**Printed paper and board food contact materials as a potential source of food contamination**

Melissa Van Bossuyta,b\*, Els Van Hoecka, Tamara Vanhaeckeb, Vera Rogiersb° and Birgit Mertensa°

*a Department of Food, Medicines and Consumer Safety, Scientific Institute of Public Health, Juliette Wytsmanstraat 14, Brussels, Belgium*

*b Department of In Vitro Toxicology and Dermato-cosmetology, Vrije Universiteit Brussel, Laarbeeklaan 103, Brussels, Belgium*

° Equally contributing authors

\*Corresponding author. *E-mail address:* Melissa.VanBossuyt@wiv-isp.be

**Abstract**

Food contact materials (FCM) are estimated to be the largest source of food contamination. Apart from plastics, the most commonly used FCM are made of printed paper and board. Unlike their plastic counterparts, these are not covered by a specific European regulation. Several contamination issues have raised concerns towards potential adverse health effects caused by exposure to substances migrating from printed paper and board FCM. In the current study, an inventory combining the substances which may be used in printed paper and board FCM, was created. More than 6000 unique compounds were identified, the majority (77%) considered non-evaluated in terms of potential toxicity. Based on a preliminary study of their physicochemical properties, it is estimated that most of the non-evaluated single substances have the potential to migrate into the food and become bioavailable after oral intake. Almost all are included in the FACET tool, indicating that their use in primary food packaging has been confirmed by industry. Importantly, 19 substances are also present in one of the lists with substances of concern compiled by the European Chemicals Agency (ECHA). To ensure consumer safety, the actual use of these substances in printed paper and board FCM should be investigated urgently.

**Keywords**

Food contact materials; printing inks; paper and board; food contamination; prioritisation

**Abbreviations**

4MBP, 4-methylbenzophenone; CEPI, Confederation of European Paper Industries; CLP, Classification, Labelling and Packaging; CMR, Carcinogenic, Mutagenic or Reprotoxic substances; COC, chemicals of concern; CoE, Council of Europe; CoRAP, Community Rolling Action Plan; EC, European Commission; ECHA, European Chemicals Agency; EFSA, European Food Safety Authority; EFTA, European Free Trade Association; ESCO WG, EFSA Scientific Cooperation Working Group; EuPIA, European Printing Inks Association; FACET, Flavourings, Additives, and food Contact materials Exposure Tool; FCM, food contact materials; FDA, Food and Drug Administration; ITX, 2-isopropylthioxanthone; NIAS, non-intentionally added substances; OML, overall migration limit; PBT, Persistent, Bioaccumulative and Toxic substances; RASFF, Rapid Alert System for Food and Feed; RCR, Risk Characterisation Ratio; REACH, Registration, Evaluation, Authorisation and restriction of Chemicals; SML, specific migration limit; SVHC, Substances of Very High Concern; vPvB, very Persistent and very Bioaccumulative substances.

**1. Introduction**

Food contact materials (FCM) are defined by the European Food Safety Authority (EFSA) as “all materials and articles intended to come into contact with food”. FCM are thus routinely involved throughout the production, processing, packaging, transport, storage, preparation and serving of food and beverages (EFSA, 2015; European Union, 2015a). Regulation (EC) No 1935/2004 depicts 17 FCM groups including plastics, paper and board, glass, but also printing inks, coatings and adhesives used in product finishing. They should all be sufficiently inert, so that constituents cannot exert any negative effect neither on consumer health nor food quality (European Union, 2004). Migration of FCM substances into food and subsequent consumer exposure has been a concern since several decades and is estimated to be the largest source of food contamination, up to 100-1000 times higher than contamination originating from pesticide residues or environmental pollution (Grob et al., 2006).

In the European Union, general requirements for FCM are described in Reg. (EC) No 1935/2004, but few harmonised legislations exist for the individual FCM types. Targeted regulations or directives have so far only been established for plastic materials [Reg. (EU) No 10/2011](European Union, 2011), recycled plastic materials (European Union, 2008), ceramics (European Communities, 1984), active and intelligent materials (European Union, 2009) and regenerated cellulose film (European Union, 2007). This implies that the vast majority of FCM is not subject to a specific EU legislation. Moreover, only Reg. (EU) No 10/2011 on plastic FCM comprises a Union List of authorised substances. FCM legislation across the European Member States is divergent regarding both scope and limit settings. National legislation is in place in 19 Member States, but none of these cover all materials and detailed requirements are rarely set (European Union, 2012 and 2015b).

Whereas migration issues in the past were predominantly related to plastics (e.g. bisphenol A), an increasing number of food crises nowadays originate from non-plastic compounds (EFSA, 2011a). In 2005, the Italian authorities notified through the Rapid Alert System for Food and Feed (RASFF) the occurrence of 2-isopropylthioxanthone (ITX) in liquid milk for babies, packaged in printed cardboard, at a concentration of 250 µg/L. ITX is a photoinitiator frequently used as a catalyst in the manufacturing of UV-cured inks. Given the very limited toxicological data on this substance, establishing the level of safety concern and the subsequent development of risk management options was a challenging task (EFSA, 2005). A second example is the RASFF notification of 4-methylbenzophenone (4MBP) by multiple Member State authorities in 2009. 4MBP, another photoinitiator, was found in breakfast cereals in concentrations up to 3728 µg/kg. Since insufficient toxicological information was available for 4MBP itself, the preliminary safety evaluation was based on a read-across approach with benzophenone and hydroxybenzophenone, two structurally related substances for which more experimental results could be consulted (EFSA, 2009). In the case of both ITX and 4MBP, EFSA concluded that short term exposure to these substances does not pose a risk to the majority of the population. However, if their use was intended to be continued, more data should be provided to allow a full risk assessment. These examples clearly illustrate that more information regarding non-plastic FCM is urgently needed in order to guarantee the safety of packed food products and prevent food crises in the future.

