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A Safety Evaluation of Printed Paper and Board Contaminants: Photo-Initiators as a Case Study

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Introduction

Consumers are exposed to a range of substances that can damage their health. Until recently, food packaging as a source of contaminants has received little attention despite its ubiquitous use (Muncke, 2009). Several food crises at the end of the previous decade highlighted the need for more information about compounds used in food contact materials (FCMs). In 2005, Italian authorities withdrew 30 million liters of infant milk from the market due to the presence of the photo-initiator 2-Isopropylthioxanthone (ITX) in a concentration ranging from 120 to 300 $\mu g\ L^{-1}$ (IBFAN, 2005), followed by additional withdrawals in France, Spain and Portugal (Aparicio and Elizalde, 2015). The impact on public opinion was so high that the Scientific Panel on Food Additives, Flavoring, Processing Aids and Materials in Contact with Food (AFC) of the European Food Safety Authority (EFSA) drafted an opinion in December of the same year on the risk for human health associated with the use of ITX in FCM. The panel concluded that the existing in vivo genotoxicity studies did not indicate a genotoxic potential for ITX and therefore the specific migration limit (SML) was set at 50 $\mu g\ kg^{-1}$(EFSA, 2005). In 2009, the photo-initiator 4-methylbenzophenone used in printing inks was found in breakfast cereals. Concentrations up to 3729 $\mu g\ kg^{-1}$of 4-methylbenzophenone and 4210 $\mu g\ kg^{-1}$ of benzophenone in cereals were reported in Belgium (FASFC, 2009). Due to the lack of toxicological data for 4-methylbenzophenone, the EFSA performed an urgent safety evaluation based on a read across approach with toxicological data from benzophenone and hydroxybenzophenone. It was concluded that 4-methylbenzophenone, like benzophenone, is expected to be a non-genotoxic carcinogen and that short-term consumption of contaminated breakfast cereals at the levels reported should not pose a risk to human health (EFSA, 2009a,b). Since then, several other alerts for food contamination due to the migration of photo-initiators and other FCM-related compounds have occurred (Aparicio and Elizalde, 2015). The growing concern related to FCMs was confirmed by EFSA and they emphasized that recent food crises were mainly originating from non-plastic components of FCMs such as printing inks, paper and board, coatings, etc (EFSA, 2012a).

In order to protect consumers against unwanted health effects caused by migration of chemical substances from FCMs into food, all materials and articles intended to come in contact with food should comply with the general criteria laid down in EU Regulation (EC) No. 1935/2004, i.e., they should not transfer their constituents into food in quantities that could endanger human health or bring about unacceptable changes in composition or organoleptic characteristics of food (European Union, 2004). In addition, EU Commission Regulation (EC) 2023/2006 on good manufacturing practice for materials and articles intended to come into contact with food ensures that the manufacturing process is well controlled (European Union, 2006a). However, specific European Regulations only exist for a limited number of materials. The most comprehensive specific EU measure is Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food. This Regulation specifies restrictions on the use of certain substances as monomers or other starting substances, additives excluding colorants, polymer production aids excluding solvents and macromolecules obtained from microbial fermentation. In order for a substance to be included in this Union list, a risk assessment by EFSA or the Scientific Committee on Food (SCF) must have been conducted (European Union, 2011). Since no harmonized European regulation is available for the majority of FCMs, the Council of Europe has established general recommendations for various types of materials such as coatings (Council of Europe, 2004a), inks (Council of Europe, 2005), paper and board (Council of Europe, 2002), rubber (Council of Europe, 2004b), etc. These recommendations contain inventory lists mentioning monomers, additives, solvents and other starting products, together with the outcome of their toxicological evaluation - whenever this information is available. However, these Resolutions are not legally binding, unless they are transposed into national legislation. In 2010, an EFSA Scientific Cooperation (ESCO) Working Group was established in order to collect the evaluations carried out in the Member States, Switzerland and Norway of the substances used in non-plastic FCM types. Substances used for the manufacture of paper and cardboard, printing inks, coatings, rubber, colorants, wood and cork and evaluated at national level were inventoried. However, many of these evaluations are old (i.e., before 1991) and do therefore not necessarily comply with the guidelines

adopted by the SCF for the evaluations of substances used for plastic FCMs, or the data and background for their evaluation could not be traced back. Therefore, substances of the ESCO inventory list are divided into two groups, according to their date of evaluation. Importantly, most of the substances are included in list B, indicating that they have been evaluated before 1991 (EFSA, 2012a).

