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In-built Triggered Enzymes to Recycle Multi-layers: an Innovation for Uses in plastic-packaging

D7.7: Report on impacts on regulatory aspects and food contact safety

WP7: Environmental and economic sustainability assessment of the developed products and food safety assessment

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Abbreviations

FMECA	Failure Mode and Effect Critical Analysis
OML	Overall Migration Limit
SML	Specific Migration Limit
FCM	Food Contact Material
GLYMO	(3-Glycidyloxypropyl)trimethoxysilane
EFSA	European Food Safety Authority
FDA	Food and Drug Administration
PFAS	Perfluoroalkyls'
PE	Polyethylene
Regulation (EC)	European Parliament and of the Council
DVS	Dynamic Vapor Sorption
PUR	Polyurethane

Executive summary

The present report aims to address the food contact safety aspects linked to the TERMINUS multilayers, as these are intended to integrate the current market as innovative food packaging alternatives. Accordingly, the document presents, on one hand, the regulation framework of food contact materials (FCM), particularly, plastic packaging for food contact applications. On the other hand, in the context of the COMMISSION REGULATION (EU) No 10/2011, a theoretical and practical exposition of the migration phenomena has been realized.

As described in the executive proposal, the main innovative feature of the TERMINUS multilayers is the presence of enzymes in the adhesive layer either polyurethane-based or tie-layer. However, as will be stated below in the document, a regulatory framework addressing the enzymes' usage in packaging is practically inexistent. Therefore, the employment of experimental and simulation tools conceived to estimate the risks linked to food contact applications in innovative materials is of prime importance. To this end, firstly, migration tests were carried out in TERMINUS multilayer prototypes coming from both adhesive lamination and blown co-extrusion. Secondly, the use of a simulation tool, FMECAengine, has allowed estimating the food contact risks by taking inputs based on the different aspects of the TERMINUS innovation: multilayer design, nature of the substances used, manufacturing, and applications.

In general, the evaluations to determine the compliance of packaging in terms of food contact follow a pretty established route:

- To collect documentary data in relation to packaging formulations
- To know the identity of molecules, level of purity, and toxicological status
- To get information about: the use, chemical nature of the packaging, thermal cycles during processing and post-treatment, the period length of food contact, etc.
- To set an action plan oriented to estimate the mass transfer under usage conditions:
    - By means of laboratory analyses concerning material's characteristics and compliances regarding overall migration limits (OML) and specific migration limits (SML),
    - By means of models or simulation to estimate food contact risks.

The global data collection following this downstream, with the exception of simulation techniques, constitutes the base documentation of compliance in relation to food contact products. It must fulfil the requirements in this matter required by the final customers. This procedure involves the transmission of information where each actor of the product life cycle has the responsibility of what is produced and what is transmitted in the corresponding cycle's phase. In this sense, and in many cases, all required informations are complicated to collect. Each stage of the system's life cycle should be as transparent as possible in order to increase the efficiency of risk control. This is why a vigilance strategy must be developed.

On the other hand, simulation techniques for risk assessment on food contact allow envisaging different scenarios from processing to applications, which is not feasible from a practical point of view. In this report, the experimental work on migration tests was complemented with the simulation technique FMECAengine on multi-layered prototypes BOPET/adhesive/LDPE to assess the potential food contact risks. The report is not exhaustive since innovative materials, as in the case of tie-layer systems, cannot be managed by the simulation technique because of the lack of data. Therefore, the prototypes based on tie-layers made by blown extrusion were only considered in the experimental part.

Concerning the specific results of the study, all the migration tests carried out were successful since the migration limits were in compliance with the Regulation (EU) N° 10/2011. To this end, two series of prototypes were analysed: (1) laboratory and pilot scale adhesive solvent-free and solvent-based multilayers and (2) Multilayers elaborated by blown extrusion based on the use of an innovative tie-layer.

On the other hand, the results of modelling were also acceptable and promising under the conditions applied, following the corresponding regulations. Accordingly, one of the most striking results of this study is that all calculated concentrations after modelling are at equilibrium, i.e., at their highest level as Figure 1 shown for the 'worst' modelling put in place. This means that the concentration of equilibrium, already in compliance, would not risk of increasing over time to hazardous values.

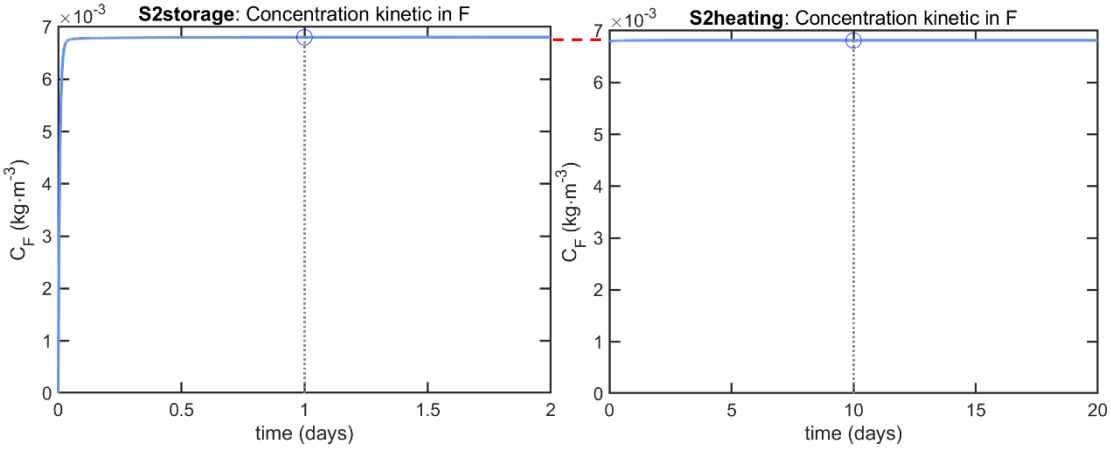


Figure 1 Evolution of the concentration of a substance targeted from the system studied to the food expected as a function of time (see Figure 24 (b)).

Nevertheless, it is also necessary to keep control of the compounds that can degrade during all the stages of the life cycle of the system studied. In this case, a concentration can indeed change over time and this is why different types of compounds have been studied for their behaviour which can influence the model applied.

It is also important to point out that if the information is not yet present in the first version of the tool, solutions exist to implement the parameters necessary for the model applied with an overview of currently available parameters according to the pair: polymer-substances. And to go further in this reflection, it is also possible to investigate and access to the parameters involved in the model with specific experiments. For example, it is possible to access the diffusion coefficient of a substance within a polymer matrix by several techniques depending on its nature:

- For 'small' molecules (in terms of weight mass) using DVS experiments,
- For 'big' molecules with Roe-Stacking experiments.

This strategy of vigilance is therefore a task that must be carried out on an ongoing basis as the project progresses. All the results presented in this report are the first basis for work to access vigilance on certain points according to the systems studied. They are of course not exhaustive and require special attention.

Deliverable report

Introduction

The problem of the interaction between packaging materials and the products to be protected, particularly foodstuff, falls notably in the scope of health risks management. That is why the key question to highlight when it comes to the elaboration of packaging for food contact applications turns out to be: 'does my packaging represent a health risk for the consumer?'. The vastity of the current plastic packaging universe in terms of materials, structures, functionalities and, nowadays, eco-design demands, makes food contact applications a subject of enormous complexity.

In order to call out the right action mechanisms face to this complexity, the actual regulation framework attempts to harmonise the concourse of all the elements involved in this matter. In this regard, key definitions, substances, design guidelines, good practices, set out of responsibilities, risks of noncompliance, etc. are some of the critical information to be kept by any actor in the food packaging sector.

Recently, some well-known scenarios on food contact concerns help to illustrate the capital relevance of the topic. For example, the reduction of limits of Bisphenol A, or even banning, it in food packaging has been subjecting of discussion in the last decade. While fully prohibited in France since 2015, the EU has reduced 2018 the migration limits to 0.05 mg/kg for most of the food plastic packaging, with the exception of those products linked to toddlers nourishing where this substance is actually banned. Bisphenol A is a substance found in polycarbonate films and epoxy coatings are considered as having potential health effects on the mammary gland, and reproductive, metabolic, neurobehavioral, and immune systems. On the other hand, an important chemical agent commonly used in the adhesive industry, particularly in the lamination of popular pouches, was set out of the market. It was the case of the silane known as GLYMO, used to promote the adhesion between the layers of the pouches, the latter of high proliferation in grocery stores. In 2017, EFSA, the European Food Safety Authority, concluded that GLYMO must be considered to have a genotoxic potential. Also, in the United States, the Food and Drugs Administration (FDA) raised concerns in the past few years regarding the presence of polyfluorocarbons (PFAS) in food from polyethylene containers. This was mainly attributed to the fluorination treatment of PE, which helps keep food and cosmetics, and other products from spoiling by providing a barrier to keep out oxygen and moisture. PFAS are considered toxic by the FDA. These substances are also widely used in packaging made of paper and cardboard to avoid the inside product to adhere.

Nowadays, in the global context of circularity and the specific one on regulations favouring the progressive increase of recycled content for food applications, more strict surveillance on food contact risks should be a must. Particularly, the actual effects of the Food Contact Regulation (EU) No 2022/1616 open up possibilities to include a series of new processes and materials from new recycling approaches to potentially be compliant with plastic packaging for food contact applications.

Description

Food Safety Regulations

Since adhesives and materials used in food and non-food packaging are usually the same, partners shall keep in mind the food safety issues, even if they have to put aside this major constraint during the early stages of their research activities. While the starting components are limited to European compliance lists, the subject is very complex.

European regulation

The framework Regulation

Regulation (EC) No 1935/2004 provides a harmonized legal EU framework. It sets out the general principles of safety and inertness for all Food Contact Materials (FCMs).
The principles set out in Regulation (EC) No 1935/2004 require that materials do not:

- Release their constituents into food at levels harmful to human health,
- Change food composition, taste and odor in an unacceptable way

Moreover, the framework provides:

- Special rules for active and intelligent materials (they are by their design not inert),
- Powers to enact additional EU measures for specific materials (e.g. for plastics),
- Procedures to perform safety assessments of substances used to manufacture FCMs involving the European Food Safety Authority,
- Rules on labelling including an indication for use (e.g. as a coffee machine, a wine bottle, or a soup spoon) or by reproducing the appropriate symbol. For more information, please refer to the following document on Symbols for labelling food contact materials,
- Documentation and traceability documents.

Finally this regulation is based on three basic requirements:

1. Principle of inertia

⇒ The studied system do not present a danger to human health, do not alter the composition of food except in the case of active packaging (if food additive) and finally do not modify the organoleptic characteristics except in the case of active packaging (if food additive).

2. Good Manufacturing Practices

⇒ The system must be manufactured following good practices (EC regulation 2023/2006), also not mislead the consumer (labeling, advertising, presentation)

3. Traceability

In order to facilitate control, withdrawal, consumer information and determination of responsibilities, identify operators, products, substances, label and document.

Therefore, the manufacturer is responsible for implementing an efficient traceability system. All partners must be involved and made aware of the importance of scrupulously providing the following information:

- identification of the products, ranging from the purchasing of raw materials to client deliveries;
- management of data acquisition, storage, use and archiving;
- management of connections between batches and the company's quality management system;
- communication between the players.

These include at least:

- the lists of suppliers and clients;
- the purchasing specifications and the relevant purchase orders;
- the verifications upon receipt, with identification of the materials delivered by the manufacturer (identification number, written declaration of compliance associated with the packaging material, verification results, date of receipt, etc.);
- the creation of a substance sample bank when possible;
- the results of the additional investigations carried out in-house or by an associated laboratory, if necessary;
- the written declaration of compliance for the finished packaging associated with the foodstuff distributed.

Guides are also available to help in the implementation of a traceability system:

- either classified by type of food contact material: 'Industrial guidelines on traceability of materials and articles for food contact';
- or classified by industrial sector - example: 'Practical guide of traceability for the table olives sector', part 2: 'Traceability for suppliers of food contact materials'.

EU support agencies on food contact policies

European Food Safety Authority. It is an agency of the European Union set up in 2002 to serve as an impartial source of scientific advice to risk managers and to communicate on risks associated with the food chain. They cooperate with interested parties to promote the coherence of EU scientific advice. They provide the scientific basis for laws and regulations to protect European consumers from food-related risks – from farm to fork.

European Union Reference Laboratory for Food Contact Materials (EURL-FCM). It organises inter-laboratory comparison exercises and conducts training courses for the benefit of *National Reference Laboratories* (NRLs) and of experts from developing countries. It is supported by a Network of National Reference Laboratories.