Printed paper and board cover a large part of the non-plastic FCM. Specifically for food packaging, these materials are used very frequently. Indeed, 90% of all manufactured foodstuffs are sold in printed package (Lago et al., 2015), whereas paper and board have been the most important packaging materials since years (Leks-Stepien, 2011). For obvious reasons, industry does not communicate detailed information on substance usage. Through the EU-funded Flavourings, Additives, and food Contact materials Exposure Tool (FACET) project, however, information on relative substance use was provided by 13 European FCM trade associations. The resulting information was collected in a freely available software tool that contains the substances confirmed to be used in the manufacturing of primary packaging FCM (Hearty et al., 2011).

In the present study, both printing inks and paper(board) used in FCM applications were investigated as a potential source of food contamination. To this extent, an inventory was created combining all substances which may be used in printed paper and board. Next, the evaluation status of these substances was examined as this has an important impact on their safety assessment. Substances for which a toxicological evaluation has been performed are considered to be safe in case their migration does not exceed the established migration limit (European Union, 2011). In contrast, non-evaluated substances that are able to migrate into the food and that are bioavailable, are assumed to be of potential concern for human health. Physicochemical data linked to migration and bioavailability potential were collected for the non-evaluated single substances. To obtain an indication of their actual use, the FACET tool was consulted for the compounds with the potential to migrate into food and become bioavailable after oral intake. For those compounds that were present in the FACET tool, inclusion in different lists with substances of (potential) concern compiled by the European Chemicals Agency (ECHA) was verified. Based on this information, a high priority list was obtained containing non-evaluated substances for which the actual use in printed paper and board FCM should be urgently investigated.

**2. Materials and methods**

**2.1. Compilation of the combined inventory**

A combined inventory of substances known and used in printed paper and board FCM was compiled based on a variety of freely available documents listing substances that can be used in printing inks or paper(board) for FCM applications. They are described in detail below.

* ***Swiss Ordinance on Materials and Articles in Contact with Food: Annex 6* (Swiss list)**

Switzerland, as member of the European Free Trade Association (EFTA), has adopted a specific legislation on printing inks used in FCM. The Swiss Ordinance on materials and articles in contact with food [RS 817.023.21](Swiss Confederation, 2005) stipulates that packaging inks may only be manufactured from the substances set out in annexes 1 and 6 of the Ordinance. Annex 1 recites substances that can be used as monomers or other starting products (list I), additives (list II) and particular requirements (list III) for the fabrication of plastic materials and articles. Annex 6 sums up the permitted substances for the manufacture of packaging inks, categorised by their function, i.e. binders (list I), dyes and pigments (list II), solvents (list III), additives (list IV) and photoinitiators (list V).

Each list in annex 6 is further subdivided into parts A and B, with part A containing the evaluated substances that have been subjected to officially recognised scientific testing (e.g. by EFSA) and part B containing the substances for which this is not the case. The global migration limit of the substances in part A is set at 10 mg/dm2 or 60 mg/kg, unless a specific migration limit (SML) is mentioned. The SML indicates the maximum amount of a substance allowed to migrate into food, whereas the global migration limit is the default value assigned to the FCM as a whole. The use of substances in part B is permitted if no transfer to food or food simulants can be detected in a migration test in the lowest possible concentration at which it may be detected applying a valid method of analysis. In no case, the detection and migration level of 0.01 mg/kg food or food simulant may be exceeded. Both the results of practical experiments and “worst case” calculations are accepted to estimate migration. The use of unlisted packaging ink substances must be reported to the Swiss authorities prior to marketing.

* ***Resolution of the Council of Europe on paper and board materials and articles intended to come into contact with foodstuffs* (CoE list)**

The Council of Europe (CoE) has compiled resolutions for several non-plastic FCM including paper and board. These policy statements are meant to serve as a guidance in case no specific regulation is adopted for a particular FCM group. Resolution ResAp (2002)1 (Council of Europe, 2009) is completed by five Technical Documents, of which the first contains a list of additives that may be used in the manufacture of paper and board materials and articles intended to come into contact with foodstuffs. The list is further divided in sublists 1 and 2.

Substances in list 1 of Technical Document 1 are approved (assessed), while substances in list 2 are not approved (not yet assessed). The temporary appendix to list 1 contains additives approved by Partial Member State Agreement or by the United States Food and Drug Administration (FDA). Monomers used for the manufacture of polymeric additives are listed separately in three additional appendices, containing a) approved, b) partially approved and c) non-approved substances.

