1. - CAS N°
1.4.2. - structure
1.4.3.- starting substances and other substances present (e.g. impurities, additives) as well as their relative amounts
1.4.4. - average molecular weight (in ponderal terms)
1.4.5.- curve of the distribution of the molecular weights (ordinate weight % of molecules having a certain MW, abscissa the MW)(see figure on pag.50)
1.4.6. - any relevant toxicological data, if they are available, because they may help accelerate evaluation.

The distinction between these categories is based on three main features:

a) the absorption by the gastrointestinal tract is negligible when the MW exceeds 1000 daltons;

b) the migration from plastic materials is very low for the higher MW substances;

c) the purification of polymeric additives and the removal of residual monomers are often easier for the lower molecular weight compounds.

2.5.3 Fatty acids, dimers and trimers

The SCF decided the following general criteria:

a) it is not longer necessary to add the notation "food grade quality" and, therefore, all the substances containing this specification may be suppressed;

b) all the fatty acids derived from natural sources are allocated in L3 with the notation "constituents of natural fats" ;

c) all fully hydrogenated and dehydrated fatty acids derived from natural sources are allocated in L3 with the notation "identical with or similar to constituents of natural fats";

d) all oils (including, for consistency, castor oil which has an ADI), all fats and all triglycerides of fatty acids monocarboxylic saturated straight chain and even C numbers are allocated in L3 with the notation "natural fats";

e) all fully hydrogenated and dehydrated oils and fats are allocated in L3 with the notation "similar to natural fats";

f) the dimers of the substances under b) are allocated in list 8.

The wg estimates that the presence of minor amounts of certain fatty acids in natural oils e.g. fatty acids with odd numbers of carbon atoms should be dealt with as impurities of the natural oil and therefore form part of the specification of the individually listed major components.

2.6. Salts

As specified in all the SCF reports "Whenever acids, phenols or alcohols have been evaluated, the assessment also includes aluminium, ammonium, calcium, iron, magnesium, potassium, sodium and zinc salts."

2.7 Foodstuffs and food ingredients

In the case of foodstuffs or food ingredients, used either as monomer and starting substances or as additives to plastics, these substances will automatically included in list 0. Apart from the evidence for their classification into foods or food ingredients no toxicological data will be required. Migration data are still needed to ensure that the

use of the plastic packaging does not violate any existing legislative requirement applicable to the packaged food (i.e. compositional restrictions for milk, cheese, chocolate).

2.8. Food additives

In the case of food additives listed in EEC Directives or Reports of the SCF, these substances will be automatically added to list 1 and no further data on toxicology will be required. However migration data are still needed, because for some food additives operate restrictions on use levels or use in certain foods. Migration from plastic packaging must not lead to any infringement of these restrictions.

3. INTERPRETATION OF RESULTS AND QUANTITATIVE RESTRICTIONS

The interpretation of the toxicological data depend on whether the required set of mutagenicity tests shows the substances to be either non-genotoxic or genotoxic.

3.1. For non-genotoxic substances a dosage level causing no observed adverse effects in laboratory animals (NOAEL) is usually determinable. If they have been evaluated already by the SCF or JECFA, a reassessment may not be required unless new scientific evidence makes this necessary. For further details see "SCF Guidelines". For other substances a "tolerable daily intake" (TDI) for man, expressed in mg/kg b.w. can be calculated by applying a safety factor which is sufficiently large to allow for:

a) possible differences between animals and man in their reaction to chemicals;

b) possible differences between individuals in any population in their sensivities to chemicals;

c) uncertainties involved in assessing the safe level in animals;

d) uncertainties due to difficulties in carrying out adequate monitoring of human populations to detect unexpected adverse effects in man.

In principle, if the data are considered adequate (e.g. all the data mentioned as " essential core set of test" in "SCF Guidelines"", point 6.1, pag. 52), a value of 100 for the safety factor is applied. However because often the available toxicological data were less extensive than in the case of food additives (e.g. reproduction, teratogenicity or mutagenicity data sometimes were incomplete or lacking), a larger safety factor than usual was chosen and a "new" concept, TDI, has been introduced.

3.2.1 if the level of migration (M) is $0.05 \leq M < 5$ mg kg of food/food simulant and a "reduced dossier" containing at least the following data:

- data demonstrating the absence of potential bioaccumulation in animals (e.g. octanol/water partition coefficient);

- 3 specified mutagenicity tests;

- 90-day oral toxicity study.

In this case, in principle, the SCF proposes a restriction less or equal to 5 mg/kg of food or food simulant;

3.2.2 if M < 0.05 mg/kg of food or food simulant and a "reduced dossier" containing at least 3 specified mutagenicity tests.

In this last case, in principle, the SCF proposes a restriction less or equal to 0.05 mg/kg of food or food simulant.

3.3. For genotoxic substances or for very highly toxic substances (e.g.sensitizers) for which the present scientific knowledge does not permit the establishment of a NOAEL, an allocation in lists 4 or 5 is, in principle, considered appropriate.

Appendix 1 to Annex 4

THE ROLE OF THE SCIENTIFIC COMMITTEE FOR FOOD

IN EVALUATING PLASTICS FOR PACKAGING

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Abstract

One of the tasks of the Scientific Committee for Food (SCF) is to advise the Commission of the European Communities on the safety-in-use of monomers, other starting substances and additives used in food packaging materials. This advice forms the basis of Community Directives for the regulation of food packaging materials by a system of positive lists of substances authorised for use. The SCF considers the available migration and toxicity data and classifies each substance into one of ten lists, reflecting whether or not there are adequate data and whether the data indicate the potential for adverse effects. This paper describes the SCF classification system and discusses the rationale behind the SCF approach to toxicity testing and evaluation of food packaging materials, with particular emphasis on the recent change which took place in 1990 when the Committee issued a new set of guidelines. These guidelines outlined a new tiered approach to toxicity testing, based on the principle that the greater the potential human exposure to a substance, the more toxicity data are required to make a sound health assessment.

Keywords European Commission, Scientific Committee for Food, toxicity, plastics, food packaging.

Introduction

The Scientific Committee for Food (SCF) was set up in 1974 to provide independent advice to the Commission of the European Communities on toxicological aspects of food, in particular, focussing on food additives and contaminants. The Commission sought advice at an early stage on substances used in food contact materials since these were recognised to have the potential to migrate into food and be consumed. The first SCF opinion on such materials addressed the toxicity and migration into food of vinyl chloride monomer (Commission of the European Communities 1975). Since that time, the SCF has played an important role in advising the Commission on the safety aspects of chemicals used in plastics for food packaging.

The need for such advice has become increasingly clear. Whilst many chemicals migrate in only negligible quantities from packaging into foods, it is apparent that others can migrate in higher quantities, in some cases, matching or even exceeding the amounts of other chemicals present in foods from their deliberate use as food additives. Thus, food contact materials warrant careful toxicological appraisal with a need for appropriate toxicity testing to support their use.

The numbers of substances used in plastics for food packaging are considerable. The SCF has evaluated over 1200 monomers and other starting substances and over 1000 additives so far. To appreciate the scale of the task, it is interesting to compare this with the 270 or so direct food additives which have been evaluated by the SCF. It was because of the very large number of substances used in packaging that the SCF set up a separate Working Group on packaging materials in the late 1970s. The Working Group makes reports and recommendations to the main SCF, which finalises all the opinions on general principles and individual substances.