The EURL-NRL network can also develop technical guidelines. The guidelines provide a unified understanding of the practical implementation. The impact has been the ability for NRLs to be able to give a harmonised competent advice in this field to their National Authority, Food Inspection and private compliance laboratories. The work is normally organised in the form of dedicated workshops and smaller task forces of volunteer experts within the NRLs. This has allowed generating several much needed guidelines within two years.

Regulation on Good Manufacturing Practices

Applicable since August 1, 2008, Regulation (EC) No 2023/2006 ensures that the manufacturing process is well controlled so that the specifications for FCMs remain in conformity with the legislation:

- Premises fit for purpose and staff awareness of critical production stages,
- Documented quality assurance and quality control systems maintained at the premises,
- Selection of suitable starting materials for the manufacturing process with a view to the safety and inertness of the final articles.

Good manufacturing practices (GMP) apply to all stages in the manufacturing chain of food contact materials, although the production of starting materials is covered by other legislation.

EU legislation on specific materials

In addition to the general legislation, certain FCMs — ceramic materials, regenerated cellulose film, plastics (including recycled plastic), as well as active and intelligent materials — are covered by specific EU measures. There are also specific rules on some starting substances used to produce FCMs and how to focus on regulatory context for these and the responsibilities involved. Figure 2 describes the strategy applied following the possible steps involved.

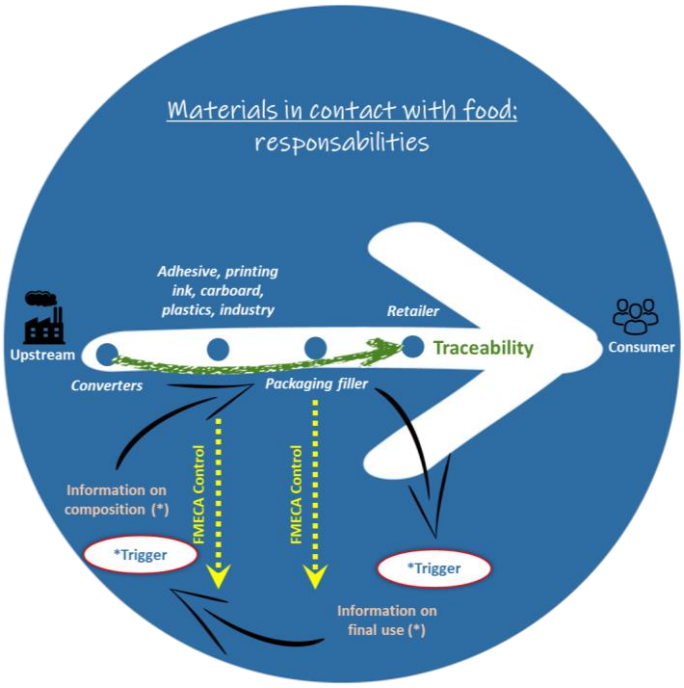


Figure 2 Summary of the responsibilities involved for materials in contact with food.

Finally, it is important to keep in mind that all actors in the value chain are concerned to be able to answer to these two questions:

1. What do I have to legally guarantee to my customers
2. What is the evidence to keep?

Plastic materials

The most comprehensive specific EU measure is Regulation (EU) N° 10/2011 on plastic materials and articles. It sets out rules on the composition of plastic FCMs and establishes a Union List of substances that are permitted for use in the manufacture of plastic FCMs. The Regulation also specifies restrictions on the use of these substances and sets out rules to determine the compliance of plastic materials and articles. This Regulation is regularly amended, therefore, a consolidated version has been also published. Indeed, a list of specific amendments has been added to this consolidated version.

An important mechanism to ensure the safety of plastic materials is the use of migration limits. These limits specify the maximum amount of substances allowed to migrate to food. For the substances on the Union list the Regulation sets out ***'Specific Migration Limits'*** (SML). These are established by EFSA on the basis of toxicity data of each specific substance.

To ensure the overall quality of the plastic, the overall migration to a food of all substances together may not exceed the '***Overall Migration Limit'*** (OML) of 60 mg/kg food, or 10 mg/dm^2 of the contact material.

The Regulation sets out detailed migration testing rules. Although migration testing in the food prevails, migration is usually tested using ***'simulants'***. These simulants are representative for a food category, e.g. acetic acid 3 % (w/v) is assigned for acidic foods. The migration testing is done under standardized time/temperature conditions, representative for a certain food use, and covers the maximum shelf life of packed food.

To ensure the safety, quality and compliance of plastic materials, adequate data on the composition of (intermediate) materials has to be communicated via the manufacturing chain, up to but not including the retail stage. For this purpose, a ***'Declaration of Compliance'*** (DoC) needs to be provided. The DoC is based on supporting documentation which documents the reasoning on the safety of a plastic food contact material, and which must be provided to enforcement authorities on their request. The supporting documentation also provides an important link to the manufacturer's responsibility under GMP (Regulation (EC) No 2023/2006).

Active and intelligent materials

Active and intelligent materials are in particular used to extend the food shelf-life by maintaining or improving the condition of packaged food, by releasing or absorbing substances to or from the food or its surrounding environment.
As a result, they are exempted from the general inertness rule in Regulation (EC) No 1935/2004. The specific rules in Regulation (EC) No 450/2009 apply to address their specific purpose, e.g.:

- Absorption of substances from food packaging interior such as liquid and oxygen,
- Release of substances into the food such as preservatives,
- Indicate expiry of food through labelling that changes color when maximum shelf life or storage temperature is exceeded

Active materials do not include systems that absorb substances entering from the atmosphere, such as active oxygen barriers. Regulation (EC) No 450/2009 foresees the establishment of a Union list of substances permitted for the manufacture of active and intelligent materials:

- EU Guidance on active and intelligent materials and articles intended to come into contact with food - in support to the implementation of Commission Regulation (EC) No 450/2009 of 29 May 2009,
- Register of substances with a valid application for authorization (Regulation (EC) No 450/2009 - active and intelligent materials and articles)

Terminus is not concerned by active and intelligent materials regarding the current definition, since there is no interaction between enzymes and food. Anyway, we think this particular point should be monitored in case of a definition modification within next years. A challenging issue is to know if protected enzymes will be considered as additives and which procedure should we follow (or develop) to obtain all the necessary food safety agreements.

Use of enzymes in packaging materials

Generality

One way to contribute of improve food safety while reducing food waste consists to use intelligent and active packaging. Active packaging protect food from contamination or degradation by creating a barrier against external conditions or by controlling the atmosphere inside the package. To be active, the package uses a technology that intentionally releases or absorbs compounds from food or headspace (or ullage) of the food packaging. This extends the shelf life of products by blocking the degradation reactions of lipid oxidation, microbial growth and moisture loss and gain. In turn, intelligent packaging can contain an external or internal indicator to provide informations on the life of the packaging (passage of time, temperature at which the food has been stored) and/or the quality of the foods, signs of spoilage and freshness).

The materials used in smart packaging do not affect the food ; they only transmit informations about the state of the food or its environment. Smart packaging systems are generally classified into three categories: sensors, indicators and radio frequency identification (RFID) systems.

There is a specific regulation for active and intelligent packaging.

United States

Active and intelligent packaging are regulated under the Food and Drug Administration (FDA) regulatory framework and submitted to the same requirements as all food contact substances. Materials used in food contact applications are submitted to a pre-market regulatory approval in the U.S if they are considered as ‘food additives’.

The Federal Food, Drugs and Cosmetics Act (FFDCA) is the central text of legislation covering food contact materials (FCM) in U.S. It defines a ‘food additive’ as a substance that may reasonably be expected to become a component of a food under the conditions of its intended use (U.S Food and Drug Administration) ***[1]***.

Indirect additives

Food additives that result from accidental exposure from packaging are considered as indirect food additives (i.e. those that are not directly added to the food). Legal exemptions from the definition of 'food additives' are provided for the substances that are Generally Recognized As Safe (GRAS) or are subject to an exception or exclusion listed in the FDCA.

The Code of Federal Regulations (CFR) provides that some food additives may be added to packaging for the purpose of having a physical or technical effect on the food (United State of America Federal Government) ***[2]***.

The regulation specifies that these additives must not exceed, where no limitation is specified, the necessary amounts to obtain the physical or technical effect expected in the article in contact with foodstuffs.

Thus, in general way, if materials of these packaging systems do not migrate to the foods or have a technical effect on foods, there are no particular regulatory problems. However, the manufacturers must take into account any additional migrants, decomposition by-products or impurities that may occur because of chemical activity in active packaging material during its storage and it shelf life.

Direct additives

For additives that are intended to have a technical effect on the foods itself, these substances can be evaluated as direct food additives. Examples : enzymes added to the inside of citrus juice packaging to break down bitter compounds in the juice; a disinfectant solution used on the inside of packaging for sterilization ends is generally evaluated by the FDA as indirect additives.

Antimicrobial treatments that are part of or are used in packaging complicate the issue. While jurisdiction over the safety of antimicrobial pesticide residues used in or on food packaging materials rests with the FDA, these products, under federal law on Insecticide, Fungicide and Rodenticide Act, may also need to be registered with the U.S. Environmental Protection Agency (EPA). In addition, where antimicrobial activity on packaging is expected to continue, the EPA has jurisdiction over food safety issues in addition to regulating the safe use and effectiveness of the antimicrobial itself.

Europe

The EC regulation n°1935/2004 (European Parliament, Council of the European Union, 2004) ***[3]*** defines the requirements for materials intended to come into contact with foods. This regulation includes an article on special requirements for active and intelligent materials and articles. In addition, a number of materials that may be subject to specific measures are mentioned. Plastics are among the materials that may be submitted to specific measures.

EU Regulation 10/2011 (European Commission, 2011) ***[4]*** defines the requirements for plastics in food packaging. Among other things, this regulation provides the establishment of a Community list of substances eligible for inclusion in food contact materials. This list can be found in the consolidated version of the regulation available on the EUR-lex website.

The European Commission's general direction of Health and Consumers published on 21 February 2004 of Union Guidelines on Regulation (EU) n°10/2011 on plastic materials and articles intended to come into contact with foods (European Commission General Direction for Health and Consumers, 2014) ***[5]***.

Active and intelligent packaging intended to come into contact with foods are submitted at regulation (EC) n°450/2009 (European Commission, 2009) *[6]*.

This regulation establishes a prior approbation system for the commercialization according to which packaging can be marketed if the substances responsible of the active and/or intelligent function are included in the Community list of eligible substances, with a few exceptions. Moreover, the packaging, as well as the substances in it, must be accompanied by a written conformity declaration.

The Regulation defines 'active materials and articles' as 'materials and articles intended to extend the shelf-life or to maintain or improve the condition of packaged food. They are designed to deliberately include constituents that release or absorb substances into packaged foods or into food environment'. It defines 'intelligent materials or articles' as 'materials or articles that control the condition of packaged foods or food environment'.

According to the EC Regulation n°450/2009 (European Commission, 2009) *[6]*, intelligent and active packaging may only be placed on the market if it is suitable for its intended use; complies with the general safety requirements applicable to all food contact packaging and with specific requirements applicable to intelligent and active materials and articles; and if they are conformed with the regulatory requirements for composition, labelling and declaration.

Exceptions to requirements that only substances included in the Community list of authorized substances are:

- The release active substances, which must comply the relevant Community and national disposition applicable to food, including the EC framework Regulation n°1935/2004 (European Parliament, Council of European Union, 2004) *[3]*;
- Other substances falling within the scope of Community or national dispositions applicable to foodstuffs, which are added or incorporated in active materials in order to have a technological effect on packaged foodstuffs.
- Substances used in components that are not in direct contact with foods or the environment surrounding foods and that are separated from the foods by a functional barrier, if they are not mutagenic, carcinogenic, toxic to reproduction or deliberately modified to particle size with chemical or physical properties that differ significantly from those of their larger scale counterparts.

The amount of an active substance released shall not be included in the overall migration value measured when an overall migration limit (OML) is established for a food contact materials into which the components is incorporated. The substances used in the components that are not in direct contact with foods or its immediate environment are limited at a migration level of 0,01 mg/kg for each group of structurally related substances and their toxicological characteristics.

The European Food Safety Authority (EFSA) published an Administrative Guide for the preparation of evaluating demands for the substances safety intended to be used in food contact plastics in 2017 (European Food Authority, 2017) *[7]*.

The safety of substances used in active and intelligent food packaging must be evaluated by the European Food Safety Authority (EFSA) before their use in the EU can be authorized. The Scientific Panel on Food Contact Materials, Enzymes and Processing Aids (CEP group) initially published a guidelines on the submission of evaluating dossier for the safety assessment of substances in active and intelligent materials and articles intended to come in contact with foods in July 2009. A revision

of these guidelines was approved by the CEP on 9 September 2020 and the revised version was implemented on 27 march 2021 (European Food Safety Authority, 2009) ***[8]***.