* ***EFSA Scientific Cooperation Working Group report on non-plastic FCM: Paper and board section* (ESCO list)**

Following the observation that FCM crises were increasingly due to non-plastic substances rather than to their plastic counterparts, the EFSA assembled a Scientific Cooperation Working Group (ESCO WG) in 2010. The working group highlighted that at the EU level, due to the lack of a specific harmonised regulation for non-plastic FCM, thousands of substances used for their manufacture have not been safety-evaluated. Nevertheless, they recognised that several Member States have gained useful evaluation experience by implying national FCM legislations. This knowledge was deemed profitable in order to anticipate future emergency situations and was therefore collected in one document, the ESCO WG report. Furthermore, information included in the ESCO WG report can also be used to prioritise the safety evaluation of FCM substances (EFSA, 2011a).

Seven FCM types were considered by the ESCO WG, including paper and board. Depending on the time of their safety evaluation, substances of each FCM type were further divided into part A and B: after 1991 (when the first version of the Scientific Committee on Food guidelines was published) or before 1991, respectively (EFSA, 2011b).

* ***Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food* (Union list)**

The Union list of authorised substances for plastic FCM applications has been established in 2011. Some of the evaluated substances have been allocated a SML, reflecting their restricted use. The overall migration to food for all substances together, however, may not exceed the overall migration limit (OML) set at 60 mg/kg food or 10 mg/dm2 of the contact material (European Union, 2011). Substances included in the Union list of Reg. (EU) No 10/2011 were added to the combined inventory since substances approved for usage in plastic FCM are likely to also get approval for the fabrication of non-plastic FCM.

* 1. **Investigation of safety evaluation status**

As discussed under 2.1., information on the safety evaluation status is included in the different documents listing substances used in printed paper and board FCM. Based on this information, substances were classified either as “evaluated” or “non-evaluated” (**Table 1**).

* 1. **Identification of substances and physicochemical data collection**

Substances were classified into four groups, namely i) single substances, ii) polymers, iii) mixtures and iv) other substances (e.g. metal complexes and inorganic substances). Next, the combined inventory was enriched with additional information regarding the identity and the physicochemical properties, retrieved from ChemSpider (Royal Societies of Chemistry, 2016), ChemIDplus (National Institutes of Health, 2016) and ECHA (ECHA, 2016) databases. More specifically, ChemSpider was used as the primary information source, whereas ChemIDplus and/or the ECHA database was consulted in case ChemSpider yielded no or ambiguous results.

Supplementary identification data were added for all substances, to avoid ambiguity for substances with multiple CAS numbers and/or names. These consisted of:

* EC number
* Synonyms
* Molecular formula

Physicochemical data were added only for the non-evaluated single substances. To estimate whether the substances have the potential to migrate and become bioavailable after oral intake, the following physicochemical parameters were used:

* Molecular weight; migration is likely if the molecular weight is < 1000 g/mol (de Fatima Poças and Hogg, 2007; Nerin et al., 2013).
* Number of “Lipinski rule of 5” (Lipinski et al., 1997) violations; bioavailability is likely if the substance has ≤ 1 violation of the following criteria (Schilter et al., 2013): a molecular weight ≤ 500 g/mol, a log P ≤ 5, maximum 5-H bond donors and maximum 10 H-bond acceptors.
* Polar surface area; bioavailability is likely if this parameter has a value ≤ 140 Angström (Ghose et al., 1999; Veber et al., 2002).
* Number of rotating bonds; bioavailability is likely if this number is ≤ 10 (Veber et al., 2002).

Substances that have a low bioavailability are unlikely to exert a toxicological effect.

* 1. **Investigation of FACET status**

The FACET tool can be downloaded for free from the corresponding FACET project website (<http://expofacts.jrc.ec.europa.eu/facet/login.php>) and contains, among others, a list of substances used for the manufacture of primary packaging FCM. For the non-evaluated single substances with the potential to migrate and become bioavailable based on their physicochemical properties as discussed in 2.3., their presence among the 5744 packaging compounds included in the FACET tool was checked.

* 1. **Investigation of REACH registration status and inclusion in ECHA lists**

In 2007, the EU adopted the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation, imposing companies to identify and manage potential risks related to substances manufactured and marketed in the EU at a level of 1 ton/year or more (European Union, 2006). The safe use of the affected substances has to be demonstrated, and risk management measures have to be communicated. The requested information is submitted to ECHA and publically available through their website (ECHA, 2016). In the present study, the ECHA website was consulted to investigate whether or not the non-evaluated single substances selected based on their occurrence in the FACET tool (2.4), are registered under the REACH regulation. Additionally, for the registered substances, their inclusion in different ECHA lists containing substances of (potential) concern was verified. The following lists were consulted:

* ***Community Rolling Action Plan (CoRAP) list***

Substances included in this list have been, or will be, evaluated by a Member State of the European Union. The evaluations are aimed to clarify the initial concern that the manufacture and/or use of these substances could pose a risk to human health or the environment. In many cases, these initial concerns are related to potential persistency, bioaccumulation and toxicity (PBT), endocrine disruption, or carcinogenicity, mutagenicity and toxicity to reproduction (CMR); in combination with wide dispersive use or consumer uses (ECHA, 2016). After evaluation, different decisions can be made: (i) no action in case the concern is not confirmed; (ii) proposal for a harmonised classification ; (iii) inclusion in the Candidate List of Substances of Very High Concern (SVHC); (iv) proposal for a restriction or (v) decision to take action under another legislation than REACH/CLP (Classification, Labelling and Packaging).