SCF Lists

SCF opinions on individual substances are set out in the form of classifications into one of ten different lists, numbered 0 - 9 (Commission of the European Communities 1987). Substances on which there are adequate toxicity data to make a proper safety assessment are classified into one of the first six lists, that is, 0 - 4, and occasionally List 5. Substances on which there are inadequate data to make a proper safety assessment are classified into Lists 6 - 9. The classification scheme is summarised in Tables 1 and 2 and described in more detail below.

List 0 substances pose no problem. They are normal food ingredients, such as butyric acid, which is present at up to 5% in butter, or cellulose, which is the main fibre found in many edible plants. Alternatively, substances in this group may be normal products of intermediate metabolism in man, such

as glucose or urea.

List 1 substances are largely those which are also used as direct food additives, for which a full or temporary Acceptable Daily Intake (ADI) has been set by the SCF or by the WHO/FAO Joint Expert Committee on Food Additives (JECFA). This list also includes a few substances which are not direct food additives, which are present naturally in food, but for which intakes need to be limited, and for which JECFA has set Maximum Tolerated Daily or Weekly Intakes. Examples include iodine, bromine, copper and phosphorus.

List 2 comprises substances which are not naturally present in foods or in the body, are not direct food additives and for which the SCF has been able to set a Tolerable Daily Intake (TDI) on the basis of the available toxicity data.

List 3 comprises substances for which the toxicity data are insufficient to set an ADI or TDI but which are acceptable for use. The explanations for inclusion in this group are somewhat varied. Some are included since they are unlikely to be present in food other than in very small quantities because they possess properties which render levels in food self-limiting. For example they may have high volatility (e.g. butane, pentane), or be reactive gases (e.g. acetylene, ethylene, azodicarbonamide) or have strong flavour and/or smell (e.g. camphor, chlorine, alpha- and beta-pinene). Also included in List 3 are substances known to be inert (silicates, zinc oxide). Lastly included in List 3 are substances of low or very low migration, for which toxicity data are adequate to establish that their use is acceptable with such low migration, but that same toxicity information is insufficient to enable the SCF to set a TDI. For these substances, a specific limit of migration or composition limit for the plastic material is set by the Commission to ensure that they cannot subsequently be used in ways that would give rise to higher migration than the maximum level the toxicity data will support. Should other uses resulting in higher migration levels be proposed, then further toxicity data must be submitted to support such uses.

List 4 contains substances known to be toxic, for which an ADI or TDI cannot be set, but their use is acceptable provided there are no detectable residues in food, as determined by an agreed, sensitive method. These substances are mostly established genotoxic carcinogens for which it is assumed there is no safe intake. The number of additives in this category at present is small (see Table 3), but the number of monomers is rather larger, reflecting the fact that many of them are, and have been for many years, essential for the manufacture of a wide range of plastics (e.g. acrylonitrile, butadiene, vinyl chloride). The SCF's general view on genotoxic carcinogens, however, is that their use should be avoided wherever possible. It is therefore unlikely that any new food packaging substances which are genotoxic or genotoxic carcinogens would be regarded as acceptable for use.

List 5 is the last category of substances for which toxicity data are sufficient for the SCF to give an opinion. The data for substances in this category are such as to indicate that they should not be used. The number of compounds in this category are few. It includes asbestos and morpholine-containing compounds which can form carcinogenic N-nitroso-morpholine derivatives in vivo. The list also includes compounds with a marked potential for bioaccumulation such as highly halogenated compounds.

List 6 contains substances for which data are insufficient or absent but serious toxicity is suspected. This suspicion may emerge from preliminary toxicity data, say, indicating possible genotoxicity, or may derive from the fact that they are closely related in structure to other chemicals with known serious toxicity, such as genotoxicty, carcinogenicity, teratogenicity or neurotoxicity. Because the possibility of serious toxicity cannot be eliminated at this stage of the evaluation, the Commission sets restrictions on the use of these substances.

List 7 substances are those for which some toxicity data exist, but they are insufficient to set a TDI. At this stage of the evaluation there are no serious toxicity alerts but the SCF requires further specified data to be submitted.

List 8 substances have little relevant or no toxicity data available and data must be submitted according to the SCF guidelines (see below).

List 9 comprises groups of substances or individual substances with inadequate chemical descriptions to enable them to be properly identified. They must be properly specified before the SCF can consider them.

Community Directives on packaging

In the European Community, regulation of substances used in food packaging materials is done by means of "positive listing" in Community Directives. Once a Directive has been implemented, only those substances which appear in the positive list are permitted for use in food contact materials traded within the Community. In the case of monomers and other starting substances, all those classified in Lists 0 - 4 are authorised for use, provided they comply with any specified restrictions. They are included in Section A of the positive list in the EC Directive on plastics 90/128/EEC (Commission of the European Communities 1990a). No further toxicity data are required on them by the SCF unless the ADI or TDI is only temporary. In the case of additives, those in Lists 0 - 4 will be included in Section A of a forthcoming EC Directive on additives. List 5 substances are, or in the case of additives will be, excluded from the positive lists in EC Directives.

However, for the majority of substances used in plastics, the SCF has been unable to give any opinion (see Table 3). Approximately 80% of monomers are classified in Lists 6 - 9 because relevant toxicity data are either totally lacking or inadequate for making a proper safety assessment. For additives, around 60% fall into these categories. This is far from satisfactory from the public health point of view as it indicates that the majority of substances currently in use in food packaging materials have not been adequately tested and assessed for safety. Such are the misunderstandings in this area that the SCF is occasionally misquoted as having deemed substances on Lists 6 - 9 acceptable for use, simply because the Committee has looked at them. Whereas, the actual situation is that the SCF has been unable to offer any reassurance about the safety of substances classified in Lists 6 - 9.

All the monomers and other starting substances in Lists 6 - 9 are at present included in Section B of the positive list in EC Directive 90/128/EEC, as substances which may continue to be used pending a decision on whether they can be transferred to Section A. However, in order to retain Section B substances in the Directive, the data required by the SCF must be submitted according to deadlines laid down by the Commission and published in the most recent edition of the Note for Guidance of Applicants (Commission of the European Communities 1991). The SCF is aware that a substantial amount of testing is required within a fairly tight time period in order to meet these deadlines. Such deadlines are essential to ensure that the present undesirable situation does not continue, whereby chemicals are in use on which there is little or no information. Recognising that there are real practical difficulties in testing large numbers of substances, the deadlines for submission of data have been staggered over a total of 7 years, reflecting the length of time taken to complete the more complex types of study.

SCF guidelines on food packaging

The first SCF guidelines for food packaging materials, published in 1977, were flexible in that they set out a range of toxicity tests, similar to those needed for approval of direct food additives, and they indicated that under certain circumstances not all the listed tests might be required (Commission of the European Communities 1977). In practice it rapidly became apparent that, apart from substances already having ADIs, full toxicological data were available for very few chemicals used in food packaging materials. For example, in the first report of the SCF on monomers covering the early recommendations of the Committee (Commission of the European Communities 1987), many of the substances which were classified in List 2 were given TDIs without the benefit of reproduction, teratogenicity and mutagenicity studies. In a few cases, TDIs were allocated solely on the basis of 4-week or 90-day oral studies. It is understandable that this

approach was taken by the SCF at that time, given the large number of substances involved in the review of plastics and that those early evaluations were carried out 10-15 years ago, when toxicity testing strategies were less advanced than nowadays. The now standard Ames test, for example, which detects gene mutations using bacteria, was only described in the early 1970s and recommended by regulatory authorites from about 1980 onwards (Department of Health and Social Security 1981; OECD 1982).