The guidelines explain that evaluation of safety will focus on the risks associated with food exposure to chemical products because of:

- The migration of the active and/or intelligent substances,
- The migration of their degradation and/or reaction products,
- Their toxicological properties.

They also point that active and intelligent substances behind a functional barrier do not require a safety assessment and fall outside of Regulation (EC) n/° 450/2009 (European Commission, 2009) ***[6]***. While, the Regulation (EC) n°450/2009 is officially entered on 18 June 2009, the relative disposition of the composition only enter after the publication of Community list of eligible substances. Until then, the relevant national provisions will continue to apply.

Any consulted documents during this synthesis contain specific disposition concerning enzymes. It should be noted that, in order to consider the presence of enzymes in the plastic formulation, reference should be made to positive list of EU Regulation 10/2011 (European Commission, 2011) ***[4]*** and that this last list do not include, at the time of writing, any enzymes. On the other hand, molecular weight of enzymes is generally, well above the limit which it is considered that there is no migration and assimilation risk by the consumer (1000 Daltons). However, it follows from different regulatory obligation that the enzymes potentially used must not be toxic et must not, because of their presence or their activity, lead to the generation of molecules that cannot be present in packaging materials.

Definition of the phenomena of interactions between container and contents

Phenomena encountered

When a packaging material (the container) comes in contact with a food product (the contents), several types of phenomena can be occurred (Figure 3).

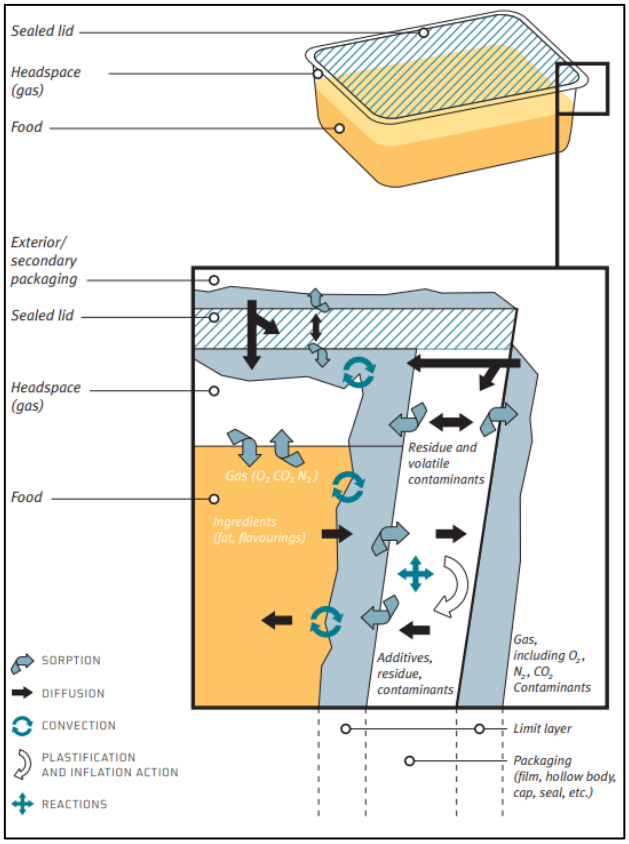


Figure 3 Main transfers between packaging & food.

They can be classified by their nature:

- ***physical***, such as wearing of the material or abrasion by rubbing.
- ***chemical***, which are often dependent on the nature of the material and of the aggressivity of the product in contact: corrosion (for metals), ion exchange (for glass and ceramics), dissolution, chemical reaction;
- ***physical/chemical***, involving the transfer of substances of the material to the food or the reverse. Thus, it is possible to observe phenomena of adsorption of substances on the surface of the material, or even of adsorption, after diffusion, in the material, coming from the food. This is particularly the case with fats and aromatic compounds, thus causing sensory modifications of the food at issue;
- ***microbiologic***, involving the contamination of the food product by microorganisms located mainly on the surface of the packaging material.

Migration

Definition

Migration does not occur in phenomena of a physical or microbiological nature. It necessarily presupposes a transfer of compounds: a chemical modification of the material without any transfer of the compounds formed to the food matrix does not qualify as migration. It most commonly occurs with plastic materials.

Strictly speaking, migration is therefore the transfer of compounds from the material into the food.

It is therefore important to distinguish:

- ***overall migration***: overall quantity of non-volatile compounds without distinction that have migrated to the product. This is a criterion of inertia that is independent of the toxicity of such overall migration;
- ***specific migration***: quantity of a given compound that is being examined and that may have migrated. This is called a migrant.

Migration, in the broad sense of the term, also includes transfers from the food to the material, which can also cause changes in the food or loss of active ingredients. Such phenomena are quite well-known today in cases of heat-treated food in plastic containers (e.g., ready meals).

It should be noted that, where molecules with a high molar mass are involved (between 200 and 2000 g/mol^{-1}), migration necessarily requires prolonged contact between the food and the packaging, so that it is designated as migration by contact (or direct contact). For volatile molecules, contamination can take place through the gaseous space around the food, so that it is designated as migration without contact (or indirect contact). The latter case is mainly observed in dry/solid products, such as biscuits packaged in a permeable flexible film with substantial headspace. The contaminants can come from the secondary packaging (cardboard box) or from the outside by simple permeation of the volatile compounds through the film.

Migrations can be determined by several methods:

- direct analysis into the food: ***reference method***,
- the ability of the substances to migrate to foodstuff and water, calculation, 100 % transfer, worst case (compositional information): ***screening method***,
- migration diffusion models (sur-estimation, accepted and validated by EFSA for plastics into food simulants to calculate migration): ***screening method***,
- migration/extraction data on the final material using food simulants with specified LOD and LOQ data of the analytical method used (experimental data): ***screening method***.

Parameters of influence

The two main factors in container-content interactions phenomena are naturally the nature of the **material** (and therefore of its components), on the one hand, and the nature of the **food product** (and therefore its composition), on the other.

The intensity of the phenomenon depends on how easy it is for the material to release compounds and on the chemical aggressivity or affinity of certain components of the food.

Accordingly, migration will be non-existent or negligible in the case of a dry product coming in contact with glass. Conversely, it may be significant when a fatty liquid food comes in contact with an additive-rich plastic.

The other parameters of influence are as follows:

- the initial concentration of compounds in the material;
- the diffusion capacity of such compounds (diffusion coefficient: D);
- their ability to solubilise to establish a concentration ratio between the material and the food (partition coefficient: K);
- their chemical affinity with the other components of the medium such as polarity;
- the temperature, which accelerates the diffusion phenomena following an exponential law (Arrhenius law);
- the duration of contact;
- the exchange surface.

Phenomena inside plastic materials

Plastic materials are polymer materials formed of macromolecules, often long chain and sometimes ramified, to which various additives are added to ensure certain protections (e.g. antioxidants) or to allow them to perform specific functions (e.g. anti-UV rays).

Such polymers may be in either amorphous form or in semi-crystalline form, with an orientation of their chains (Figure 4). The amorphous phase itself has two states, one being vitreous and the other rubbery, and the change from one to the other occurs at the temperature called 'vitreous transition temperature'

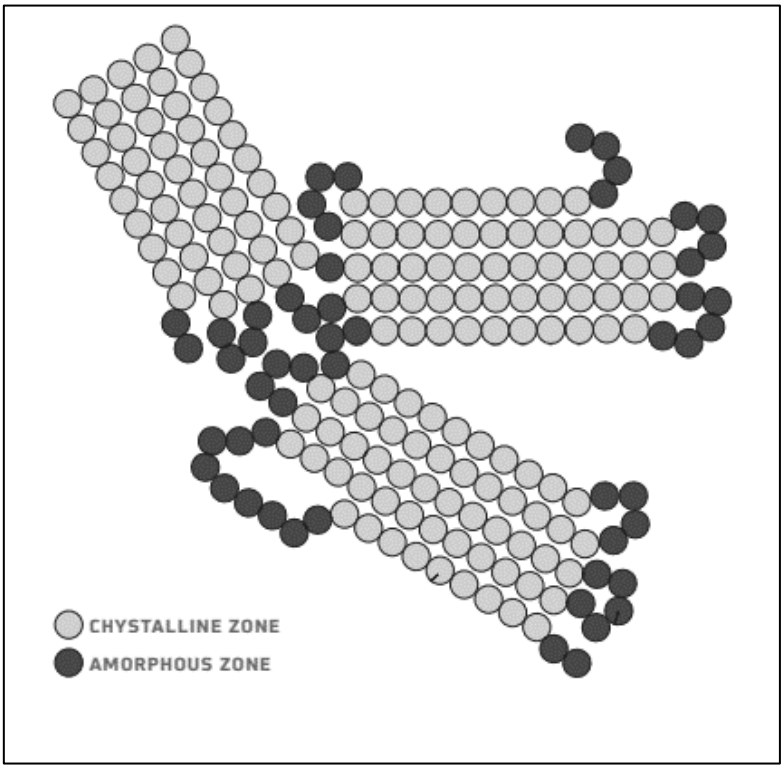


Figure 4 Combination of amorphous and crystalline structures in a polymer.

The risk of migration of certain compounds of the plastic to the food is directly related to its state. These characteristics are summarized in Table 1.

Table 1 Food contact: assessment of compliance.

State of the polymer at ambient temperature	Example of material	Level of risk contamination
Vitreous semi-crystalline	Polyethylene terephtalate (PET)	Very low
Rubbery semi-crystalline	Polyolefins (polyethylene, polypropylene)	Low to medium
Vitreous amorphous	Polystyrene, coating	Low
Rubbery amorphous	Elastomers	Very high

There are two major plastic materials families: thermoplastics and thermosetting plastics. They differ chemically by the nature of their intermolecular bonds.

In the field of packaging, the main products used are thermoplastics and only certain adhesives and coatings can be considered as thermosetting plastics (family of epoxy resins, unsaturated polyesters, phenolic resins).

Given the formulation of polymers and the processing methods used, the substances likely to migrate to the food after contact are the following:

- either compounds added intentionally, additives such as pigments, antioxidants, plasticizers, the concentration of which is assumed to be known;
- or reaction residue (polymerisation, secondary reactions), degradation products, the concentration and even the nature of which are not known at the start: these are neo formed compounds.

Case of a plastic material without interaction with the constituents of the food. The migration of a migrant compound **(M)** to the food depends on:

- the initial concentration of the compound **(C_i)** in the polymer;
- the diffusion of the compound in question in the material expressed by the diffusion coefficient **D**. The diffusion coefficient **D** is a function of the temperature **(T)** according to an exponential law (law of Arrhenius): higher temperatures therefore accelerate migration (Figure 5);
- the ratio of concentrations of the compound between the material and the food in a state of equilibrium, defined by the partition coefficient **K**;
- the exchange surface **(S)** with the food;
- time **(t)**.

$$\mathbf{M = f(C_i, D, T, K, S, t)}$$

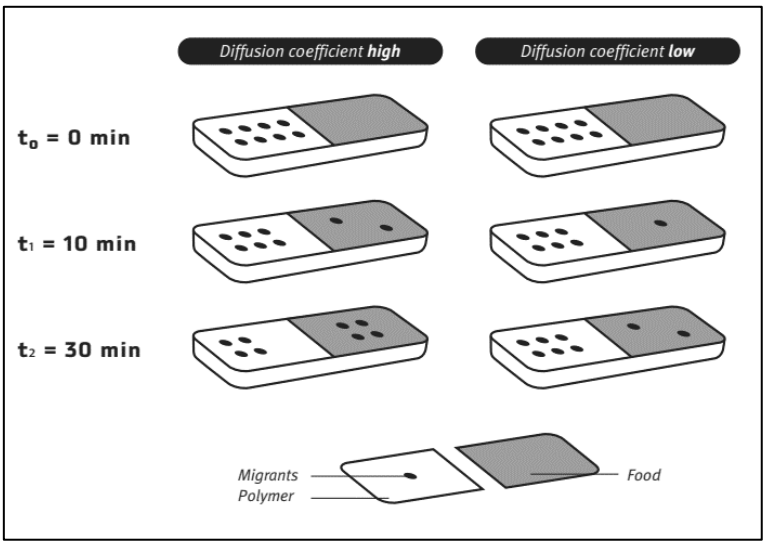


Figure 5 Illustration of the diffusion coefficient.

The partition coefficient ***K*** illustrates the difference in terms of solubility of a substance between the packaging (**P** = packaging) and the food (**F** = food) consequently the value of $K_{F/P}$ can be greater or smaller than or equal to 1 (Figure 6).