* ***Candidate List of Substances of Very High Concern (SVHC list)***

Substances fulfilling the criteria laid out in article 57 of the REACH regulation may be placed on the SVHC list. These include:

1. substances classified as carcinogenic category 1A or 1B in accordance with Regulation (EC) No 1272/2008;
2. substances classified as germ cell mutagenic category 1A or 1B in accordance with Regulation (EC) No 1272/2008;
3. substances classified as toxic for reproduction category 1A or 1B in accordance with Regulation (EC) No 1272/2008;
4. substances which are PBT in accordance with the criteria set out in Annex XIII of the REACH Regulation;
5. substances which are very persistent and very bioaccumulative (vPvB) in accordance with the criteria set out in Annex XIII of the REACH Regulation;
6. substances — such as those having endocrine disrupting properties or those having PBT or vPvB properties, which do not fulfil the criteria of points (d) or (e) — for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59 of the REACH Regulation.

Both Member States and ECHA, at the request of the Commission, can propose a substance to be identified as a SVHC (ECHA, 2016).

* ***Annex XIV and Annex XVII***

Any substance included in the Authorisation list (Annex XIV) is intended for phase-out and a sunset date for this phase-out is established upon adoption (Geueke et al. 2014). Substances included in the Restriction list (Annex XVII) are substances for which manufacture, placing on the market or use is limited or banned in the European Union (ECHA, 2016).

**3. Results**

**3.1.Combined inventory**

Compilation of the Swiss list (5067 substances), the CoE list (1401 substances), the ESCO list (542 substances) and the Union list (867 substances) resulted in a combined inventory containing 7877 substances. In this context, it is important to note that a substance can be included in one or more lists. In **Figure 1**, the amount of compounds listed is represented as a function of the FCM type. This figure illustrates that within the paper and board group, 174 substances are indeed mentioned in both the CoE and the ESCO list. After removal of these 174 duplicates, the number of substances included in the combined inventory could be reduced to 7703.

As the same substance can also appear in the lists of different FCM types, **Figure 2** depicts the overlap between the lists of the different FCM types. As shown in **Figure 2A**, 883 substances were found in both the list of printing inks and paper/board FCM. Removing these 883 duplicates further decreased the total number of substances included in the combined inventory to 6820. Most of the duplicate substances, i.e. 715, are present in both the Swiss list and the CoE list. In **Figure 2B**, the overlap of the lists of printing inks and paper and board with the Union list is presented. Interestingly, most of the substances of the Union list of Reg. (EU) No. 10/2011, i.e. 747, are also included in at least one of the lists of printing inks and paper/board FCM. Sixty-three substances are even present in all four lists. After removal of the 747 duplicates, the final combined inventory was obtained, containing 6073 unique substances. Of these, 63% (3798) are only present in the Swiss list.

**3.2. Composition of the combined inventory by safety evaluation status**

The safety evaluation status of each substance in the different lists was determined by applying the criteria described in 2.2. **Table 2** illustrates that, in each list, the evaluated substances are outnumbered by the non-evaluated ones. Evidently, zero non-evaluated substances are included in the Union list of Reg. (EU) No 10/2011, as all substances have been authorised for use in the manufacture of plastic FCM. In the final combined inventory, a substance was considered “evaluated” when it was classified as such in at least 1 of the lists. Consequently, 77% (4690) of the unique substances is “non-evaluated”. The lists in which they are included is provided in **Figure 3**. Seventy-six percent (3565) of the non-evaluated compounds is intended to be used in printing inks but not in paper and board.

**3.3.Composition of the combined inventory by substance type**

**Figure 4** illustrates the classification of the 6073 unique substances of the combined inventory by substance type. Single substances account for the largest part of the inventory (42%), followed by polymers and mixtures. Finally, 20% are other substances, comprising among others metal complexes and inorganic substances.

Sixty-nine percent (1769) of the single substances are non-evaluated (**Figure 5**), which again is considerably higher than the percentage of evaluated ones. Most of the non-evaluated single substances are intended to be used in printing inks.

**3.4. Physicochemical properties of the non-evaluated single substances**

**Figure 6** shows the results of the analysis of the physicochemical properties of the 1769 non-evaluated single substances. One thousand seven hundred and twenty-one (97%) of the non-evaluated single substances have a molecular weight below 1000 g/mol, indicating that the vast majority has the potential to migrate from the FCM into the food. Substances with a low molecular weight could also become bioavailable after oral intake and consequently, induce a toxic effect. As 1530 (86%) of the non-evaluated single substances show not more than 1 violation of the Lipinski rule, these are likely to become bioavailable. Oral bioavailability has furthermore been linked to a polar surface area below or equal to 140 Angström and a number of rotating bonds below or equal to 10, which is the case for 1634 (92%) and 1339 (76%) of the compounds, respectively. Altogether, 1131 (64%) compounds meet all of the above criteria.

**3.5. Use of the non-evaluated single substances showing high migration and bioavailability potential for the manufacture of primary packaging FCM**

Of the 1131 substances that demonstrate physicochemical properties related to high migration and bioavailability potential, 1095 (97%) are used to produce primary packaging FCM, as indicated by the FACET tool.