A major disadvantage of the earlier guidelines was that whilst they indicated the acceptance of a flexible approach, they gave little guidance about what circumstances might warrant a different approach to that of embarking on the full range of toxicity tests. They did indicate that the nature of the chemical, its metabolism, short-term toxicity and man's likely exposure might play a part in deciding the need for long-term studies, and the minimum requirements were described as acute and 90-day oral studies in two species. However, there was no guidance on what degree of exposure might be regarded as significant and no guidance on when reproduction and teratogenicity studies might be required. Not only was this situation disadvantageous for industry in planning what work needed to be undertaken, but it became evident to the SCF that it created problems in maintaining consistency of decisions on data requirements, if they had to be made on a case-by-case basis, over a period of several years. So by the end of the 1980s, the SCF thought it was timely to take a fresh look at the guidelines, both to update them in the light of current practice in toxicology and migration testing, and to see if some clearer guidance could be given on what toxicity tests were appropriate, given the wide variability of migration into food of different substances. This was done and the new guidelines were published in 1990, with minor revisions in 1991 (Commission of the European Communities 1990b, 1991).

Core tests: migration 5 - 60 mg/kg

The new guidelines set out a core set of tests which should generally be sufficient to identify any main targets of toxicity (Table 4). These tests are required for any substances migrating in excess of 5 mg/kg, up to the maximum of 60 mg/kg of food or food simulant, which is the overall limit for all substances migrating out of any food packaging. If it is assumed as a "worst case" that 1 kg of food wrapped in a particular type of packaging may be consumed by an individual in any one day, the maximum possible intake of a single substance by a consumer is 1 mg/kg bodyweight/day. The core set of tests has been drawn up bearing in mind this potential maximum exposure, the need to have adequate knowledge of potential toxicity, if any, and, for those substances that are toxic, the need to establish the size of safety margins. Only then can a decision be reached on whether a substance remains acceptable for use.

It has been questioned whether there is a need for any food packaging substances to be tested to this degree. However, consideration of potential intakes of some substances illustrates the necessity for toxicological testing. Detailed examination here of intakes of substances migrating from food packaging materials is not possible because migration data submitted to the SCF are confidential. However, in general terms, a considerable number of substances reviewed by the SCF migrate into food in amounts in excess of 5 mg/kg of food. This is particularly true of fat-soluble additives. Some idea of the extent of migration into food of certain plasticisers, however, can be given since these have been studied in some detail and the results published.

Data from UK surveys carried out in 1986 and 1988 have shown that migration of plasticisers into wrapped fatty foods such as cheese, meats, cakes, sandwiches and confectionery readily occurs at levels in excess of 5 mg/kg of food (Ministry of Agriculture, Fisheries and Food 1987, 1990b). The plasticisers involved are shown in Table 5. The highest levels of migrants were found in cheese, with levels of DEHA up to 225 mg/kg and ATBC up to 137 mg/kg of food. It was possible to estimate the maximum daily intakes of these plasticisers using data on the average diet in 1986; they ranged from 16 mg/person/day for DEHA to 0.05 mg/person/day for ATBC, the difference in maximum daily intakes reflecting the then differing estimates of the extent of usage of films containing these particular plasticisers. The subsequent UK survey carried out in 1988 showed a reduction in DEHA levels in wrapped fatty foods, attributable to a change in the formulation of cling-type films in which some of the DEHA was replaced by other plasticisers. The maximum daily intake of DEHA calculated from the average diet was then 8.2 mg/person, giving an estimated extreme intake of 0.14 mg/kg bodyweight/day for a 60kg person. Estimated maximum daily intakes of other plasticisers studied in the two surveys are given in Table 5.

By comparison, extreme intakes of a number of direct food additives, such as sweeteners (Ministry of Agriculture, Fisheries and Food 1990a), emulsifiers and stabilisers, can be in the range 1-10 mg/kg bodyweight/day. However, the estimated extreme intakes for some other direct food additives are low, from around 0.1 mg/kg bodyweight/day down to one or two orders of magnitude less than this (Ministry of Agriculture, Fisheries and Food, unpublished data). Thus, the estimated extreme intakes of some substances used in food contact plastics are in the same range as that for some direct food additives. For the latter, not only is a full range of studies required but, for most of the types of studies, tests on a minimum of at least two species will be required. The SCF food packaging guidelines do not lay down the number of animal species to be used for testing, and, depending on the circumstances, one species may suffice. In the light of all these considerations, the SCF concluded that it was necessary to ask for the full core set of tests for substances in the

highest migration range.

Reduced testing: migration 0.05 - 5 mg/kg

In circumstances where migration is below 5 mg/kg of food or food simulant, not all the core tests may be required. As a general guide, if migration is between 0.05 and 5 mg/kg, then only three types of data are required: bioaccumulation (for which the octanol/water partition coefficient can be measured), 3 mutagenicity tests and a 90-day oral study.

The rationale for this reduced set of tests is that, for this migration range, intakes from food should not exceed 0.1 mg/kg bodyweight/day and at this low level of exposure, long-term, reproductive or teratogenic effects are extremely unlikely to occur. It is not possible to review here all the background on dose-effect relationships for these endpoints in toxicity, however, some brief illustrations of the evidence can be given.

For long-term effects, studies from the UK Centre for Medicines Research (Lumley and Walker 1985, 1986), along with others, have shown that there are very few effects other than carcinogenicity which are not detected in a thorough short-term, repeat-dosing study. Thus, provided the mutagenicity tests are all clearly negative so that the possibility of the substance being a genotoxic carcinogen is ruled out, a reduced set of testing is acceptable since non-genotoxic carcinogens are generally only active at relatively high, sustained exposures (Weisburger and Williams 1981).

On the reproductive side, one of the most potent known human teratogens is the retinoid drug, isotretinoin, used for treating acne. The lowest doses at which it is active in humans are 0.5 - 1.5 mg/kg bodyweight/day (Rosa et al. 1986). Similarly the pesticide, dibromochloropropane, which has a very potent anti-fertility effect in men, has a lowest effect dose of 0.5 mg/kg bodyweight/day (Council on Environmental Quality 1981). There are examples of substances where repeated, lower, daily exposures are known to have reproductive effects in humans, but these are ones which bioaccumulate (e.g. polychlorinated biphenyls) and so are active because of longer-term build up in the body from repeated intake of residues in food.

As in many other areas of judgement about safety of chemicals, it is impossible to completely exclude the possibility that one day a very potent toxic chemical is not detected, using a reduced range of tests. However, the SCF considered the possibility so remote that it would be reasonable to evaluate substances with lower migration on a reduced range of toxicity data. The Committee also noted that theoretical extreme intakes calculated from migration data are worst case situations and so for the vast majority of consumers there is an additional safety factor due to a considerably lower actual

intake.