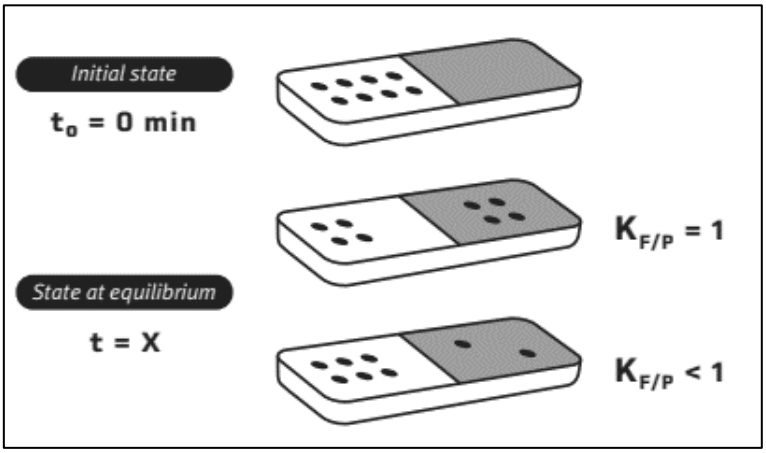


Figure 6 Illustration of the partition coefficient.

In a certain number of cases, there is sorption of the food constituents by the polymer whose diffusion characteristics are therefore modified by swelling, or even plasticisation, which causes a change in the vitreous transition temperature.

The diffusion coefficient then depends locally on the concentration of molecules absorbed in the polymer. To assess the risk, the diffusion coefficient of the swelled polymer should be used.

This case particularly applies to foods having a high content of fats or of certain flavourings. This is, for instance, the case with polyolefins, in case of contact.

The main factors influencing the contamination of the food by constituents of plastic materials are described in Table 2.

Table 2 Factors influencing food contamination.

Stages	Factors	Influence	Examples
Formulation of the material	Concentration in potentially contaminant additives	++	Plasticized PVC
	Small size of the constituents	++	Monomers, plasticizers
Shaping of the material	Rubbery state of the polymer	+++	Elastomers
	Presence of degradation products	+ to +++ depending on the polymer	Carbonyl compounds of the PE in the presence of fats
Contact with the materials	Contact surface	+++	Width of seal, surface of adhesive
	Chemical affinity of the components of the material for the food	+++	Hydrophobic fatty foods
	Chemical affinity of constituents of the food for the polymer	++	Sorption of flavourings
Processing of the packaging/food couple	High processing temperature	+ to +++ (if T > Tg)	Hot filling
	High stabilisation temperature	++	Pasteurisation, sterilisation in the packaging
	Hydrostatic pressure	-	High pressure treatment
Use of the packaging/food couple	Increased contact time	+	Increase of the BBD
	High usage temperature	+ to ++	Cooking heating in the packaging: water bath, classic oven, microwave oven

Calculation and modelling

Introduction

To go further into the production chain of Terminus project finished products, another study of the food suitability of these materials will be presented in the rest of this report.

Indeed, in addition to the migration tests **(1)** previously carried out, others strategies can be envisaged in order to predict and/or study the behaviour of a packaging in contact with foodstuffs through modelling methods **(2)** or calculation **(3)**.

In the framework of the terminus project), the first two complementary methods described in Figure 7. At this point of the project, calculations from the Qm value was not retained because too complicated to consider due to the large unknowns linked to the system studied.

Hypothesis will be required and the remainder of this section will present the strategy adopted in the modelling investigations.

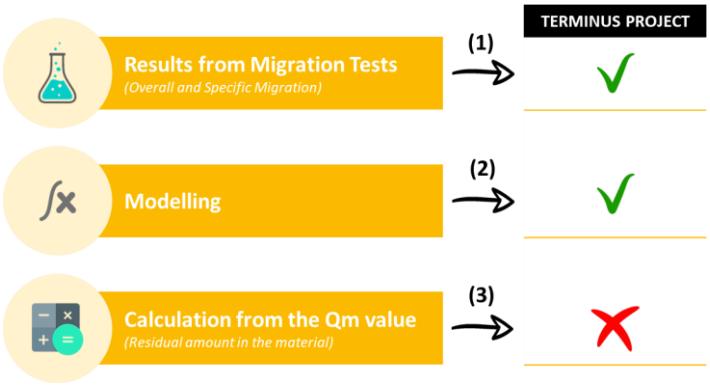


Figure 7 Framework of the project.

Thus, when the instrumental analysis does not provide results with the required level of uncertainty, the complementary of these methods could be a help for a decision-making tool or to underline a warning strategy to investigate different packaging solutions. It is from this perspective, that we will apply modelling to the project.

The use of modelling tools for container-content interactions (CCI), or more precisely for the migration of chemical substances from the material to the product in contact, is part of a threefold context: regulatory, scientific and industrial. This context will form the basis for the rest of the report.

Regulatory framework

Before explaining the modelling strategy put in place for the project, it is important to focus to the part of the EU Regulation 10/2011 that deals with modelling. This fact is mentioned in its Annex V, Conformity testing, Chapter 2, §2.2, Examination methods, and indicates the possibility of using alternative methods to the classical specific migration tests.

This part of the regulation is included below:

> 2.2.3. *Migration modelling*
>
> To screen for specific migration the migration potential can be calculated based on the residual content of the substance in the material or article applying generally recognised diffusion models based on scientific evidence that are constructed such as to overestimate real migration.

The calculation methods, as well as the models developed, must be based on verified scientific data.

	Input datas	Actions	Output data/Reactions
	Calculations	Qualitative and quantitative data collected from suppliers.	The maximum quantities of substances likely to migrate are determined by calculation. To examine specific migration, potential migration can be calculated from the residual content of the substance in the material, or in the article in the event of complete migration.
	Models	Data collection: composition, contact conditions, exposure.	To examine specific migration, potential migration can be calculated from the residual content of the substance in the material or article, by applying generally recognised diffusion models, based on scientific data, and established in such a way as to overestimate the actual migration.

Principles

Five principles define the migration modelling:

1. ***Conservatism*** is that modelling and related calculations should overestimate the real migration or contamination.
2. ***Reliability*** implies that the foreseen mass transfer pathways and substances obey well-described mechanisms, accepted conditions (e.g., uniform distribution), and proper implementation in software.
3. ***Consistency*** is that inputs in the model are known or guessed in a way that fulfils the requirements of the first principle.
4. ***Parsimony*** states that sophisticated and refined scenarios should be considered only when simpler ones cannot demonstrate compliance or safety.
5. Proportionality is that non-compliance cannot be demonstrated by calculation.

The principle of the use of modelling applied to the determination of the final specific migration in food is based on the flow chart shown in Figure 8.

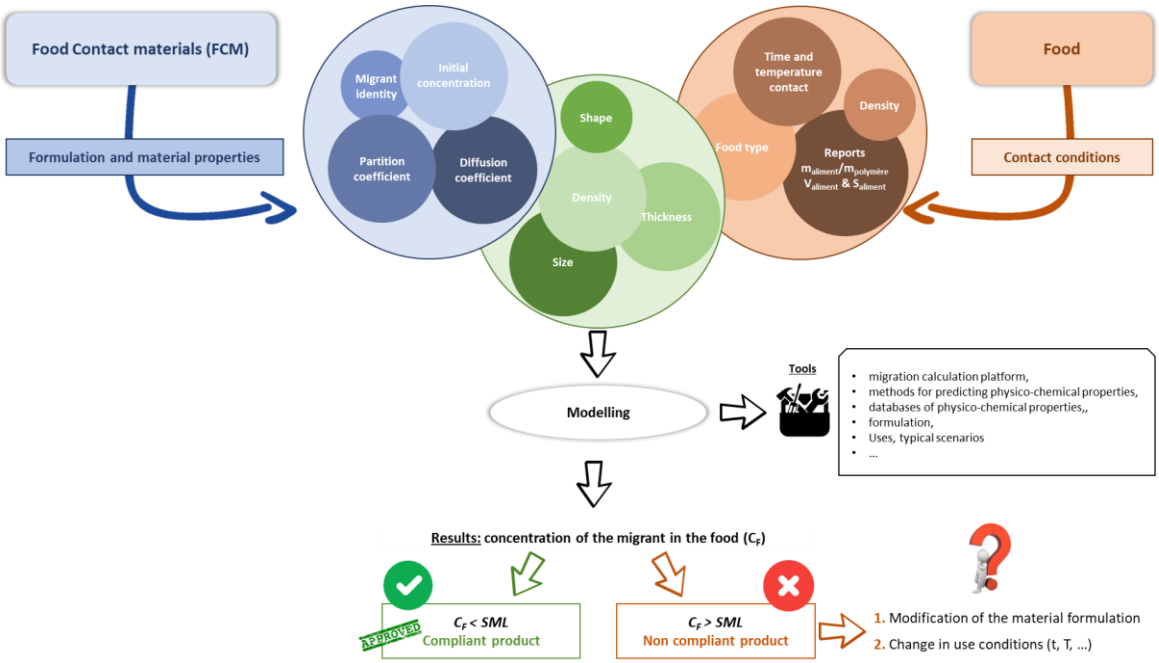


Figure 8 Flowchart managing the modelling, with C_F: Final concentration of the substance in food and SML: Specific migration limit of the substance.

Scientific background

The modelling of the migration of substances from a material to another compartment, in this case from the material to the food, is therefore applicable based on the fundamental laws of transfer and partition.

The first parameter to consider is the partition coefficient. This thermodynamic parameter is governed by Henry's law. Applying it to a layer J, this equation is defined as:

$$\boldsymbol{p_j(x) = k_j C_j(x)}$$

With: p_j, partial pressure of the substance,

C_j, concentration of the substance,

k_j, Henry's constant.

At equilibrium, p_j equals itself in each of the layers, which implies:

$$\boldsymbol{p_{j_1}^{eq} = p_{j_2}^{eq} \Leftrightarrow K_{j_1/j_2} = \frac{Cj_1}{Cj_2} = \frac{kj_2}{kj_1}}$$

With: K_{j_1/j_2} partition coefficient of the substance between the two layers

The second parameter of interest is the molecular diffusion coefficient. This kinetic parameter is defined from Fick's law applied to the J layer.

$$J_j = -D.\rho_j.\frac{\partial C}{\partial x}$$

With: J_j in kg.m^{-2}.s^{-1}

D in m^{-2}.s^{-1}

ρ_j in kg.m^{-3}

$$\frac{\partial C}{\partial t} \approx \lim_{x_1 \to x_2} \frac{J_1 - J_2}{x_1 - x_2} = \frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right) = D\frac{\partial^2 C}{\partial x^2}$$

J material flow

D diffusion coefficient (velocity)

$\frac{\partial C}{\partial x}$ is the concentration gradient.

It is based on these parameters that a transfer model can be envisaged as shown in Figure 9.

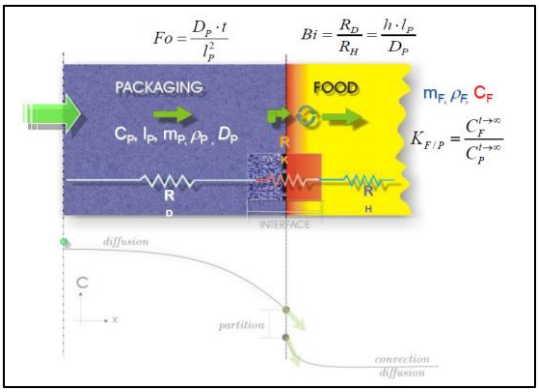


Figure 9 2D modelling of a monolayer material.

All the factors that can affect migration are taken into account in the modelling. They are represented by the expression Mt, migration at the end of time t (Figure 10).

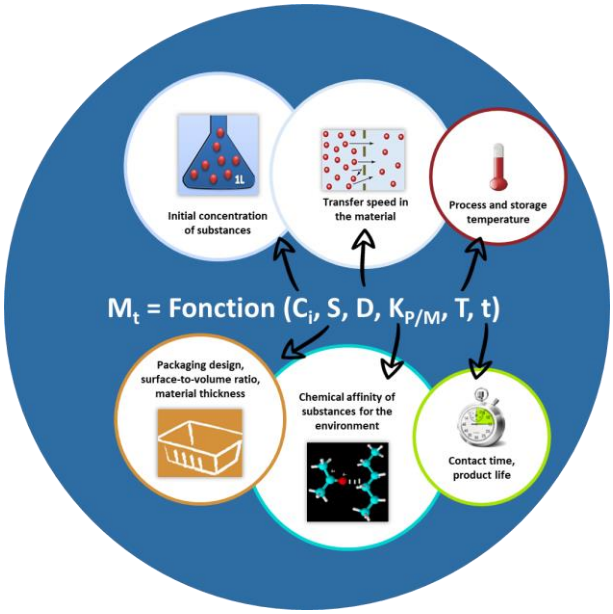


Figure 10 Factors influencing migration (Mt) as a function of time.