**3.6. Registration under REACH and inclusion in lists with chemicals of (potential) concern compiled by ECHA**

Fifty-six percent (613) of the substances demonstrating physicochemical properties related to high migration and bioavailability potential and included in the FACET tool, are registered under the REACH regulation. For the registered substances, inclusion in ECHA lists containing substances of (potential) concern was verified. Up to 5959)to 59 ns eds dezelfde woorden te gebruiken...ken aangezien de inventory documents freely available zijn were found in the CoRAP list. An overview of these substances and their corresponding concerns is presented in Table 1 of the supplementary data. Eighteen of the registered substances were present in the SVHC list (**Table 3**). Toxicity to reproduction was the most prevalent reason of concern, followed by carcinogenicity. Importantly, two out of these 18 substances were included in Annex XIV, i.e. bis(4-aminophenyl)methane (CAS No: 101-77-9) and bis(2-methoxyethyl)ether (CAS No: 111-96-6). The phase-out of bis(4-aminophenyl)methane is caused by its carcinogenicity whereas bis(2-methoxyethyl)ether has been included in Annex XIV due to its toxicity to reproduction. Finally, one substance i.e. diethyleneglycol methyl ether (CAS No: 111-77-3), used as a solvent in printing inks, was found in Annex XVII. Since 27 June 2010, this substance can no longer be placed on the market for supply to the general public, as a constituent of paints, paint strippers, cleaning agents, self-shining emulsions or floor sealants in concentrations equal to or greater than 0.1 % by weight.

**4. Discussion**

As a result of food contamination issues due to migration of non-evaluated substances from non-plastic FCM, several initiatives have emerged in order to prevent similar food crises in the future. Most of these, however, are hampered by the lack of specific harmonised EU regulations for non-plastic FCM. Nevertheless, valuable information is already available in a number of documents, including the ESCO WG report on non-plastic FCM, the policy statements assembled by the Council of Europe on a variety of FCM and the Swiss Ordinance on materials and articles in contact with food. Furthermore, the Union list of authorised substances in plastic FCM is also an important information source for non-plastic FCM. In the current study, these four lists were combined into one inventory in order to investigate the extent to which printed paper and board FCM might contribute to food contamination issues. Although there was an overlap between the different lists for printing inks and/or paper and board, more than 6000 unique substances that can be used in the manufacture of printed paper and board FCM were identified.

The combined inventory provides a comprehensive overview of all these substances, together with information on their identity, physicochemical properties, type of use and evaluation status. Most of the substances included in the combined inventory are single substances, which was to be expected as the inventories were mainly built from the starting substances used in the manufacture of printed paper and board (and plastic) FCM. However, also a surprisingly high number of 1189 polymers is mentioned, of which the majority (828) is listed for use as additives in printing ink substances. The ‘other substances’ group is least represented, reflecting either limited application or lacking knowledge about their presence.

The majority of the substances present in the combined inventory are intended to be used in printing inks, which represents a higher concern compared to the rather ‘natural’ constituents of paper and board. Since 2005, more than 100 cases on the presence of photoinitiators in food have been reported via the RASFF tool (Lago et al., 2015; European Commission, 2016). This number is high, taking into account that photoinitiators represent only one type of compounds frequently used in printing inks. Furthermore, for some photoinitiators the available chemical information suggests that they are unsuitable for FCM use (Lago et al., 2015). 2,2-Dimethoxy-2-phenylacetophenone is such an example. The compound appears in part B of the Swiss list, where it is mentioned in both the additive and photoinitiator sublists. Although 2,2-dimethoxy-2-phenylacetone generates by-products like methyl benzoate, which is unsuitable for food packaging application because of its significant odour (Lago et al., 2015), the compound is still used by the printing ink industry (EuPIA, 2013).

For most of the substances included in the combined inventory, no (recent) safety evaluation has been performed. In reality, the fraction of non-evaluated compounds present in printed paper and board FCM is probably even higher, since the inventory lists mainly consist of starting substances. Non-intentionally added substances (NIAS) such as reaction products, intermediates and impurities should also be considered, since they have shown to be responsible for health risks in several cases (Nerin et al., 2013).

Non-evaluated substances will only be of concern for human health in case they migrate into the food. Consequently, it is important to examine their migration potential. Besides experimental testing, migration can be estimated using computer-based models. The FACET tool for example, includes a module to predict exposure to substances migrating from food packaging. However, modelling requires knowledge on many material-specific characteristics like number of layers in the packaging material, thickness and density of each layer and the area of contact between each layer and the food. Furthermore, migration of substances between packaging materials and food can only be modelled when the diffusion coefficient and partition coefficient are known. Identification of these parameters for all non-evaluated substances that can be used in a broad range of printed paper and board FCM is impossible. Determination of the exposure due to migration of the non-evaluated substances could therefore not be performed.

However, a first indication can be obtained through inspection of the substances’ physicochemical characteristics. The role of molecular weight and polarity in migration modelling has indeed been demonstrated previously (Hauder et al., 2013; Zülch and Piringer, 2010). Most non-evaluated single substances have a molecular weight below 1000 g/mol, indicating that they are likely to migrate. Depending on their hydrophilic-lipophilic character, they can also become bioavailable after oral intake and, consequently, exert (toxic) effects. Thus additional parameters linked to bioavailability are important to consider, e.g. the water solubility/octanol-water partition coefficient (log P) (Schilter et al., 2013), polar surface area (Ghose et al., 1999; Veber et al., 2002) and number of rotating bonds (Veber et al., 2002). The so-called Lipinski rule combines multiple parameters to estimate bioavailability. Although designed to identify biologically active compounds during drug development, the rule can also be of toxicological interest. About 70% of the non-evaluated single substances fulfilled all four criteria used to evaluate bioavailability and therefore, they are estimated to become bioavailable after oral intake. As already indicated, the parameters used here only provide a rough estimation. Refinement through switching from cut-off values to ranges could help to increase the prediction confidence (e.g. substances with a log P below 0 are unlikely to display bioavailability, implying a decreased risk for toxic effects). At present, such ranges have not yet been defined for FCM substances.