However, it is important to note that the SCF retains the flexibility to request further tests on substances falling within the lower range of migration. If, for example, preliminary toxicity data are available suggesting the substance may be teratogenic then a proper evaluation of this possibility would be required. Similarly, if comparison with structurally related substances suggests that it might be toxic then further tests would again be required. Examples of this include the alkyl esters of adipic, azelaic, citric, phosphoric, phthalic, or sebacic acid, which mainly function as plasticisers. Some of these are known to exhibit adverse effects on the embryo and fetus and on male reproduction. Thus they have been classified in List 6B with requests for reproduction and teratogenicity studies. They are also known or suspect peroxisome proliferators in the liver. This phenomenon is associated with liver tumours in rodents, though it is not yet known if the peroxisome proliferation, which occurs at low doses, is causally associated with the tumours, which are only seen at very high doses. These compounds are also non-genotoxic. Thus the SCF may not require long-term carcinogenicity studies on these substances, but does require targeted studies to establish no-effect levels for peroxisome proliferation in the liver, since this is usually the most sensitive toxicological change seen with such substances.

It has been questioned as to why, in principle, the SCF no longer allocates TDIs for substances in the migration range 0.05 - 5 mg/kg, when it has done so previously on the basis of a reduced data package (see earlier). The SCF is not the only body to raise the criteria for allocating ADIs and TDIs; other national and international bodies have done so to take account of more recent thinking in hazard assessment. There is now a clearer view that ADIs and TDIs should only be allocated when the data are adequate to cover a number of endpoints in toxicity and that it is not best practice to merely increase safety factors to try and cover for gaps in the data. Mutagenicity and 90-day or long-term studies, for example, may give no relevant information regarding possible effects on adult fertility or on the embryo and fetus. Yet, there are many examples of substances known to have adverse effects on reproduction and very little or no effect on other organ systems. ADIs or TDIs derived from a reduced range of toxicity tests also run the risk that those without access to the background data may assume that intakes within the ADI value are safe, say from the reproductive point of view, when in fact there may be no information at all on those endpoints.

A further consideration is that the majority of ADIs and many TDIs are based on long-term studies, or less frequently multigeneration studies. This is because prolonged dosing tends to give the lowest no-effect levels. The values so derived are usually lower than those which would have been obtained had just the corresponding 90-day oral studies been used. Moreover, many TDIs based on 90-day oral studies would

give values higher than 0.1 mg/kg bw. This could be confusing in the particular case under consideration of migration in the range 0.05 - 5 mg/kg of food, where intakes should not exceed 0.1 mg/kg bodyweight/day. Other considerations aside, the SCF did not think it would be sensible to impose an artificial ceiling of 0.1 mg/kg bodyweight on TDIs for substances in this group, since it would be contrary to the general principle adhered to around the world of deriving ADIs and TDIs solely from the toxicity data.

Reduced testing: migration <0.05 mg/kg

There are substances of very low migration, less than 0.05 mg/kg of food, for which the maximum possible intake is only 1 µg/kg bodyweight/day and, in practice, likely to be much less than this for the average consumer. For these the only tests required are three mutagenicity tests to establish that they are free of genotoxic potential. The SCF is aware that the need for three rather than two mutagenicity tests has been queried, since two tests can address each of the two major endpoints, that is, single gene mutations and chromosome aberrations. This is not an unreasonable question to ask since for the marketing of industrial chemicals within the European Community, two mutagenicity tests have been acceptable under the base-set requirements for low tonnages (Commission of the European Communities 1992). However, substances migrating from packaging materials are in rather a different category from most industrial chemicals, in that exposures may be low but there is widespread exposure of the general public via the oral route. For such chemicals it is now widely agreed by mutagenicity experts that a third test to look for gene mutations in mammalian cells in vitro is necessary because the combination of an Ames test and an in vitro test for chromosome aberrations will not detect a small proportion of substances with mutagenic potential. This third test can pick up these residual positives (Department of Health 1989).

Hydrolysis studies

Lastly, mention should be made of hydrolysis studies, which the SCF has requested for many List 7 substances. Hydrolysis studies are requested for substances with little or no toxicity data whose chemical structure suggests they might readily hydrolyse in foods or in the body into substances known to be non-toxic. If the substances do hydrolyse, then this will obviate the need for further testing, thus avoiding the unnecessary use of animals, as well as unnecessary expenditure. The level of hydrolysis demonstrated, however, needs to be fairly substantial, of the order of 95% or more, to give reassurance that the parent compound does not need to be tested further. Recommended methods for hydrolysis testing are given in the Note for Guidance of Applicants

(Commission of the European Communities 1991).

Conclusions

This paper sets out to explain the thinking behind the SCF's introduction of a tiered approach to toxicity testing for substances used in food packaging materials. Such an approach is thought to be toxicologically sound, both from the perspective of providing sufficient data on food packaging substances to ensure protection of public health, and from the point of view of avoiding unnecessary testing. The new guidelines are also hopefully a step forward in that they indicate much more clearly than in previous guidelines the range of testing that is required.

Acknowledgements

This paper is based on discussions which have taken place during the last five years in the SCF and its Working Group on Packaging Materials. The author is grateful to her colleagues in the Working Group, Drs Bohme, Carstensen, Elias, Feigenbaum, Rossi, van der Heijden and van Apeldoorn, and to colleagues in the Department of Health for their helpful comments during the preparation of the manuscript.

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Table 1. SCF classification scheme for substances used in food packaging materials: data sufficient for evaluation.

List	ADI	TDI	Explanation
0	-	-	Food ingredients or normal body metabolites
1	+ / +		Or t-ADI, MTDI, PMTDI, PTWI set by SCF or JECFA
2	-	+	Or t-TDI set by SCF
3	-	-	Use self-limiting or very low migration
4	-	-	Migration not detectable
5	-	-	Bioaccumulate or too toxic for use

Table 2. SCF classification scheme for substances used in food packaging materials: data insufficient for evaluation.

List	Explanation
6	Insufficient/no data Suspect toxicity:
A	carcinogenicity
B	other toxicity
7	Some useful toxicity data but insufficient to set ADI. SCF specifies required data
8	Insufficient/no data. Data needed according to guidelines
9	Inadequate chemical specification

Table 3. Numbers of substances classified into each list by the SCF up to 1991.

List	Monomers	Additives	
0	50	36	}
1	29	121	}
2	86	220	} Sufficient data
3	50	66	} for SCF opinion
4	36	8	}
5	5	12	}
6A	114	15	}
6B	10	52	} Insufficient data
7	158	122	} for SCF opinion
8	430	158	}
9	243	183	}
Totals	1211	993	

Table 4. SCF guidelines on food packaging materials: core tests.

90 day oral study
3 mutagenicity tests
i) Gene mutations in bacteria (Ames test)
ii) Chromosomal aberrations in cultured mammalian cells
iii) Gene mutations in cultured mammalian cells
Absorption, distribution, metabolism, excretion
Reproduction
Teratogenicity
Long-term toxicity/carcinogenicity

Table 5. Estimated maximum daily intakes of plasticisers from UK surveys.

Substance	Extreme intake (mg/kg bw/day)	
	1986	1988
Di-2-ethylhexyl adipate	0.26	0.14
Dibutyl phthalate	0.03	-
Dicyclohexyl phthalate	0.02	-
Epoxidised soya bean oil	-	0.02
Acetyl tributyl citrate	0.001	0.025
Di-isodecyl phthalate	0.0003	-
Di-2-ethylhexyl phthalate	0.0003	-
Di-isooctyl phthalate	0.0003	-
Polymerics	-	0.007

Source: Ministry of Agriculture, Fisheries and Food 1987, 1990b.