Industrial context

Manufacturers are responsible for meeting regulatory requirements to ensure the safety of the end consumer. They must therefore provide proof of this by specifying the necessary information through documentation enabling a certificate of conformity to be drawn up.

The latter must include the regulatory, technical, and methodological references which made it possible to establish it.

To go beyond a simple regulatory response, it is also important for the industrial partner to initiate a risk analysis process applied to the migration of chemical substances to the food or other product in contact.

The set of control measures is summarised in Figure 11.

Figure 11 Means of risk control.

Results and Discussion

Migration tests

Scope

Suitability for food contact is evidenced by means of quantitative data, test results, calculations, and estimations shown in Table 3.

Table 3 Approach to follow to investigate suitability for a FCM.

Input data	Actions	Output data/Reactions
Tests Nature of the material	Verification of the nature of the material/composition *(FTIR, spark spectrometry, ICP, GC, HPLC, X-ray(1))*	Identification Elementary content (%) Quantification (%, ppm, etc.) To be compared with the regulatory requirements
Tests Overall migration	Choice of simulant Choice of contact conditions: duration and temperature (2) (3)	Results in mg/kg or mg/dm2 To be compared with the regulatory requirements (4)
Tests Specific migrations	Choice of simulant Choice of contact conditions: duration and temperature Method detection limits consistent with the thresholds (5)	Identification and quantification of the elements and molecules subject to restrictions: FTIR, GC, HPLC, etc. Results in mg/kg or mg/dm^2 To be compared with the regulatory requirements
Tests Organoleptic inertia	Selection of contact conditions: Duration and temperature	Absence of organoleptic modifications (6)

(1) Physical/chemical and microbiological testing methods chosen based on the nature of the material and the criteria to be measured [Briefing note DGCCRF].
(2) [Briefing note DGCCRF n° 2004-64]
(3) A little practical information: regulatory directions for the selection of contact conditions, in the case of plastic materials, from Regulation (EU) 10/2011.
(4) Keep close to the values set out in the regulations:
- migration expressed in mg/surface or mass of food;
-at least three repetitions coming within the tolerance range.
(5) One of the difficulties concerning the measurement of transfer to food lies in the limited number of harmonised protocols at the European level (example: series of NF EN 13130 standards and XP-CEN/TS 3130), when hundreds of substances are subject to specific restrictions. Specific protocols must sometimes be developed on a case-by-case basis. The method detection limits used must be consistent with the announced SML.
The European Commission publishes a guide for performance criteria and validation procedures of analytical methods used in controls of food contact materials: 'Guidelines for performance criteria…'. Analytical tolerances are not set at the regulatory level, except in a few cases. They are a function of the analytical method used (instrumentation, operating mode developed by the laboratory). These values are to be assessed on a case-by-case basis.
(6) Standard NF ISO 13 302 of January 2004, 'Sensory analysis - Methods for assessing modifications to the flavour of foodstuffs due to packaging' proposes methods for the preparation of samples (placement in contact) and procedures for discriminative and descriptive sensory methods

To develop these tests, a simulant must therefore be chosen (Table 4).

Table 4 Simulants to be used during determinations of overall and/or specific migrations.

Food simulants	Abbreviation
10 % EtOH (v/v)	Simulant A
3 % acetic acid (m/v)	Simulant B
20 % EtOH (v/v)	Simulant C
50 % EtOH (v/v)	Simulant D_1
Vegetable oil (*), *could be replaced by 95 % EtOH (v/v) and/or isooctane*	Simulant D_2
Poly (2,6-diphenyl-p-phenylene oxide), *particle size 60-80 mesh, pore size 200 nm*	Simulant E

** Any vegetable oil having a fatty acids distribution as defined in Regulation (EU) n° 10/2011*

Food simulants are generally used to substitute certain foodstuffs:

- ***simulants A, B and C*** are assigned to study hydrophilic foodstuffs;
- ***simulant B*** is used for foodstuffs having a pH under 4.5;
- ***simulant C*** is used for alcoholic foodstuffs having an alcohol content of at most 20 % and foodstuffs containing a significant quantity of organic ingredients making them more lipophilic;
- ***simulants D_1 and D_2*** are used for lipophilic foodstuffs that can extract lipophilic substances. simulant D_1 is used for alcoholic foodstuffs having an alcohol content of at most 20 % and for oil in aqueous emulsions. Simulant D_2 is used for foodstuffs containing free fats on the surface;
- ***simulant E*** is used for testing specific migration in dry foodstuffs.

The others parameters to take into account is the test conditions. Table 5 describes the conditions to be applied according to the target contact conditions.

Table 5 Standardised methods during the determination of the overall migration (OM).

Test number	Contact time in days [d] or hours [h] at contact temperature in [°C]	Intended food contact conditions
OM_1	10 days at 20°C	*Any contact in the frozen state & refrigerated state*
OM_2	10 days at 40°C	*Any long term storage at room temperature or below, including when packaged under hot-fill conditions, and/or heating up to a temperature T where 70 °C ≤ T ≤ 100 °C for a maximum of t = 120/2^((T-70)/10) minutes*
OM_3	2 hours at 70°C	*Any food contact conditions that include hot-fill and/or heating up to a temperature T where 70 °C ≤ T ≤ 100 °C for maximum of t = 120/2^((T-70)/10) minutes, which are not followed by long term room temperature or refrigerated storage*
OM_4	One hour at 100°C	*High temperature applications for all types of food at temperature up to 100 °C*
OM_5	Either 2 hours at 100°C or at the reflux T°C, i.e. 1 hour at 121°C	*Applications at high temperature at a maximum temperature of 121°C*
OM_6	4 hours at 100°C or at the reflux T°C	*Any food contact conditions at a temperature exceeding 40 °C, and with foods for which point 4 of Annex III assigns simulants A, B, C or D1*
OM_7	2 hours at 175°C	*High-temperature applications with fatty foodstuffs in conditions exceeding those of the OM_5 test*

* in days [d] or hours [h] at the contact temperature [°C], source: Regulation (EU) n° 10/2011

In case it is technically not feasible to perform OM7 with food simulant D2 the test can be replaced by test OM 8 or OM9. These two situations are described in Table 6.

Table 6 Complementary methods during the determination of the overall migration (OM).

Test number	Testing conditions	Intended food contact conditions	Covers the expected of contact described in
OM_8	10 days at 20°C	Only applications at high temperature	OM_1, OM_3, OM_4, OM_5 and OM_6
OM_9	10 days at 40°C	Applications at high temperature with long-term storage at room T°C	OM_1, OM_2, OM_3, OM_4 OM_5 and OM_6

Table 7 Duration of contact during the determination of specific migrations.

Duration of contact in the worst foreseeable conditions of use	Test conditions
t ≤ 5 minutes	5 minutes
5 minutes < t ≤ 0,5 hour	0,5 hour
0,5 hour < t ≤ 1 hour	1 hour
1 hour < t ≤ 2 hours	2 hours
2 hours < t ≤ 6 hours	6 hours
6 hours < t ≤ 24 hours	24 hours
1 day < t ≤ 3 days	3 days
3 days < t ≤ 30 days	10 days
> 30 days	See the specific conditions

Table 8 Contact temperature during determination of specific migrations.

Contact temperature in the worst foreseeable conditions of use	Test conditions
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 (*)
150°C < t < 175°C	175°C (*)
t > 175°C	*Adjust the temperature to the real temperature at the interface with the food (*)*

* in days [d] or hours [h] at the contact temperature [°C]

Procedure applied for the project

For the purpose of a vigilance strategy, the tests were performed by contacting the samples with EtOH 95% (v.v) as simulant ('Strong' simulant) for 10 days at 40°C. For that, a cell that can cover the analysis of a certain area in cm² (S) was used with a defined contact volume (V). Regarding our equipment, the film is in contact with the simulant on just one side (Figure 12).

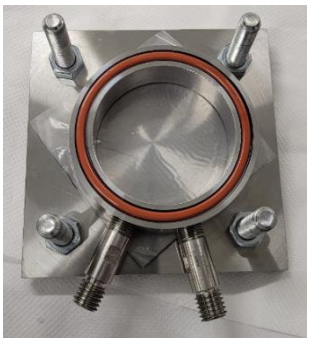


Figure 12 Cell used for migration tests.

The film is placed against the bottom metal plate, and the simulant is in the ring above the film. Another metal plate is then screwed on the top of the system, and all cell is put in an oven to achieve the desired conditions of the test.

After the test, the analysis have been split in **2 steps**:

1. Overall migration: the simulant is recovered, evaporated and the residue is weighed. These analyses have been determined according to the NF EN 1186-1, NF EN1186-3 and NF-EN 1186-14. The reference documents are the following:

- Regulation UE 1935/2004,
- Regulation UE 10/2011 and its amendments including UE 2020/1245.

2. Specific migration: 1 mL of simulant was recovered to analyse specific migration analysis to target possible migrating molecules. These analyses were carried out on the basis of a screening performed on a GC/MS device from Perkin Elmer Clarus 500 with two independent method:

- GC method:
  - Initial temperature: 40 °C for 5.00 min
  - Ramp 1: 5.0 °C/min to 340 °C, hold for 5.00 min
  - Run time: 70.00 min
- MS Method:
  - Solvent delay: Time 0.00 to 2.00 (mins)
  - MS Scan: Time 2.00 to 70.00, Mass 33.00 to 620.00 EI+
  - Transfer line [T°C] 280°C
  - Source [T°C] 250°C
- Others parameters:
  - Column: Agilent Technologies DB-17HT (Length (m): 30, diam (mm): 0.250, film (µm): 0.15) *(Polar phase medium)*
  - Injection volume: 1µL

Results

The results obtained will be presented in a table with the items below:

- Sample observations after test;
- Observation of the simulator liquid;
- Observation of the evaporation residue;
- Individual values of Overall Migration in mg/dm^2 and in mg/kg foodstuff;
- Average value in mg/dm^2 and in mg/kg foodstuff;

The regulatory limits are fixed at 10 mg/dm^2 and 60 mg/kg foodstuffs.

Overall migration and specific migration (SM) will be expressed in mg/dm^2 and mg/kg simulant respectively

Series 1

Introduction

The first migration tests were performed on lab scale laminated films made at FTMC with their manual lamination equipment. The samples are described in Table 9.

Table 9 Samples reference of the serie 1.

Reference	Reference experiment	Plastic I	Plastic II	Adhesive thickness (µm)	Adhesive	Number of sheets
FL30-PET/2BN/OH	**FL30**	BOPET	PE/EVOH/PE	2	Demo-SB	2
FL31-PET/2BC/OH (*)	**FL31**	BOPET	PE/EVOH/PE	2	Demo-SB+**1%T46**	3 (1 wrinkled)
FL32-PET/4BC/OH	**FL32**	BOPET	PE/EVOH/PE	4	Demo-SB+**1%T46**	1
FL33-PET/2BN/PE	**FL33**	BOPET	LDPE	2	Demo-SB	2
FL34-PET/3BN/PE	**FL34**	BOPET	LDPE	3,5	Demo-SB	2
FL35-PET/3BC/PE (*)	**FL35**	BOPET	LDPE	3	Demo-SB+**1%T46**	2
FL36-MAT/2BN/OH	**FL36**	BOPP-Matte	PE/EVOH/PE	2	Demo-SB	2
FL37-MAT/3BN/OH	**FL37**	BOPP-Matte	PE/EVOH/PE	3	Demo-SB	2
FL38-MAT/2BC/OH (*)	**FL38**	BOPP-Matte	PE/EVOH/PE	2	Demo-SB+**1%T46**	1
FL39-MAT/3BC/OH (*)	**FL39**	BOPP-Matte	PE/EVOH/PE	3	Demo-SB+**1%T46**	1
FL40-MAT/4BC/OH (*)	**FL40**	BOPP-Matte	PE/EVOH/PE	4	Demo-SB+**1%T46**	1

As a visual simplification, a star (*) is added to indicate the presence of enzyme in the composition of the systems studied.

Observation of samples

Some differences were noted in the appearance of the films after the test. A white deposit was formed inside the films containing enzymes (Figure 13).

a) b) c)

Figure 13 Samples observed after migration tests for FL30 (a), FL31 (b) and FL32 (c).

Moreover, it seems that some bubbles were formed and the adhesion between the layers is lost. Every sample containing the enzyme T46 showed this deposit/bubbles.

Our first hypothesis is that the migration test conditions (10 days at 40°C) activated the enzymes and thus, the adhesive started to degrade.

Even if this might not be an issue for food contact requirements (depending on the results of overall and specific migration results), this might be a problem: 10 days at 40°C could be a storing time for these packaging, and mechanical properties might be degraded if the adhesive is not as strong as planned. Moreover, the final consumer might be repelled by packaging visually degraded.