A large number of non-evaluated single substances has thus the potential to migrate into food and become bioavailable after oral intake. One limitation of the combined inventory is the lack of information with respect to the actual use of the different substances. Indeed, the appearance of a compound in the inventory indicates that its potential use as a printing ink and/or paper(board) FCM constituent has been recorded at least once. Whether it is still used today and at what frequency is unknown. This constraint has also been mentioned by Geueke and colleagues (2014), who compared FCM databases with inventories of chemicals of concern (COC) to identify potential toxic components. Preliminary information on the actual use of substances in FCM can however be obtained from the FACET tool, which contains a list of substances used for the manufacture of primary packaging FCM. This list has been compiled in collaboration with industry, hence non-evaluated substances present in this list are more likely to be used in FCM than those that are not included.

More than 95% of the non-evaluated substances with the potential to migrate and become bioavailable were indicated to be used in primary packaging FCM by the FACET tool. For these substances, the registration status under the REACH Regulation was checked. About 60% of the substances was found to be registered under REACH. Assuming that the unregistered substances are in agreement with the registration deadline, their production volume should be below 100 ton/year. Although registered non-evaluated substances are more likely to be produced in higher volumes than the non-registered ones, this does not necessarily implicate that they will be used more frequently in FCM. However, for these registered substances, inclusion in the ECHA lists containing substances of (potential) concern could be verified. Interestingly, 59 of the non-evaluated substances with the potential to migrate and become bioavailable were found in the CoRAP list. For these substances, initial concerns that they pose a risk to human health or environment have been raised. The outcome of the Member State evaluation will clarify whether the initial concern was justified or not, information that is also extremely relevant regarding their use in printed and board FCM. For the majority of the 59 substances, the Member State evaluation has not yet started or is still on-going. Interestingly, 18 substances were included in the SVHC and these substances are thus of real concern. In addition, two out of these 18 substances were even present in the Authorisation list. One additional substance was found on the Restriction list. For these 19 substances, the actual use in printed paper and board FCM should thus urgently be investigated.

Additional information is also required for many of the other non-evaluated compounds. Indeed, for the registered substances, it should be noted that the majority has not been subject to an independent evaluation. Information on the ECHA website has been introduced by the registrant. ECHA may examine any registration dossier to verify if the information submitted by registrants is compliant with the legal requirements, but these compliance checks are only required for 5% of the registration dossiers per tonnage band. Additionally, the number of substances for which a detailed assessment of the risks to human health or the environment has been performed by the European Member States, is limited. Furthermore, no data are available for all unregistered substances.

The problems associated with migration of non-evaluated substances from printed paper and board have also been recognised by the FCM industry. As a response, several manufacturers and industry organisations have recently implemented (in-house) guidance documents with lists of substances that can be used and/or should be avoided in the production of FCM. Some examples are the Nestlé Guidance Note on Packaging Inks (Nestlé, 2014) and the Industry guideline for the Compliance of Paper & Board Materials and Articles for Food Contact drafted by the Confederation of European Paper Industries (CEPI, 2012). Other interesting initiatives include for example the introduction of new barrier films for dry foods (pasta, cereals, rice) by different companies. These barriers should prevent migration of inks and their constituents from the packaging into the food (Seltenrich, 2015). At present, the efficacy of the barriers towards the large number of chemically divergent substances that can be used in printed paper and board FCM is not clear.

Ideally, the toxicological profile of all substances used in printed and board FCM should thus be characterised. As an in-depth safety assessment of this large number of non-evaluated substances is not feasible in the short term, strategies should be developed to further assign priority. One possibility would be to investigate which compounds are migrating from printed paper and board. However, as already indicated, migration depends on the characteristics of the food contact material (thickness, density,…) and of the type of food in contact with the material. Therefore, it is not feasible to evaluate the migration potential of all substances in all applications and all materials possible. Furthermore, compounds migrating in low quantities may remain undetected whereas they could have a bigger impact on human health than those migrating at higher levels (e.g. genotoxic carcinogens).

A promising approach consists of the application of *in silico* tools, computer-based methodologies that allow investigating the toxicological properties of compounds without experimental testing. Substances showing alerts for particular toxicological endpoints, could be assigned a high priority for further evaluation. The information required to perform the *in silico* predictions has already been included in the database. Consequently, the combined inventory could serve as a basis for future priority setting of non-evaluated substances used in printed and board FCM.

**5. Conclusion**

Analysis of available legislative and inventory documents shows that over 6000 unique substances can be used in the manufacture of printed paper and board FCM. The vast majority of them are considered non-evaluated, pointing out an important knowledge gap in the safety evaluation of these substances. Furthermore, based on a preliminary study of the physicochemical properties of the substances, it is estimated that 64% of the non-evaluated single substances have the potential to migrate into the food and become bioavailable after oral intake. Importantly, 19 of these are present in one of the lists with substances of concern compiled by the European Chemicals Agency (ECHA). To prevent future food safety issues, the actual use of these substances in printed paper and board FCM should be urgently investigated.