Appendix 2 to Annex 4

Publication of Mr Feigenbaum

DATA REQUESTED FOR ASSESSMENT OF SUBSTANCES TO BE USED IN PACKAGING MATERIALS
(lecture given at Gothemburg, March 93)

DATA REQUESTED FOR ASSESSMENT OF SUBSTANCES TO BE USED IN PACKAGING MATERIALS

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What are the data to be supplied to the European Commission (EC) for the evaluation of substances intended to be used in the manufacture of food contact plastic materials ? These data are examined by the working group "packaging materials" of the Scientific Committee for Food (SCF), which has to evaluate the substances (Commission, 1993). The basic principle of this evaluation is to *guarantee the safety of the consumers.*

What the SCF needs to know from an application for a substance **X** intended to be used for the manufacture of food contact plastic materials can be summarized into the following series of questions :
a- technical and analytical data : if this substance **X** is used, to which chemicals may the consumer be exposed, and what are the highest possible amounts he may ingest ?
b- toxicological data : what are the possible consequences of the ingestion of **X** on the health of the consumer ?

The substances for which the applicants have not submitted complete dossiers
- are not authorized (case of new substances)
- or are temporarily authorized (case of old substances) by the Commission.

They are classified into lists 5 - 9 by the SCF (Barlow, 1993) which corresponds to the annex B of the Commission. The technical and analytical data needed are far less expensive than those for toxicity. Nevertheless, there are hundreds of substances whose evaluation cannot be finalized, because their technical and analytical data are incomplete. They have been put together in SCF list 9 ; in 1992, this concerned 243 monomers (directive 90/128 EC amended by 92/39/EC) and 183 additives for plastic materials. For industry, this situation is difficult to understand while the toxicological section already contains many useful data. Therefore, we will now mainly focus on list 9 substances through the examples selected.

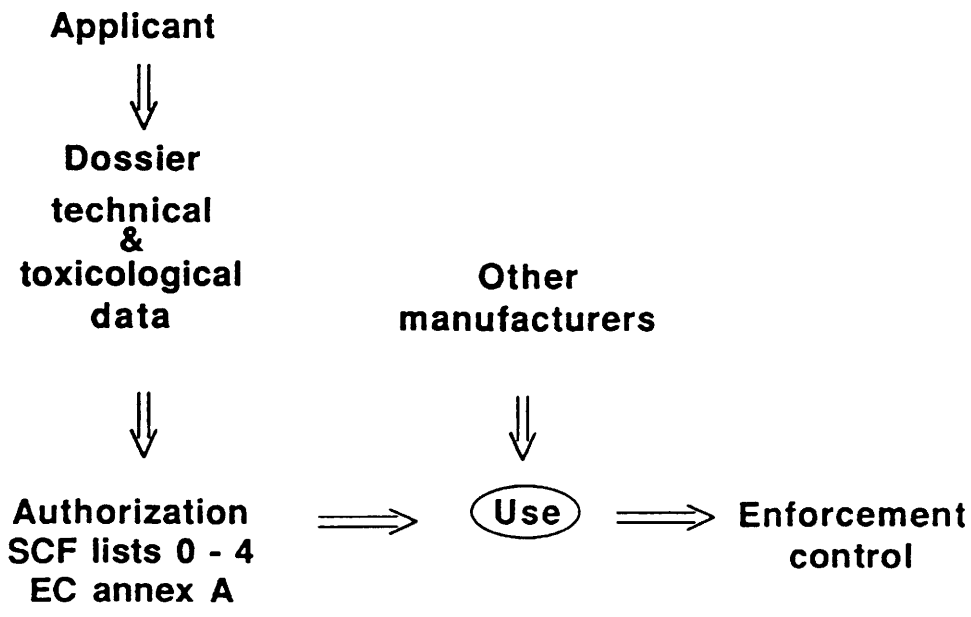


Figure1

1. IDENTITY OF THE COMPOUND X

The usual procedure involves :

- submission of the dossiers of substance **X** to the Commission by the applicant,
- examination of the technological and toxicological dossiers by the SCF,
- if the substance **X** is safe, the Commission authorizes its use, and publishes its name in annex A of a plastics directive.

The substance **X** may then be manufactured by any other company, with a different process, with a different level of purity. THE WAY TO AUTHORIZE THE SUBSTANCES SHOULD BE PRECISE ENOUGH SO THAT SMALL VARIATIONS IN THE LEVEL OF PURITY OR IN THE COMPOSITION CANNOT AFFECT PUBLIC HEALTH. The data required by the SCF must are needed in order to foresee the consequences of these variations.

On the other hand, any restriction of use of the substance **X** should also be made in such a way that control should be facilitated, whenever possible. This control may occur at different levels :

- at the **manufacturer**, who checks the migration of its substance ;
- at the **food industry**, user of the packaging material, and
- at the **enforcement** laboratories.

These different levels have sometimes contradictory requirements concerning control methods. When there is no method available, then analytical research is needed, in order to help protecting the consumers. In order to simplify this approach, the applicants are now requested to submit the analytical method they use for the determination of **X**.

1.1. GENERAL CRITERIA

In the technical dossier, there must be scientific data demonstrating the structure of the substance **X** : all relevant spectroscopic data should be furnished :
- for the purified compound, and
- for the commercial grade which has been submitted to toxicological screening.

1.2 NAME AND STRUCTURE

The name should describe the substance as precisely as possible. The SCF and the EC may apply a name which is different from that used by the applicant. This is raised by the need of using a homogeneous and unequivoqual nomenclature. The SCF uses rules which are intermediate between those of CAS and those of IUPAC.

E.g. : octadecyl is stearyl for some applicants, n-octadecyl or C_{18} alkyl for others. The Commission has kept only n-octadecyl.

With some descriptions used by applicants, the number of possible substances corresponding to the name is so great, that there is no relationship between the name, the chemical structure and, hence, the toxicological behaviour of **X**.

E.g. : nonylphenol bears two undeterminations : how is nonyl : n, or branched ? and where is nonyl on the ring ? Figure 2 shows some possible isomers.

It is in the interest of both the applicant and the consumer that the substance is accurately described.

Obviously, generic names cannot be accepted :
E.g. : isooctyl may apply to "alkyl (C_7 - C_9), linear and branched, with C_8 predominant", but also to 6-methylheptyl.
E.g. : alkyl vinyl ether : these compounds hydrolyse in the stomach into the corresponding alkanols.
In both examples, these "alkyl" may include 2-ethylhexyl.

All these substances will remain in list 9 until the applicant clarifies the structure of the particular isomer he uses ; if this information is not received before the deadline set by the Commisssion, the substance will be deleted from the positive list.

1.3 MIXTURES

1.3.1 DIFFERENCIATION BETWEEN IMPURITIES AND MINOR CONSTITUENTS OF MIXTURES

In the area of food safety, a substance present in a minute amount may represent a major risk to the consumer's health. With food packaging, this is even more dramatic, since, due to the great variability in migration tendancy, a substance present in the material in a small amount may be a major migrant in food.