This being said, these films are lab-scale made, and thus can be not representative of the final films made during the project.

Overall migration results

From the overall migration tests, all systems meet the regulation for food contact: the requirements are less than 10 mg/dm^2 and 60 mg/kg foodstuffs from regulations. Table 10 presents results obtained and one can see that no film tested reached these limits.

Table 10 Results obtained after overall migration tests for series 1.

Samples ** with enzyme*	Samples observations	Observation of the simulator liquid	Observation of the evaporation residue	Individual values of overall migration		Compliance	
				mg/dm²	*mg/kg foodstuff*	*mg/dm²*	*mg/kg foodstuff*
FL30	NTP (•)	Clear	NTP (•)	**< 1,0**	**< 1,0**	**YES**	**YES**
FL31 (*)	**Opaque**	Clear	NTP (•)	**3,8**	**22,6**	**YES**	**YES**
FL32 (*)	**Opaque**	Clear	NTP (•)	**2,8**	**17,0**	**YES**	**YES**
FL33	NTP (•)	Clear	NTP (•)	**1,9**	**11,3**	**YES**	**YES**
FL34	NTP (•)	Clear	NTP (•)	**1,4**	**8,5**	**YES**	**YES**
FL35 (*)	**Opaque**	Clear	NTP (•)	**< 1,0**	**2,8**	**YES**	**YES**
FL36	NTP (•)	Clear	NTP (•)	**1,9**	**11,3**	**YES**	**YES**
FL37	NTP (•)	Clear	NTP (•)	**1,4**	**8,5**	**YES**	**YES**
FL38 (*)	**Opaque and delamination**	Clear	NTP (•)	**1,4**	**8,5**	**YES**	**YES**
FL39 (*)	**Opaque**	Clear	NTP (•)	**< 1,0**	**5,7**	**YES**	**YES**
FL40 (*)	**Opaque**	Clear	NTP (•)	**< 1,0**	**2,8**	**YES**	**YES**

•NTP=nothing to report

Specific migration results

When the 1 mL of simulant was analysed by GC/MS equipment, 2 compounds were identified (Table 11).

Table 11 Results of specific migration for series 1.

Samples * with enzyme	Compound 1 detected (✓/✗)	Compound 2 detected (✓/✗)
Control simulant	✗	✓
FL30	✗	✓
FL31 (*)	✓	✓
FL32 (*)	✓	✓
FL33	✗	✓
FL34	✗	✓
FL35 (*)	✓	✓
Control simulant		✓
FL36	✗	✓
FL37	✗	✓
FL38 (*)	✓	✓
FL39 (*)	✓	✓
FL40 (*)	✓	✓

The second compound came from a migration inside the simulant bottle, so it was not related to the film compositions. But the 1st compound is more intriguing. It was identified as a diethyl adipate substance at a retention time of 22.88 min (Figure 14Figure 14 Chemical composition of compound 1).

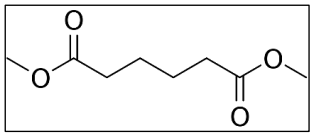


Figure 14 Chemical composition of compound 1.

Since it is observed only when enzymes are in the composition, and given its chemical structure, it seems to be consistent with our hypothesis of an adhesive degradation due to the activation of enzymes: these kinds of molecules could be a residue of adhesive, which, given its size, could have migrate to the simulant.

Series 2

The second sample series concerns the system made by IPC with adhesive from Solvent Free (SF) demo. Systems studied are described in Table 12.Table 12 Samples reference of the serie 2

Table 12 Samples reference of the serie 2.

Refence samples	System
SF1	BOPET / SF Demo / LDPE ENZYMES
SF2	BOPET / SF Demo / PE-EVOH-PE ENZYMES

Figure 15 describes the samples after migration tests and there is nothing to report after ten days at 40°C.

Figure 15 Samples (Series 2) after migration test.

Regarding overall migration results, these two samples are under the migration limit of 10 mg/dm^2 and the results obtained from the simulant after screening are shown in Figure 16.

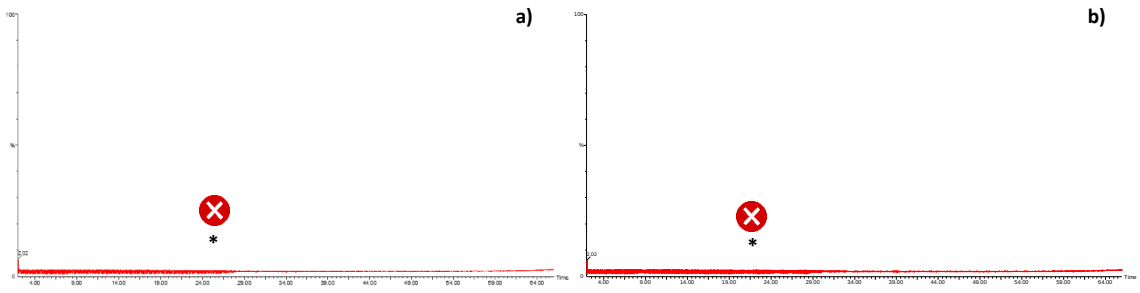


Figure 16 Chromatograms obtained after screening of the simulant for SF1 (a) and SF2 (b).

Compared to serie 1, no peaks were identified at the retention time (*) of Ethyl adipate

Series 3

The third series studies samples which have been developed with the pilot scale lamination equipment at IPC from adhesive made with Solvent Base (SB) demo.

Table 13 Samples reference of the serie 3.

Refence samples	System
SB1	BOPET / SB Demo / LDPE
SB2	BOPET / SB Demo + enzymes / LDPE

Visually, there is nothing to report on these samples.

Regarding overall migration results, these two samples are also under the migration limit of 10 mg/dm^2 and the results obtained from the simulant after screening are shown in Figure 17Figure 16.

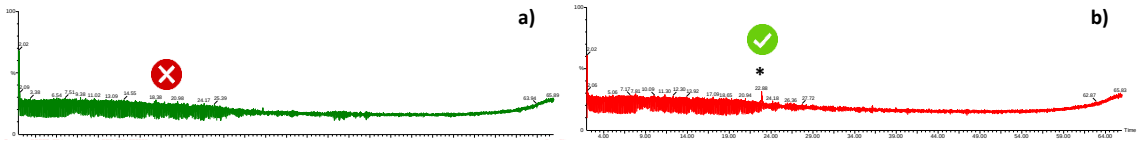


Figure 17 Chromatograms obtained after screening of the simulant for SB1 (a) and SB2 (b).

Diethyl adipate has been detected (*) inside the simulant after the migration of 10 days at 40°C for the sample with SB Demo + enzymes but the quantity appears lower compared to the previous detection for the samples analysed for series 1.

Series 4

The fourth series concerns multilayers samples made from NORNER based on Tie layers. Table 14 describes the reference studied

Table 14 Samples reference of the serie 4.

Refence samples	System
NTL-2-02	
NTL-2-03	
NTL-2-04	
NTL-2-05	
NTL-2-06	
NTL-2-07	
NTL-2-08	
NTL-2-09	

Visually, nothing to report on the whole samples after 10 days at 40°C in contact with EtOH95. Moreover, in terms of overall migration, all the samples tested were in compliance with the regulation (< 10 mg/dm^2).

The chromatograms of the migration simulants show some peaks in small quantities, the same peaks are observed in the chromatogram of the control simulant (Figure 18). It is also important to add that their identification is impossible (very low probability).

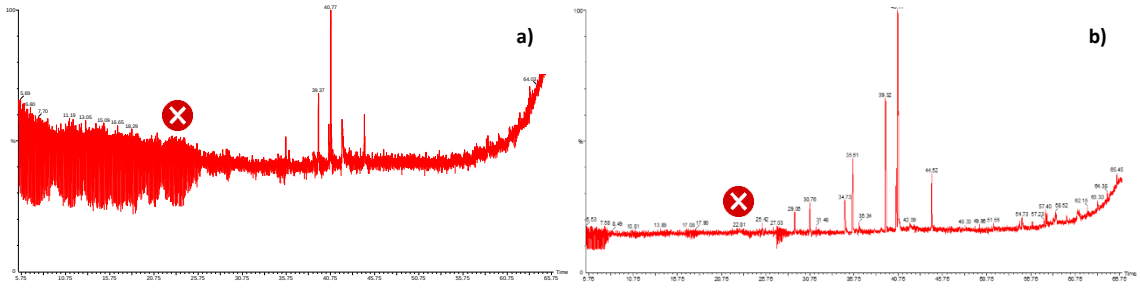


Figure 18 Chromatograms obtained after screening of the simulant for NTL-2-09 (a) and control simulant (b).

Series 5

Table 15 Samples reference of the serie 5.

Refence samples	System
0028-30-Face A (PET)	BOPET / Demo SB / LDPE with DB?
0028-31-Face B (PET)	BOPET / SB + 0.5-5% enzymes (50 à 100µm) / LDPE with DB?

Visually, nothing to report on these two samples after 10 days at 40°C in contact with EtOH95. Moreover, in terms of overall migration, they are in compliance with the regulation (< 10 mg/dm^2).

The chromatograms shown in Figure 19 did not identify any additional peaks.

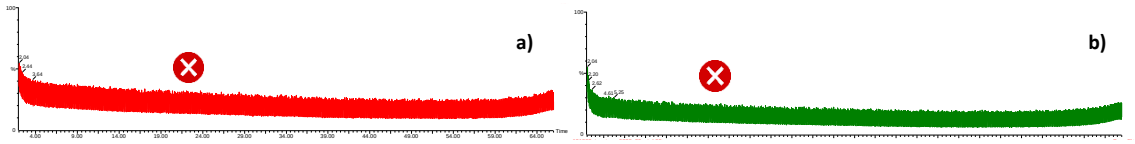


Figure 19 Chromatograms obtained after screening of the simulant for 0028-30 (a) and 0028-31 (b).

Modelling using FMECAengine tool

Introduction

FMECAengine is an open-source modelling tool available at the following address https://github.com/ovitrac/FMECAengine. It will simulate the migration of organic molecules based on actual use conditions, e.g. reference concentration of a pollutant in the initial material, and conditions of use of the packaging.

This software has been developed in the framework of the ANR research program: 'SafeFoodPackDesign' with the partners ACTIA, LNE, IPC, INRAe, AgroParisTech.

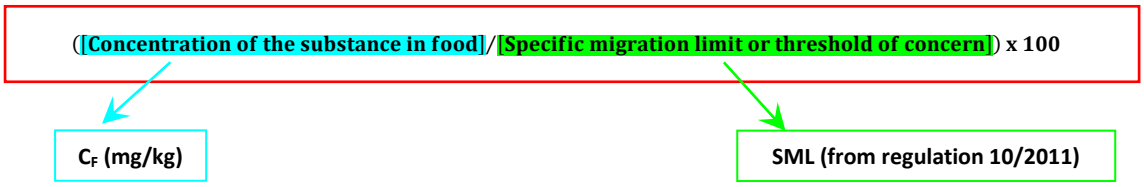
Description of the approach applied to the TERMINUS project.

The proposed approach is based on the FMECA (Failure Modes and Effects Analysis) method. This predictive study focuses on all the input data of the product/packaging pair as well as on the characteristics of the chemical molecules studied (diffusion coefficient, partition coefficient, etc.).

To carry out this study, the FMECAengine tool was used. It has several advantages:

- it is free of charge,
- based on risk analysis
- extended to the entire value chain.

It allows the construction of scenarios, and the chaining of operations between them, and is based on the concept of severity represented as the ratio:



This indicator will be the witness of the dangerousness of the studied substances according to the conditions applied for the product/packaging couple. It is also important to remember that this tool is only efficient for studying the migration of organic molecules

As illustrated in Figure 20, the method is based on:

- collecting, analysing, and processing the input data
- the coding of the scenario from an adapted template via a specific spreadsheet,
- calculation (using Matlab) and acquisition of output data,
- analysis and representation of output data (kinetics, pareto diagram, etc.),…)

Figure 20 FMECAengine presentation.

Indeed, a template was set up to facilitate the link between the data collection and the modelling part with the Matlab interface. It is divided into several tabs presented in Figure 21.