**Conflicts of interest**

The authors declare that there are no conflicts of interest.

**Acknowledgements**

This work was supported by the Belgian Scientific Institute of Public Health.

**References**

CEPI, 2012. Industry guideline for the Compliance of Paper & Board Materials and Articles for Food

Contact. Available from: <http://www.cepi.org/system/files/public/documents/publications/foodcontact/2012/Industry%20guideline-updated2012final.pdf> (last accessed 08.06.16).

Council of Europe, 2009. Resolution ResAp (2002) 1 on paper and board materials and articles

intended to come into contact with foodstuffs. Available from: <http://www.coe.int/t/e/social_cohesion/soc-sp/public_health/food_contact/PS%20PAPER%20AND%20BOARD%20Version%204%20E.pdf> (last accessed 08.06.16).

de Fatima Poças, M., Hogg, T., 2007. Exposure assessment of chemicals from packaging materials in

 foods: a review. Trends Food Sci. Tech. 18, 219-230.

ECHA, 2016. ECHA Database. Available from: http://[www.echa.europa.eu](http://www.echa.europa.eu)/ (last accessed 15.06.16).

EFSA, 2005. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and

Materials in Contact with Food on a request from the Commission related to 2-isopropylthioxanthone (ITX) and 2-ethylhexyl-4-dimethylaminobenzoate (EHDAB) in food contact materials. EFSA J. 293, 1-15.

EFSA, 2009. EFSA statement on the presence of 4-methylbenzophenone found in breakfast cereals,

 EFSA J. RN-243, 1-19.

EFSA, 2011a. Report of ESCO WG on non-plastic Food Contact Materials. Available from:

http://www.efsa.europa.eu/sites/default/files/scientific\_output/files/main\_documents/139e.pdf (last accessed 08.06.16).

EFSA, 2011b. EFSA Scientific Cooperation Working Group non-plastic food contact materials table.

Available from: <http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/139eax1.xls> (last accessed 08.06.16)

EFSA, 2015. Food Contact Materials. Available from:

<http://www.efsa.europa.eu/en/topics/topic/foodcontactmaterials> (last accessed 08.06.16).

EuPIA, 2013. EuPIA Suitability List of Photo-Initiators for Low Migration UV Printing Inks and

Varnishes. Available from: <http://www.eupia.org/uploads/tx_edm/130219_corr3_EuPIA_Suitability_List_of_Photoinitiators_for_Low_migration_UV_Printing_Inks_and_Varnishes.pdf> (last accessed 08.06.16).

European Commission, 2016. Rapid Alert System in Food and Feed. Available from:

 <http://ec.europa.eu/food/safety/rasff/portal/index_en.htm> (last accessed 08.06.16).

European Communities, 1984. Council Directive 84/500/EEC of 15 October 1984 on the

approximation of the laws of the Member States relating to ceramic articles intended to come into contact with foodstuffs. Off. J. Eur. Communities L227, 12-16.

European Union, 2004. Regulation (EC) No 1935/2004 of the European Parliament and of the Council

of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC. Off. J. Eur. Union L338, 1-20.

European Union, 2006. Regulation (EC) No 1907/2006 of the European Parliament and of the

Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Off. J. Eur. Union L396, 1-849.

European Union, 2007. Commission Directive 2007/42/EC of 29 June 2007 relating to materials and

articles made of regenerated cellulose film intended to come into contact with foodstuffs. Off. J. Eur. Union L172, 71-82.

European Union, 2008. Regulation (EC) No 282/2008 of the European Parliament and of the Council

of 27 March 2008 on recycled plastic materials and articles intended to come into contact with foods and amending Regulation (EC) No 2023/2006. Off. J. Eur. Union L86, 9-18.

European Union, 2009. Regulation (EC) No 450/2009 of the European Parliament and of the Council

of 29 May 2009 on active and intelligent materials and articles intended to come into contact with foods. Off. J. Eur. Union L135, 3-11.

European Union, 2011. Regulation (EC) No 10/2011 of the European Parliament and of the Council of

14 January 2011 on plastic materials and articles intended to come into contact with food. Off. J. Eur. Union L12, 1-138.

European Union, 2012. Food Contact Materials – Specific provisions for materials other than plastics

– implementing measure (Roadmap). Available from: http://ec.europa.eu/governance/impact/planned\_ia/docs/2014\_sanco\_005\_fcm\_specific\_provisions\_for\_materials\_other\_than\_plastics\_en.pdf (last accessed 08.06.16).

European Union, 2015a. Food Contact Materials brochure. Available from:

http://ec.europa.eu/food/safety/docs/cs\_fcm\_brochure\_en.pdf (last accessed 08.06.16).

European Union, 2015b. References of the European and national legislations (Working document-

Updated version February 2015). Available from: http://ec.europa.eu/food/safety/docs/cs\_fcm\_non-harmonised.pdf (last accessed 08.06.16).

Geueke, B., Wagner, C.C., Muncke, J., 2014. Food contact substances and chemicals of concern: a

comparison of inventories. Food Add. Contam. Part A. Chem. Anal. Control Expo. Risk Assess. 31:8, 1438-1450.

Ghose, A.K., Viswanadhan, V.N., Wendoloski, J.J., 1999. A knowledge-based approach in designing

combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. J. Comb. Chem. 1, 55–68.