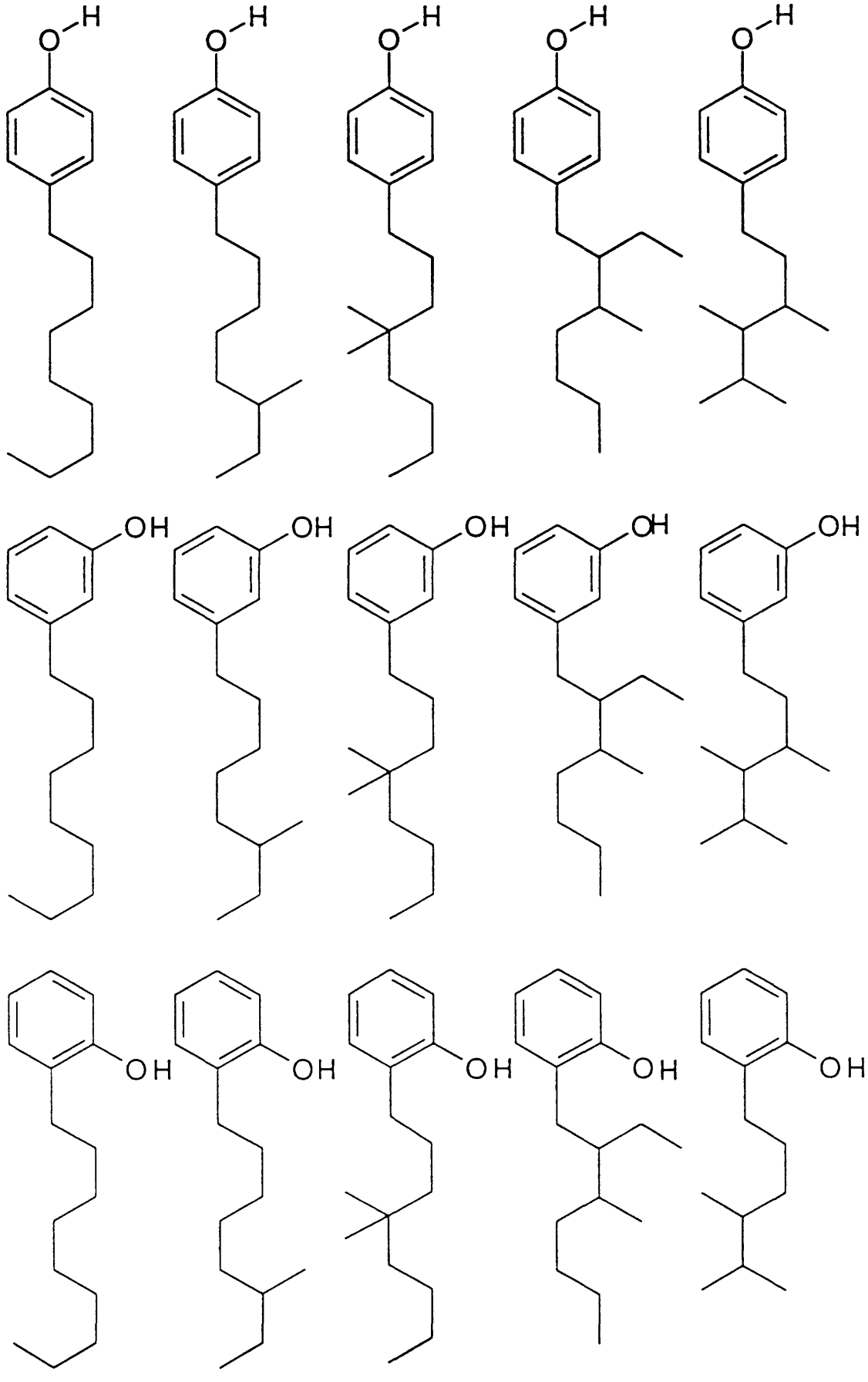


Figure 2 : some isomers of "nonylphenol"

There are two situations where the chemical structure and the composition of the substance are not totally described by its chemical name :

- when the substance contains impurities ;
- when the substance is a mixture.

With mixtures derived from natural sources (fats, petrol), the composition may fluctuate and a substance which is a minor constituent one day can be present in higher amounts in another batch, or in the product made by another manufacturer. It seems therefore adequate to define an impurity as a compound which has in principle no intended and foreseen function in the material or in the polymer (table 1).

Type	Function	Description
Impurity	has no intented technological function	Its presence is not necessarily indicated by the name
Constituents of a mixture	They have the same intended and foreseen function in the polymer or material	Their presence should be covered by the name of the substance whenever possible.

Table 1 : impurities and constituents of mixtures

1.3.1.1 SYNTHETIC MIXTURES

Mixtures made from several compounds available separately will not be taken into consideration by the SCF. This does not mean that their use is forbidden, but only that their impact on the health of the consumers will be examined separately. The dossier of a mixture will only be examined if it includes the demonstration that its components cannot easily be separated, and that this separation is of no practical use.

1.3.1.2 SIMPLE MIXTURES

Simple mixtures contain a small number of well identified substances. This is the case for instance of a reaction product :

starting substances ----- *reaction* -----> $X_1 + X_2 + X_3 + X_4$

The relative percentages of the constituents X_1, X_2, X_3, X_4 are x_1, x_2, x_3, x_4 respectively. The SCF has several possibilities :

a- evaluate the mixture as it is, and **INTRODUCE X AS A MIXTURE IN THE POSITIVE LIST** ; but this presents several disadvantages :

* the relative percentages must be specified on the positive list, which raises the difficult problem of the tolerance on the relative percentages ;
* another manufacturer, which would obtain a mixture with the same constituents X_1, X_2, X_3, X_4, but in different percentages would have to make a new application ;
* the enforcement and the control of the use of a mixture is not simple.

b- evaluate the mixture as it is, and introduce **EACH CONSTITUENT SEPARATELY IN THE POSITIVE LIST.** This can be done assuming in a worst case evaluation that all the toxicity of the mixture is due to each of its constituents. Then a temporary TDI can be allocated to the main constituents of the mixture :

t-TDI(X_1) = TDI(mixture) . x_1	SML(X_1)= 6 t-TDI(X_1) = 6 x_1 TDI(mixture)
t-TDI(X2) = TDI(mixture) . x_2	SML(X_2)= 6 t-TDI(X_2)
t-TDI(X_3) = TDI(mixture) . x_3	SML(X_3)= 6 t-TDI(X_3)

Table 2 : TDI and SML of constituents of simple mixtures
TDI in mg kg^{-1} b. w. ; SML in mg dm^{-2} material ;
1 kg food wrapped with 6 dm^2 material eaten by a consumer of 60 kg b. w.

If X_4 has a TDI allocated separately, then this value which will be used for the determination of the specific migration limit.
The advantages of this approach are numerous :

* easy control of X_1, X_2 ... which can be analyzed and detected individually ;
* this takes into account the fact that the distribution of X_1, X_2, X_3, X_4 in the migrate may be different from that in the material ;
* there is no longer the problem of tolerance ; any other manufacturer may produce and use any mixture of X_1, X_2, X_3 and X_4, as long as the migrations do not exceed the SMLs thus calculated. If the migration of one of these compounds exceeds the corresponding SML calculated in table 2, then a new application should be made, including a toxicity study demonstrating that this migration does not represent a danger for the consumers.

The data required in order that these substances are transferred from list 9 into other lists of the SCF include a detailed description of the identity of the constituents of the mixture, with their relative amounts. If the toxicity data are sufficient, the individual t-ADIs will be allocated to the constituents.

1.3.1.3 COMPLEX MIXTURES WHOSE CONSTITUENTS HAVE BEEN EVALUATED SEPARATELY

This is typically the situation of *fatty acids derived from an edible oil.* There are many applications received by the Commission with a name such as :
XX oil, fatty acids (e.g. : olive oil, fish oil, sunflower oil ...)
or
XX oil, fatty acids, dimers ;
This raises the problem of mixtures of natural origin, whose composition may vary depending on the source. A first approach consists in authorizing only food grade quality mixtures of fatty acids, or in allocating lower TDI's to those mixtures which are not food grade. But the reference to a Codex such as the Codex Alimentarius does not provide sufficient information and specifications for these acids.