Both the inventory lists of the Council of Europe and the ESCO WG highlight that for thousands of substances used in non-plastic FCMs, no safety evaluation has been performed at the European level. Therefore, a strategic approach is urgently needed in order to assign priority to compounds requiring further evaluation. Printed paper and board cover a large part of the non-plastic FCMs. Specifically for food packaging, these materials are used very frequently. Indeed, 90% of all manufactured food is sold in printed packages (Lago et al., 2015), and paper and board have been the most important packaging materials for years (Leks-Stepien, 2011).

In this article, an overview of the most common contaminants originating from printed paper and board FCMs are given. Specific attention is paid to one class of substances, i.e., photo-initiators that are widely used in UV-cured inks. A case study evaluating the potential human health risks associated with migration of these photo-initiators is presented. First, the exposure to a selection of 17 photo-initiators was evaluated using the results of a Belgian market. Next, a preliminary risk assessment was performed for the detected photo-initiators. For the evaluated substances, the concentrations in the food were compared to their Specific Migration Limit (SML). For the other substances, it was assessed whether the photo-initiators had been subjected to a toxicological evaluation at the European level in a non-FCM context. In cases where adequate toxicological information could be retrieved from these evaluations, a risk assessment was performed using these data. For the other substances, the Threshold of Toxicological Concern (TTC) approach was applied.

Contaminants Originating From Printed Paper and Board Food Contact Materials

Printed paper and board FCMs can contain a large number of non-evaluated substances that may migrate into food (European Parliament, 2016; Liu et al., 2016; Muncke et al., 2014; Van Bossuyt et al., 2016). As a result, concerns have been raised about potential adverse health effects associated with these migrants. The concerns are justified especially since migration from FCMs is estimated to be the main source of food contamination, quantitatively exceeding most others including pesticide residues by a factor of 100–1000 (Grob et al., 2006).

Different inventories on substances known and used in FCMs have been developed over recent years. One of the most comprehensive databases is the 'Database of substances known by the Member States of the Council of Europe and used in FCM.' This database includes nearly 10,000 substances known by the Member States of the Council of Europe and used in FCMs and was developed based on the information available from national legislations, Regulations and Directives of the European Commission and Resolutions of the Council of Europe for all types of FCM. It is a comprehensive database containing both evaluated and non-evaluated substances with references to existing regulations. Each entry within the database consists of a chemical identifier in the form of name or CAS number which was used to retrieve information on chemical and physical properties of the substance from PubChem. Subsequently, information related to carcinogenicity, mutagenicity, reproductive toxicity and skin sensitization potential of the compounds was added based on the predictions of the in silico tool VEGA-QSAR, a platform for predictive toxicology comprising QSAR models for regulatory purposes. The database can be accessed at: https://fcm.wiv-isp.be/ and is currently being used as a unique and valuable resource by companies, regulatory bodies and research institutions for obtaining documented information on substances used in FCMs. Access to the database for public stakeholders is granted free of charge, whereas industries and industrial organizations can obtain an access after the payment of a yearly subscription fee.

Geueke et al. (2014) have also developed an inventory by combining the following three lists of FCM substances: the 2013 Pew Charitable Trusts database of direct and indirect food additives legally used in the United States (1) (Neltner et al., 2013), Annex I of EU Regulation No 10/2011 containing all substances that are allowed to be used in plastic FCMs (2) and the list of substances authorized in non-plastic FCMs by the European Member States, Switzerland and Norway and compiled by the ESCO WG of EFSA (3) (EFSA, 2012a). Afterward, this inventory was compared with the Substitute it Now! (SIN) list 2.1., which includes the chemicals fulfilling the criteria listed in Article 57 of Regulation (EC) No. 1907/2006 (REACH), and the TEDX database of endocrine disrupting chemicals. A total of 175 chemicals used in FCMs were identified as Compounds of Concern (COCs) (Geueke et al., 2014). Although this strategy clearly demonstrated how toxicological information available in different databases like the SIN list and TEDX database can be used for the prioritization of the substance, many substances specific for printed paper and board and listed in the Resolutions of the Council of Europe was not taken into consideration in this study.

An inventory dedicated only to printed paper and board FCMs was developed by Van Bossuyt et al (Van Bossuyt et al., 2016). The inventory was based on a variety of documents listing substances that can be used in printing inks or paper and board FCMs:

- Swiss Ordinance on Materials and Articles in Contact with Food: Annex six

Switzerland, as a member of the European Free Trade Association (EFTA), has adopted specific legislation on printing inks used in FCMs. 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 the annexes of the Ordinance. Each annex is further subdivided into parts A and B, with part A containing the evaluated substances that have been subjected to officially recognized

scientific testing (e.g., by EFSA) and part B containing the substances for which this is not the case. The use of substances in part B is permitted if no transfer to food or food simulants can be detected with a limit of detection of 0.01 mg kg^{-1} simulant.