Grob, K., Biedermann, M., Scherbaum, E., Roth, M., Rieger, K., 2006. Food contamination with

organic materials in perspective: Packaging materials as the largest and least controlled source? A view focusing on the European situation. Cri. Rev. Food Sci. Nutr. 46:7, 529-535.

Hauder, J., Benz, H., Rüter, M., Piringer, O.-G. 2013. The specific diffusion behaviour in paper and

migration modelling from recycled board into dry foodstuffs. Food Contam. Add. Part A. Chem. Anal. Control Expo. Risk Assess. 30:3, 599-611.

Hearty, A., Gibney, M.J., Vin, K., LeClercq, C., Castle, L., O’Mahony, C., Oldring, P. K. T.,

Volatier, J. L., Mckevitt, A., Tennant, D., McCamara, C., Kettlitz, B. 2011. The FACET

project: a chemical exposure surveillance system for Europe. Food Sci. Technol. 25, 26-29.

Lago, M.A., Rodríguez-Bernaldo de Quirós, A., Sendón, R., Bustos, J., Nieto, M.T., Paseiro, P., 2015.

Photoinitiators: a food safety review. Food Add. Contam. Part A. Chem. Anal. Control Expo. Risk Assess. 32:5, 779-798.

Leks-Stepien, J., 2011. Paper packaging materials and food safety. Int Circ Educ Inst Graph Arts:

 Technol Manag. 4, 49–51.

Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 1997. Experimental and computational

approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 23, 3-25.

National Institutes of Health, 2016. ChemIDplus Database. Available from:

 <http://chem.sis.nlm.nih.gov/chemidplus/> (last accessed 14.03.16).

Nerin, C., Alfaro, P., Aznar, M., Domeno, C., 2013. The challenge of identifying non-intentionally

 added substances from food packaging materials: A review. Anal. Chim. Acta. 775, 14– 24.

Nestlé, 2014. Nestlé guidance note on packaging inks.

Royal Society of Chemistry, 2016. ChemSpider Database. Available from:

 http://[www.chemspider.com](http://www.chemspider.com)/ (last accessed 14.03.16).

Schilter, B., Benigni, R., Boobis, A., Chiodini, A., Cockburn, A., Cronin, M.T.D, Lo Piparo, E., Modi, S.,

Thiel, A., Worth, A., 2013. Establishing the level of safety concern for chemicals in food without the need for toxicity testing. Reg. Tox. Pharm. 68, 275-296.

Seltenrich, N., 2015. A Hard Nut to Crack: Reducing Chemical Migration in Food-Contact Materials.

 Environ. Health. Perspect. 123, A174–A179.

Swiss Confederation, 2005. Ordinance of the FDHA on articles and materials of 23 November 2005

(RS 817.023.21). Available from: <https://www.admin.ch/opc/fr/classified-compilation/20050179/201304010000/817.023.21.pdf> (last accessed 08.06.16).

Veber, D.F., Johnson, S.R., Cheng, H.Y., Smith, B.R., Ward, K.W., Kopple, K.D., 2002. Molecular

properties that influence the oral bioavailability of drug candidates. J. Med. Chem. 45, 2615–2623.

Zülch, A., Piringer, O., 2010. Measurement and modelling of migration from paper and board into

foodstuffs and dry food simulants. Food Contam. Add. Part A. Chem. Anal. Control Expo. Risk Assess. 27:9, 1306-1324.

**Figure 1.** Number of substances listed for printing ink, paper(board) and plastic FCM. Union list, Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food; CoE list, Resolution of the Council of Europe on paper and board materials and articles intended to come into contact with foodstuffs; ESCO list, EFSA Scientific Cooperation Working Group report on non-plastic FCM: Paper and board section; Swiss list, Swiss Ordinance on Materials and Articles in Contact with Food: Annex 6.

**Figure 2.** Number (%) of substances per FCM application (list). A) Printing inks and/or paper(board); B) Printing inks and/or paper(board) and/or plastic. The list abbreviations used are as indicated in Figure 1.

**Figure 3.** Number (%) of non-evaluated substances per FCM application (list). The list abbreviations used are as indicated in Figure 1.

**Figure 4.** Composition of the combined inventory by substance type

**Figure 5.** Distribution of (non-)evaluated single substances

**Figure 6.** Physicochemical properties of non-evaluated single substances related to migration (molecular weight) and bioavailability (other). The dotted line indicates the predefined cut-off. Red bars, substances with results below the cut-off; blue bars, substances with results above the cut-off; grey bars, no data. A) Molecular weight (g/mol); B) Number of Lipinski rule of 5 violations; C) Polar surface area (Angström) and D) Number of rotating bonds.

**Table 1.** Classification of printed paper and board substances by their evaluation status. N/A: not applicable

**Table 2.** Number (%) of evaluated and non-evaluated substances among printing ink (Swiss list), paper(board) (CoE and ESCO list) and plastic (Union list) FCM substances. The list abbreviations used are as indicated in Figure 1. N/A: not applicable

**Table 3.** Overview of the substances demonstrating physicochemical properties related to high migration and bioavailability potential and included in both the FACET tool and the Candidate List of Substances of Very High Concern (SVHC) (consulted on June 15, 2016). PBT: Persistent, Bioaccumulative and Toxic substances; vPvB: very Persistent and very Bioaccumulative substances.