An alternative approach is the following : the Commission recognizes that all edible fats are made from a small number of fatty acids, whose toxicological behaviour is well known. Consequently, all these fatty acids will be authorized, and only these. Miscellaneous fatty acids can only be tolerated
- after submission of specific toxicity data

- as impurities if they are present only in trace amounts (see section 2.1.1).

It should be noted here again that the approach of the SCF simplifies the control of packaging, since it is easier to detect a fatty acid than the origin of an oil (e.g. olive oil or fish oil) in a migrate.

The substances concerned have been transferred from list 9 into the lists 0 - 3 of the SCF, without any new data needed. This modification will appear in the SCF synoptic 6 document. Since the migration is restricted to 60 ppm, the small difference between the acceptable intake of ricinoleic acid and other fatty acids can be omitted in the legislation for food packaging.

In a second step, after consultation of the industrial and the national experts, this approach could be extended to accept all edible oils using the following description : *"glycerol, mono, di and triesters of the authorized fatty acids"*. This avoids to provide complete specifications of edible oils and fats

1.3.1.2 COMPLEX MIXTURES WHOSE CONSTITUENTS HAVE NOT BEEN EVALUATED SEPARATELY

This is a complex problem to be treated in a very general manner, and a case by case approach will be useful. However, here again, the SCF developed a new approach. A typical example is that of derivatives of oxo alcohols. These are primary alcohols obtained by reductive carbonylation of petroleum hydrocarbon cuts. Such a mixture may contain dozens of chemical isomers and also some homologs. Plasticizers, which are usually di-, tri- or tetraesters of these alcohols may contain hundreds of substances. It is not realistic here to evaluate each constituent of the mixture individually. There are several possibilities available for evaluating such mixtures :

a- test the mixture as it is, and give the **AUTHORIZATION ONLY FOR THE COMPOSITION OF THE MIXTURE WHICH HAS BEEN TESTED**. It must be kept in mind however that a detailed description of these complex mixtures is almost impossible. Therefore, setting an SML to the mixture will cause great analytical difficulties.

b- test **REPRESENTATIVE COMPOUNDS** of the mixture, **AND SET GROUP LIMITS OF MIGRATION**. If the alkyl esters are suspected to be toxic, it is mainly because the bis(2-ethylhexyl) derivatives (adipate or phthalate), which have been studied in detail, exhibit toxic properties, such as peroxisome proliferation. Therefore, the toxicity of mixtures of related compounds can be linked to that of the representative compound, namely bis(2-ethylhexyl) ester, even if it is a minor constituent of some of these mixtures. This approach requires :

* that experimental data exist, showing that the toxicity of alkyl esters can be linked to their structure ; the evaluation would be facilitated if the 2-ethylhexyl compounds proved to be the most toxic ones, which seems to be the case (Macherey, 1993) ; then :

t-TDI(oxo ester) ≥ TDI(2-ethylhexyl ester)

Safety factors can be applied by assuming that :

t-TDI(oxo ester) = TDI (2-ethylhexyl ester)

and that, because of the similarities of the constituents of these mixtures, their toxicities are likely to be cumulative :

t-TDI(mixture) = TDI(2-ethylhexyl ester)

This approach has to be validated by the independent determination of the TDI of one of these mixtures.

* that analytical approaches are developed, allowing to detect the migration of the whole mixture whatever its detailed composition. For plasticizers, such approaches involve hydrolysis of the ester, followed by a chromatographic determination of the corresponding acid (adipic or phthalic), or determination of the ester moiety in the food simulant by infrared (Monroy, 1993).

This approach, which is the most scientific for complex mixtures, should also facilitate the control in food industries, by replacing specific migration measurements of numerous individual substances by the determination of whole groups of substances at once, without the need of the knowledge of the detailed composition of the mixture (Van Lierop, 1988 ; Ehret-Henry, 1992).

Such substances are currently in list 9 not because there is lack of data, but because the SCF is elaborating criteria which will facilitate their evaluation.

2. SITUATIONS WHERE THE CONSUMER IS EXPOSED TO SUBSTANCES WHICH ARE NOT DESCRIBED BY THE NAME OF THE SUBSTANCE X USED

Chemicals whose presence cannot be deduced from the name of the substance may endanger the health of the consumers. They may be present in the substance **X** itself, as impurities ; they may also be formed during the polymer process or during the food process. Their formation may also occur in the gastrointestinal tractus. The kinds of situations where this is likely to occur are summarized in table 3.

2.1. IMPURITIES

The substances used for the manufacture of plastics intended to come in contact with food should be of high purity. As a general rule, the Commission understands that impurities may be present, but if these impurities are not themselves on the positive list, they remain under the responsibility of the manufacturer (EC practical guide). However, there are some situations where the presence of impurities is foreseeen by the SCF.

2.1.1 In mixtures of fatty acids : Odd fatty acids

The fatty acids authorized are in the positive list. However, some edible oils of animal origin, contain fatty acids with odd carbon numbers. These acids are mainly C_{15} and C_{17} and may have linear or branched structure. Since they may be present up to 5 % in fish oils, these acids are tolerated in food. On the other hand, since their toxicological behaviour is less described than that of usual fatty acids of edible oils, they are not cited in the positive list, and are only tolerated with the status of impurities for the manufacture of plastic materials.

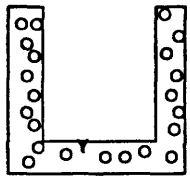
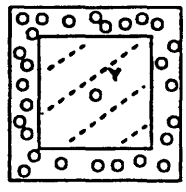
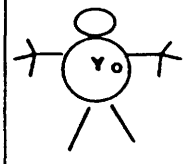
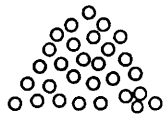
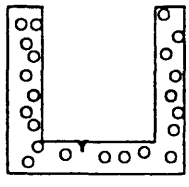
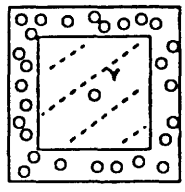
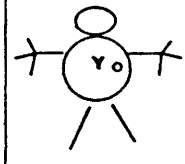
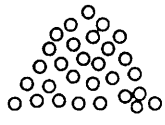
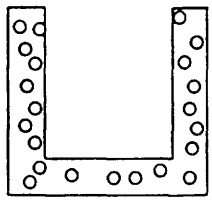
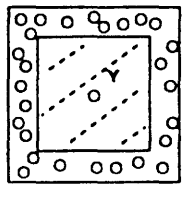
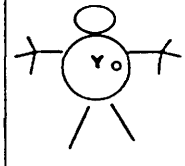
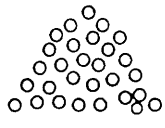
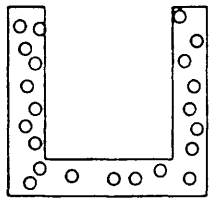
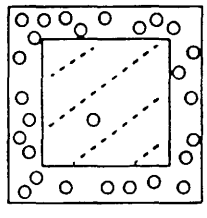
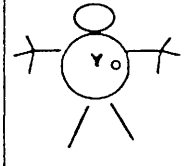
STARTING SUBSTANCES	POLYMER PROCESS	FOOD PROCESS, MIGRATION	INGESTION	COMMENT : ORIGIN OF Y
 Impurity Y				IMPURITY : - OF STARTING SUBSTANCES - SIDE PRODUCT OF SYNTHESIS
	 Impurity Y			CONTAMINANT FORMED DURING POLYMER PROCESS
		 Impurity Y		CONTAMINANT FORMED BY REACTION WITH FOOD DURING FOOD PROCESS
			 Xenobiotic Y	XENOBIOTIC FORMED IN THE GASTRO INTESTINAL TRACTUS

Table 3 : situations where the consumer can be exposed to chemicals not described by the name of the authorized substance X

2.1.2 IN POLYMERIC ADDITIVES : TRACES OF STARTING SUBSTANCES

Many polymers with low molecular weight are used as additives : as plasticizers, as stabilizers. If their molecular weight is greater than 1000, these polymers are considered not to represent a danger for the public health since :

- they do not migrate to an appreciable extent into foodstuffs ;

- they are not absorbed by the gastrointestinal tractus.