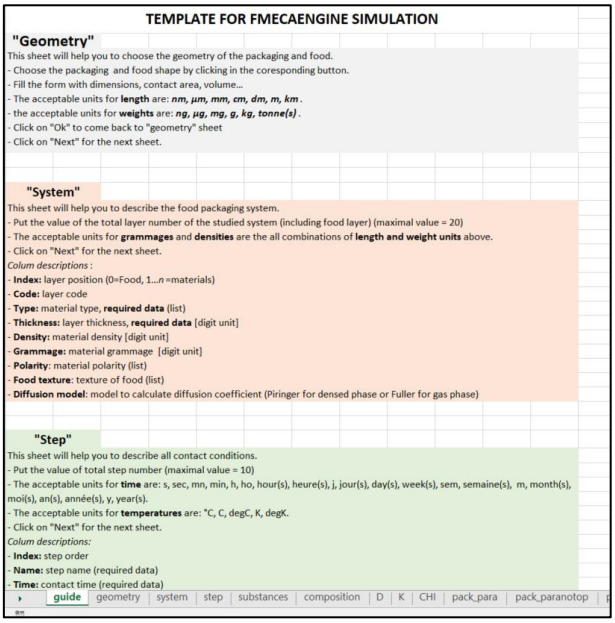


Figure 21 Template used both for data collection and as input for calculations in the Matlab interface.

However, the modelling has its limitations. It refers to the worst-case principle, i.e. placing oneself in a 'worst case' situation, using over estimators. Thus, when the calculated concentration in the food is lower than the SML or the defined threshold of concern, it can be concluded that there is inertia under real conditions. Otherwise, it will be necessary to validate by an analytical approach.

Within the framework of the Terminus project, the exercise consists of evaluating the transfer risk under defined conditions. Modelling calculations are carried out using the known or estimated contents of the target substances in the material, depending on the project targets. By validating the

input data, the potential chemical risks related to the product will have to be identified and analysed by associating different stages or not of the product life cycle.

The objective will be to provide initial elements of migration levels based on the calculation of residual contaminant concentrations for given uses before considering experimental trials.

For this purpose, different scenarios have been taken into consideration:

- Variation in concentration
- Investigation of enzyme degradation with a defined strategy

Modelling set up.

Use case chosen

To be most efficient in our comparison with the results obtained for the experimental part, a defined system has been investigated shown in Table 16. 6 dm^2 of a multilayer are put in contact with 1 kg of food. The ratio $\mathbf{Surface}\ (\mathbf{S})/\mathbf{Volume}\ (\mathbf{V})$ is equal at 4.9.

Table 16 Geometry studied.

GEOMETRY SUMARY (SI units)							
component	form	contacte surface	unit	volume	unit	masse	unit
packaging		0.06	m2	0.001221	m3		
food						1	kg

Table 17 describes the multilayer system studied in accordance with informations shared by STTP. Three different materials are investigated. The first raw (F) of this table defines the food chosen to be in contact with the system: EtOH 95 (v/v).

Table 17 System studied.

mandatory	mandatory	mandatory	madatory	madatory	madatory	optional	optional	optional
Index	Code	Type	Thickness	Density	Grammage	Polarity	Food texture	Diffusion model
0	F	food	0.02035m	919 kg/m3		Polar		Biot=1000
1	P1	LDPE	50µm	925 kg/m3	1 kg/m2	apolar		Piringer
2	P2	AdhesivePU	2µm	1000 kg/m3	1 kg/m2	apolar		Piringer
3	P3	PET_sup_Tg	12µm	1385 kg/m3	1 kg/m2	polar		Piringer

The contact conditions are listed in Table 18: 10 days at 40°C. The first raw (*) is mandatory in the implementation of the tool.

Table 18 Contact conditions.

mandatory	mandatory	mandatory	mandatory	optional
Index	Name	Time	Temperature	Biot numbe
* 1	storage	1days	25°C	1000
2	heating	10days	40°C	1000

First strategy: focus on concentrations in L1 (LDPE) and L3 (BOPET)

For a first approach in the modelling work, only the molecules present in the outer layers L1 and L3 will be considered (Table 19).

Table 19 Substances of interest (first strategy).

mandatory	mandatory	mandatory	mandatory	optional	optionnal	mandatory	mandatory	optional
Index	Code	Name	CAS number	Toxicological class	SML	Formula	Mw (g/mol)	Polarity
1	S1	Acideterephthalique	0000100-21-0	low	7.5ppm	C8H6O4	166,008	Apolar
2	S2	Ethyleneglycol	0000107-21-1	moderate	30ppm	C2H6O2	62,028	Polar
3	S3	Diethyleneglycol	0000111-46-6	high	0.04ppm	C4H10O3	106,05	Polar
4	S4	hexafluoropropylene	0000116-15-4	moderate	30ppm	C3F6	150,02	Apolar
5	S5	vinylidene fluoride	0000075-38-7	high	0.1ppm	C2H2F2	64,03	Apolar

The work consists to compare different concentrations mentioned in Table 20. A factor of 1000 was used between configuration a) and b). These concentration correspond to the quantities introduced inside the materials before

Table 20 Concentration of the substances targeted (first strategy).

a) [C1]

mandatory	mandatory	mandatory	mandatory	mandatory	mandatory	mandatory
Index	Code	Name	CAS number	Concentration_L1	Concentration_L2	Concentration_L3
1	S1	Acideterephthalique	0000100-21-0	0.5ppm	0ppm	0ppm
2	S2	Ethyleneglycol	0000107-21-1	3.0ppm	0ppm	0ppm
3	S3	Diethyleneglycol	0000111-46-6	3.0ppm	0ppm	0ppm
4	S4	hexafluoropropylene	0000116-15-4	0ppm	0ppm	0.1ppm
5	S5	vinylidene fluoride	0000075-38-7	0ppm	0ppm	0.1ppm

x 1000

b) [C2]

mandatory	mandatory	mandatory	mandatory	mandatory	mandatory	mandatory
Index	Code	Name	CAS number	Concentration_L1	Concentration_L2	Concentration_L3
1	S1	Acideterephthalique	0000100-21-0	500ppm	0ppm	0ppm
2	S2	Ethyleneglycol	0000107-21-1	3000ppm	0ppm	0ppm
3	S3	Diethyleneglycol	0000111-46-6	3000ppm	0ppm	0ppm
4	S4	hexafluoropropylene	0000116-15-4	0ppm	0ppm	100ppm
5	S5	vinylidene fluoride	0000075-38-7	0ppm	0ppm	100ppm

Levels reached after modelling are very low. Table 21 presents the results obtained. The column mentioning CF in mg/kg are the one of interest.

Table 21 Results obtained.

Substances	[C1]		[C2]	
	CF (kg/m³)	CF (mg/kg)	CF (kg/m³)	CF (mg/kg)
S1	2.64E-07	**3.22E-14**	2.64E-04	**3.22E-11**
S2	6.81E-06	**8.31E-13**	6.81E-03	**8.31E-10**
S3	6.81E-06	**8.31E-13**	6.81E-03	**8.31E-10**
S4	1.93E-08	**2.36E-15**	1.93E-05	**2.36E-12**
S5	2.30E-08	**2.80E-15**	2.30E-05	**2.80E-12**

To further develop the vigilance strategy, substance with the high concentration: S2 can be investigated. Indeed, it is the one with the highest concentration, but at a relatively low level compared to the concentrations targeted by the regulation.

To assess this fact, the concentration during the time can be monitored. Figure 22 presents the evolution of its concentration in function of the time. Aim is to validate that this substance is at the equilibrium. This status is achieved very quickly during the beginning of the storage step.

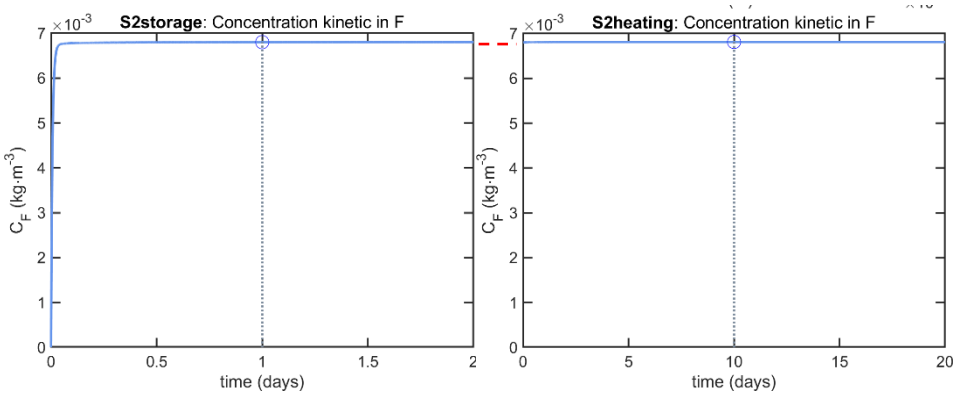


*Figure 22 Evolution of the concentration of substance **S2** as a function of time.*

Second strategy: focus on L2 (PUR adhesive)

The second way is to focus on several compound with different weight and polarity. These substances of interest can be separated in two categories according to their molar weight.

Table 22 Substances of interest (second strategy).

mandatory	mandatory	mandatory	mandatory	optional	optionnal	mandatory	mandatory	optional	
Index	Code	Name	CAS number	Toxicological class	SML	Formula	Mw (g/mol)	Polarity	
1	S1	Acideterephthalique	0000100-21-0		7.5ppm	C8H6O4	166,008	Apolar	
2	S2	Ethyleneglycol	0000107-21-1		30ppm	C2H6O2	62,028	Polar	
3	S3	Diethyleneglycol	0000111-46-6		0.04ppm	C4H10O3	106,05	Polar	
4	S4	hexafluoropropylene	0000116-15-4		30ppm	C3F6	150,02	Apolar	
5	S5	vinylidene fluoride	0000075-38-7		0.1ppm	C2H2F2	64,03	Apolar	
6	S6	vinylidene fluoride	0000075-38-7		0.1ppm	C2H2F2	64,03	Apolar	
7	S7	Ethyl-2-hexanol	0000104-76-7		30ppm	C8H18O	130,134	Apolar	
8	S8	amethylenediisocyar	0000822-06-0		60ppm	C8H12N2O2	168,076	Apolar	
9	S9	atede2-methyl-m-pl	0000091-08-7		60ppm	C9H6N2O2	174,028	Apolar	Apolar compound
10	S10	atede4-methyl-m-pl	0000584-84-9		60ppm	C9H6N2O2	174,028	Apolar	
11	S11	butyl-2,6-methyl-4-l	0000128-37-0		3ppm	C15H24O	220,182	Apolar	
12	S12	henylmethanediisoc	0005873-54-1		60ppm	C15H10N2O2	250,06	Apolar	
13	S13	iisocyanate(melang	0000101-68-8		60ppm	C15H10N2O2	250,06	Apolar	
14	S14	Irganox1076	0002082-79-3		6ppm	C35H62O3	530,466	Apolar	
15	S15	1,2-Diaminoethane	0000107-15-3		12ppm	C2H8N2	60,064	Polar	
16	S16	Ethyleneglycol	0000107-21-1		60ppm	C2H6O2	62,028	Polar	Polar compound
17	S17	Diethyleneglycol	0000111-46-6		60ppm	C4H10O3	106,05	Polar	
18	S18	(hydroxymethyl)-1-b	0000077-99-6		6ppm	C6H14O3	134,082	Polar	

Table 23 Concentration of the substances targeted (second strategy).