Knowledge of the molecular weight distribution is therefore essential for the evaluation of these substances :

- if the lower end of their molecular weight distribution is greater than M_w = 1000, their use can be accepted, provided that they do not release toxic monomers ;
- if the molecular weight distribution curve shows the polymer to contain a considerable amount of constituents with M_w < 1000, their toxicity must be described, as with other additives.

The data to be supplied include a M_w distribution curve (with M_N and polydispersity). But since the absolute molecular weight determination in gel permeation chromatography may depend on the structure of the polymer, a careful calibration including two set of standards : a) a polystyrene standard and b) a standard whose structure is close to that of the polymeric additive. The latter should be a reference of the polymeric additive itself, whose M_w has been determined by another technique. The value M_w = 1000 should be in the linear part of the calibration curve (SCF Guidelines, 1993).

On the other hand, the residual starting substances, that is the monomers used for the synthesis of the polymeric additives, are known to migrate and may be toxic. For both types of polymeric additives, the SCF may require migration and toxicity data on their monomers. However two types of situations may occur :

- these monomers or starting substances have already been evaluated by the SCF. Then, even if they are toxic, their migration is de facto limited by the directive 90/128/EC :
- when the monomers have not already been evaluated, the SCF may require toxicity data on these substances.

E.g. : polyethyleneimine : this polymer may contain residual traces of ethyleneimine, the highly toxic monomer, which may migrate into the foodstuffs in contact. However ethyleneimine has already been evaluated and its specific migration is limited by the 90/128/EC directive. Therefore, the only problem associated to the evaluation of low molecular weight polyethyleneimine is the toxicity of this polymer itself.

E.g. : hydrogenated cyclopentadiene resins ; the starting substance is dicyclopentadiene, which is thermally cracked into an unstable monomer : cyclopentadiene ; after the polymerization and the purification, the low molecular weight resin is hydrogenated, so that these polymers have no real corresponding monomers.

The SCF knows by experience that many monomers are toxic, and that traces of these compounds cannot be accepted in the human food, and he may require toxicity data on these monomers. Here, the dialog between the industry and the SCF is essential, because it is a complicated field, where each decision can have consequences both on the public health and on the economy of plastics industry. If the applicant believes (as he generally does) that there is no need to provide toxicity data on his starting substances,

he has to convince the SCF. In this dialog, he will have to point out specific situations which should be taken into consideration, for instance the fact that monomers or starting substances can be efficiently removed during the normal process
- by physical processes, such as azeotropic distillation
- by chemical reactions, such as hydrogenation
- by a combination of physical and chemical processes.
Obviously, analytical data should in first instance be supplied showing whether the monomers or starting substances (or their reaction products) are not detectable in the polymeric additive.

The status of such resins is currently under discussion. Whatever the opinion of the applicant, the final decision about the toxicity tests to be carried out depends on the SCF.

2.2 REACTIVE SUBSTANCES

2.2.1 - REACTION DURING THE MATERIAL PROCESS : POLYMERISATION, EXTRUSION, MOLDING ...

In the technical dossier, there are questions about the reactivity of the substances used for the manufacture of plastics additives. This section is often not well filled in the dossiers for application and this leads to a waste of time.

It is well known that stabilizers like antioxidants and light stabilizers react in the polymers, in the framework of their normal function : phosphites are transformed into phosphates, phenolic derivatives into quinones, hindered amines into aminoxyls. Often, these reaction products are also likely to be metabolites of the additives, so that they do not require themselves an extensive dossier. It is therefore essential to report carefully all the available information on the reactivity of the substance in the chemical dossier.

Some compounds give numerous reaction products, through several reaction pathways, and this could complicate their evaluation.
E.g. : This is the case with fluorine, for which a petition has been presented to the Commission. An evaluation of fluorine based on its potential toxicity on animals would lead to forbid its use for the manufacture of food contact plastics. However, fluorine is such a highly reactive chemical, that it is not likely to be present after the process. In this case, the toxicological evaluation should not be based on the dossier for fluorine itself, but rather on a study of the products which may be formed during its reaction with polyolefins and with polymer constituents.

2.2.2 REACTION IN FOOD AND IN FOOD SIMULANTS

There is now some scientific knowledge on reactions which take place in foodstuffs (Piringer, 1980 ; Rijk, 1990 ; Sen, 1988 ; Marqué, 1992). These reactions include mainly oxidation of common additives, nitrosation of secondary amines, and hydrolysis of epoxydes. Recently, Gilbert and Castle showed that even in food simulants, under

normal migration conditions, many substances may be degradated, so that migration figures do not reflect the true contamination (table 4) (Castle, 1993). The section of the GUIDELINES about the stability in food simulants must be filled with great accuracy, and the stability of the migrants in the simulants under the conditions of migration testing must be checked with great accuracy. Often, the answer to this question was "excellent stability in simulants", but after all the work already carried out on the stability in food and food simulants, the experiments will have to be described in detail, and the stability must be checked (with amounts of migrants in the same order of magnitude than the reported migration).

Simulant ⇒ Monomer ⇓	Acetic acid 40 °C	Water	Olive oil 10 days, 40 °C	Olive oil 0.5 h, 150 °C
Formaldehy de	55		80	100
Styrene	40	31	10	25

TABLE 4 : percentage of degradation of monomers in simulants
(with the kind authorization of Dr. L. Castle)

2.2.3 REACTIONS IN THE GASTROINTESTINAL TRACTUS

There is a situation where the knowledge of the reactivity may simplify the application to the Commission. When the substance is quantitatively transformed into substances which have already been evaluated, there is no need to proceed again to toxicity studies. This situation is likely to occur for esters, amides and ethers. Therefore, when the experience of the SCF leads to the impression that this could occur, the substances are provisionaly put in list 7, with the indication : "needed : hydrolysis data". Conditions for the simulation of gastrointestinal hydrolysis have been published by the Commission (Commission, 1993). It must however be pointed out that in order to mind a toxicity study, the hydrolysis must be quantitative.

CONCLUSION

The data required are specified step by step. If the applicant wishes to have soon its compound quickly evaluated, he should furnish very soon all the relevant data. The objective of this talk was to indicate the approach followed by the SCF. Once this understood, the dossier can be easily built up. What I wanted to show you is that the true guideline for the SCF is the common sense. But in the SCF guidelines, this common sense is split into such a high number of questions, that an overview and an explanation of the general philosophy may sometimes be useful. I hope that this objective is now reached which should facilitate the construction of applications.

ACKNOWLEDGEMENT

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THE END!