a) [C3]

mandatory	mandatory	mandatory	mandatory	mandatory	mandatory	mandatory
Index	Code	Name	CAS number	Concentration_L1	Concentration_L2	Concentration_L3
1	S1	Acideterephthalique	0000100-21-0	0.5ppm	0ppm	0ppm
2	S2	Ethyleneglycol	0000107-21-1	3ppm	0ppm	0ppm
3	S3	Diethyleneglycol	0000111-46-6	3ppm	0ppm	0ppm
4	S4	hexafluoropropylene	0000116-15-4	0ppm	0ppm	0.1ppm
5	S5	vinylidene fluoride	0000075-38-7	0ppm	0ppm	0.1ppm
6	S6	vinylidene fluoride	0000075-38-7	0ppm	1ppm	0ppm
7	S7	Ethyl-2-hexanol	0000104-76-7	0ppm	1ppm	0ppm
8	S8	amethylenediisocyan	0000822-06-0	0ppm	1ppm	0ppm
9	S9	atede2-methyl-m-pl	0000091-08-7	0ppm	1ppm	0ppm
10	S10	atede4-methyl-m-pl	0000584-84-9	0ppm	1ppm	0ppm
11	S11	-butyl-2,6-methyl-4-l	0000128-37-0	0ppm	1ppm	0ppm
12	S12	henylmethanediisoc	0005873-54-1	0ppm	1ppm	0ppm
13	S13	iisocyanate(melange	0000101-68-8	0ppm	1ppm	0ppm
14	S14	Irganox1076	0002082-79-3	0ppm	1ppm	0ppm
15	S15	1,2-Diaminoethane	0000107-15-3	0ppm	1ppm	0ppm
16	S16	Ethyleneglycol	0000107-21-1	0ppm	1ppm	0ppm
17	S17	Diethyleneglycol	0000111-46-6	0ppm	1ppm	0ppm
18	S18	(hydroxymethyl)-1-b	0000077-99-6	0ppm	1ppm	0ppm

x 1000

b) [C4]

mandatory	mandatory	mandatory	mandatory	mandatory	mandatory	mandatory
Index	Code	Name	CAS number	Concentration_L1	Concentration_L2	Concentration_L3
1	S1	Acideterephthalique	0000100-21-0	0.5ppm	0ppm	0ppm
2	S2	Ethyleneglycol	0000107-21-1	3ppm	0ppm	0ppm
3	S3	Diethyleneglycol	0000111-46-6	3ppm	0ppm	0ppm
4	S4	hexafluoropropylene	0000116-15-4	0ppm	0ppm	0.1ppm
5	S5	vinylidene fluoride	0000075-38-7	0ppm	0ppm	0.1ppm
6	S6	vinylidene fluoride	0000075-38-7	0ppm	1000ppm	0ppm
7	S7	Ethyl-2-hexanol	0000104-76-7	0ppm	1000ppm	0ppm
8	S8	ɔmethylenediisocyar	0000822-06-0	0ppm	1000ppm	0ppm
9	S9	ɔatede2-methyl-m-pl	0000091-08-7	0ppm	1000ppm	0ppm
10	S10	ɔatede4-methyl-m-pl	0000584-84-9	0ppm	1000ppm	0ppm
11	S11	-butyl-2,6-methyl-4-p	0000128-37-0	0ppm	1000ppm	0ppm
12	S12	ɔhenylmethanediisoc	0005873-54-1	0ppm	1000ppm	0ppm
13	S13	liisocyanate(melang	0000101-68-8	0ppm	1000ppm	0ppm
14	S14	Irganox1076	0002082-79-3	0ppm	1000ppm	0ppm
15	S15	1,2-Diaminoethane	0000107-15-3	0ppm	1000ppm	0ppm
16	S16	Ethyleneglycol	0000107-21-1	0ppm	1000ppm	0ppm
17	S17	Diethyleneglycol	0000111-46-6	0ppm	1000ppm	0ppm
18	S18	(hydroxymethyl)-1-b	0000077-99-6	0ppm	1000ppm	0ppm

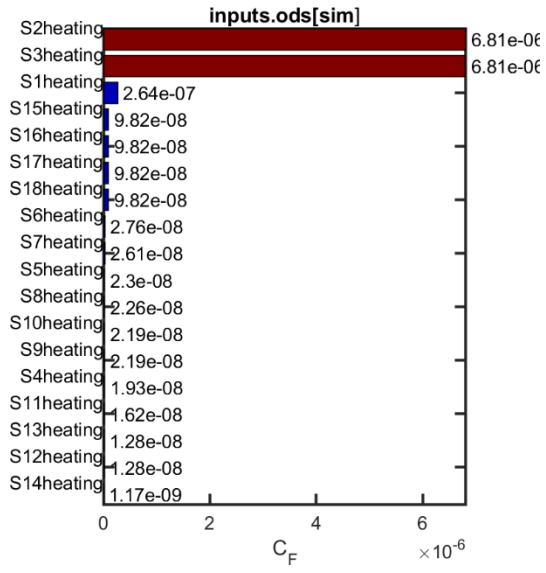
To investigate these strategy [C3] and [C4] has been independtly coupled with [C1] and the same work has been achieved with [C2].

Figure 23 and Figure 24 describe respectively the modelled concentrations obtained from the conditions applied with [C1] and [C2]. All concentrations are classified in an order of vigilance and presented in the format kg/m^3. The conversion in mg/kg can be easily realized by considering the density of the tested food (in this case 819.4 kg/m^3).

$$C_F\ (\mathrm{mg/kg}) = \frac{C_F\ (\mathrm{kg/m^3})}{(8{,}194.\,10^6)}$$

[C1]

[C3] (a)



[C4] (b)

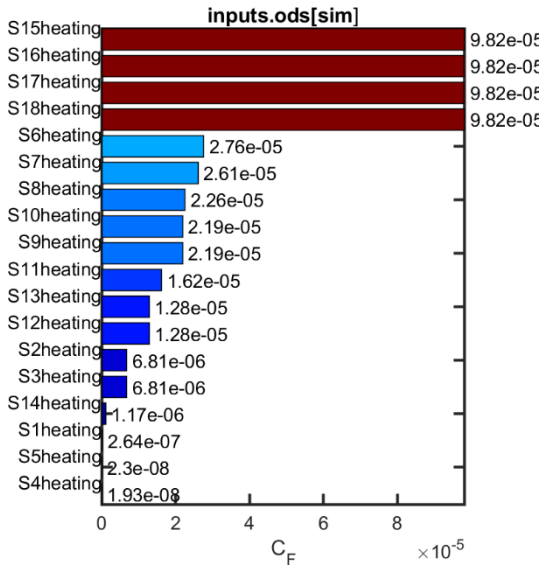


Figure 23 Modelled concentrations from [C1] for each substances targeted function to the step studied.

[C2]

[C3] (a) **[C4] (b)**

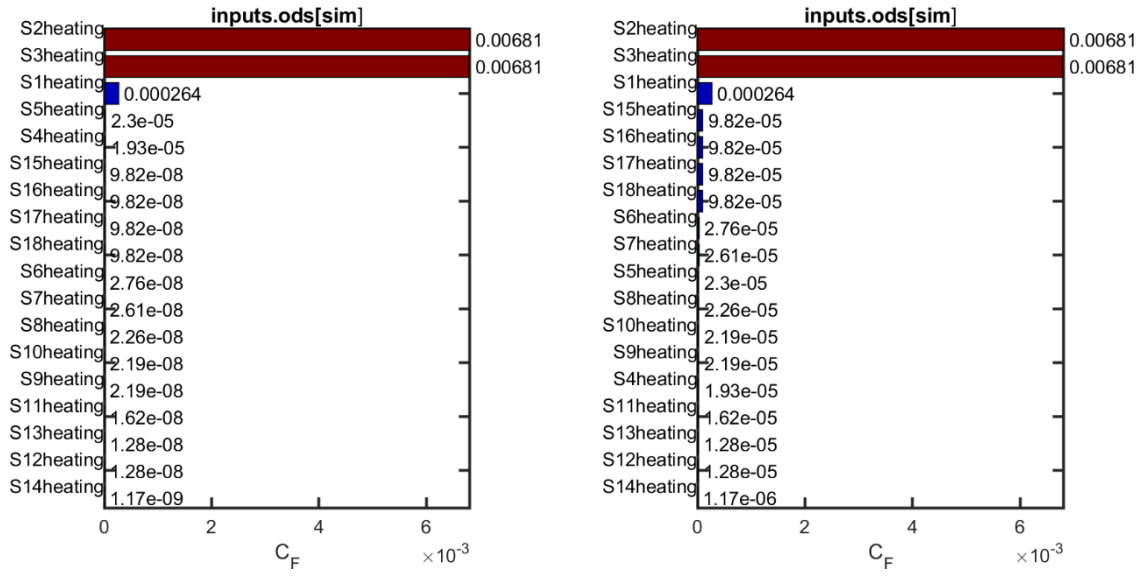


Figure 24 Modelled concentrations from [C2] for each substances targeted function to the step studied.

As seen for the first strategy, all calculated concentrations tend to be in equilibrium. Due to the chemical structure, this equilibrium takes more or less to achieve for certain molecules.

Conclusion on modelling

The calculated concentrations did not identify any substances to be monitored under the modelling conditions applied. This simulation work on the FMECA tool shows promising results to consider a food safety compliance.

Finally, if the substances presented in the system studied are controlled and according to the conditions applied, no vigilance is required.

Conclusion and perspectives

Additional investigations were carried out from a regulatory, experimental, and theoretical point of view as part of the work carried out so far for the TERMINUS project.

All these informations are included in the deliverable and report on report on regulatory aspects and food contact safety in order to be published to promote results.

First of all, from a regulatory point of view, among the current regulations, presented in the first part of this report, any of them contains specific dispositions concerning enzymes in plastic food packaging. In this scenario, the strategy TERMINUS to the assessment of risks on food contact was based on two complementary routes: one, according to the regulations for FCM and especially for plastics in contact with food and, second, the use of modelling to enlarge the scope of the assessment. This is, to complete our vigilance in accordance with the regulation, a modelling tool named FMECAengine was used to employ different approaches and investigate in more detail the behaviour of certain compounds as a function of their molar mass, polarity, and implementation within a material in the process conditions. The advantage of this tool is multiple when used as a safe design tool.

Specifically, results regarding the migration tests were fully in compliance with the limits set by the corresponding regulation i.e. specific migration limit (SML) and Overall migration limit (OML). Two big multilayers system were analysed: (1) multi-layered prototypes based on PUR-Adhesives solvent-free and solvent-based types elaborated at laboratory and pilot scale and (2) multi-layered prototypes based on innovative tie-layers elaborated by blown co-extrusion.

When it comes to modelling using FMECAengine, only PUR adhesive –based TERMINUS prototypes were able to be examined. Once more, the lack of information regarding innovative materials proposed by TEMINUS i.e. innovative tie-layer for multilayers made by blown co-extrusion, prevents, for the time being, go further concerning the nature of the multilayer system. At the same time, this circumstance opens up an area of opportunity to develop more striking tools on food contact risks assessment for novel materials. Specifically, on the modelisation results, it was shown that the calculated concentrations did not point out to any substance to be monitored under the modelling conditions applied since values are in compliance with regulations. Furthermore, the equilibrium concentrations remain constant not showing any tendance to evolve to hazardous values. In summary, this simulation work on the FMECA tool shows promising results to assess food safety compliance for further analysis of innovative materials.

Nevertheless, according to the great diversity of the study, this opens up room enough for multiple perspectives:

- Control of the parameters of the degradation of enzymes as worst case scenario since the degradation action is to be triggered at the end of life of the packaging
- Implement the tool with innovative materials (Biopolymers)
- Adjusting process conditions
- Assessing the best storage conditions

From the above, it is important to underline that although the degradation of enzymes must be controlled both in relation to the use of the packaging and to any compounds formed, so far no

evidence has been found pointing to a degradation phenomenon outside the treatment intended to trigger it.

References

[1] GUILLOU, Delphine, 2020. Food Contact Materials *(FCM)*. 4 March 2020. S.l. : Cetim. *https://www.contactalimentaire.fr/sites/default/files/media/file/field_media_file/Regles_generales_alimentarite_2020_03.pdf*.

[2] UNITED STATE OF AMERICA FEDERAL GOVERNMENT. *General provisions applicable to indirect food additives*. S.l. : s.n. *https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-174/section-174.5*.

[3] EUROPEAN PARLIAMENT and COUNCIL of EUROPEAN UNION, 2004. *Regulation (EC) n° 1935/2004 of European Parliament and Council of 27 october 2004 concerning food contact materials and articles and abrogating the directives 80/590/CEE and 89/109/CEE. 27 october 2004. S.l. : s.n. [Accessed the 13 December 2022].* *http://data.europa.eu/eli/reg/2004/1935/oj/fra*.

[4] EUROPEAN COMMISSION, 2011. Regulation (EU) n°10/2011 of Commission of 14 January 2011 concerning food contact materials and articles. Text presenting interest for EEE. 14 January 2011. S.l. : s.n. [Accessed the 13 December 2022]. *http://data.europa.eu/eli/reg/2011/10/oj/fra*.

[5] EUROPEAN COMMISSION OF GENERAL DIRECTION of HEALTH and CONSUMERS, 2014. Guidelines of Union on Regulation (EU) n°10/2011 concerning food contact materials and articles. 21 February 2014. S.l. : s.n. *https://www.contactalimentaire.fr/sites/default/files/media/file/field_media_file/guidelines_reg_10-2011_du_21-02-2014_fr_.pdf*.

[6] EUROPEAN COMMISSION, 2009. Regulation (EC) n°450/2009 of Commission of 29 May 2009 concerning food contact, active and intelligent materials and articles. (Text presenting interest for EEE). 29 May 2009. S.l. : s.n. [Accessed the 13 December 2022]. *http://data.europa.eu/eli/reg/2009/450/oj/fra*.

[7] EUROPEAN FOOD SAFETY AUTHORITY, 2017. Administrative Guidance for the preparation of applications for the safety assessment of substances to be used in plastic Food Contact Materials. In : *EFSA Supporting Publications*. 2017. Vol. 14, n° 5, pp. 1224E. DOI *10.2903/sp.efsa.2017.EN-1224*.

[8] EUROPEAN FOOD SAFETY AUTHORITY, 2009. Guidelines on submission of a dossier for safety evaluation by the EFSA of active or intelligent substances present in active and intelligent materials and articles intended to come into contact with food. In : *EFSA Journal*. August 2009. Vol. 7, n° 8. DOI *10.2903/j.efsa.2009.1208*.