- Resolution of the Council of Europe on paper and board materials and articles intended to come into contact with food

The Council of Europe has compiled resolutions for several non-plastic FCMs including paper and board. These policy statements are meant to serve as guidance in case no specific regulation is adopted for a particular FCM group. Resolution ResAp (2002)1 (Council of Europe, 2002) is completed by Technical Documents listing the additives and monomers for the manufacture of polymeric additives that may be used in paper and board FCMs. These lists are further divided into sub-lists of substances that are approved (i.e., assessed) and substances that are not approved (i.e., not yet assessed). Furthermore, a third sub-list contains substances approved by Partial Agreement MS or by the United States Food and Drug Administration (FDA).

- EFSA Scientific Cooperation Working Group report on non-plastic FCM: Paper and board section (EFSA, 2012a)

In 2010, EFSA assembled an ESCO WG in order to gather the information on substances used in non-plastic FCM that were evaluated in the European Member States, Switzerland and Norway. Seven FCM types (i.e., paper and board, colorants, rubber, silicones, printing inks, coatings, and cork and wood) were considered. Depending on the time of their safety evaluation, substances 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, 2012a).

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

The European Union list of authorized substances for plastic FCM applications was established in 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 FCMs are likely to also get approval for the fabrication of non-plastic FCMs.

Although there was an important overlap between the different lists for printing inks and/or paper and board, more than 6000 unique substances were identified that can be used in the manufacture of printed paper and board FCMs.

The combined inventory of Van Bossuyt et al. (2016) provides a comprehensive overview of all these substances, together with information on their identity, physicochemical properties, type of use and evaluation status. The majority of the substances (77%, i.e., 4690 out of 6073 substances) were considered non-evaluated in terms of potential toxicity. Since detailed safety evaluation of all these substances is not feasible, a pragmatic approach was developed in order to identify substances that might be of potential concern for human health and that would require further evaluation. Van Bossuyt et al. (2017) developed such an approach based on the in silico predictions for genotoxicity using a combination of 4 (quantitative) structure-activity relationship ((Q)SAR) tools. Within the strategy, focus was put on genotoxicity as this important toxicological endpoint has been associated with serious health effects including cancer, degenerative diseases, reduced fertility and inherited diseases (Erickson, 2010; Hoeijmakers, 2009; Kong et al., 2012). Consequently, results of genotoxicity tests are key elements in the risk assessment of chemicals in general, including those present in food and feed (EFSA, 2011). For substances intended to be included in Annex I of Regulation (EU) No. 10/2011, genotoxicity tests also have to be performed, independent of the level of migration of the compound.

The (Q)SAR models were selected in such a way that they were sufficiently diverse, not only regarding their prediction method (SAR/QSAR), but also with respect to their availability (free/commercial). For each system, the prediction model(s) related to Ames mutagenicity was (were) applied. An overview of the selected in silico tools present in the strategy of Van Bossuyt et al. (2017) and their specifications is given in **Table 1**.

However, it should be noted that not all non-evaluated substances could be evaluated using the in silico tools. Most of the substances were not eligible for straightforward in silico processing due to their chemical structure (e.g., polymers, mixtures, complexes, inorganic substance) or the absence of a CAS No. and/or SMILES (i.e., Simplified Molecular-Input Line-Entry System) that are needed to process the substances in the different in silico tools. Therefore, only 1723 (out of 4690) substances were retained for the analysis. The results are demonstrated in **Fig. 1**.

One hundred and six substances were predicted positive in the 4 (Q)SAR Ames mutagenicity tools, while 572 substances were predicted negative in all tools. Subsequent priority ranking to determine the urgency for an in-depth safety evaluation was

Table 1 Model descriptions used in the strategy of Van Bossuyt et al., 2017

Software	*Version*	*Model name*	*Method*	*Applicability domain (AD)*	*Availability*
Toxtree	Toxtree (2.6.0)	In vitro mutagenicity alerts (Ames test) by ISS	SAR	Not available	Freeware
VEGA	VEGA (1.1.1)	Mutagenicity (Ames test) model (CAESAR) v.2.1.13	QSAR	VEGA ADI	Freeware
		Mutagenicity (Ames test) model (SarPy/IRFMN) v.1.0.7	QSAR	VEGA ADI	
		Mutagenicity (Ames test) model (ISS) v.1.0.2	SAR	VEGA ADI	
Derek	Derek Nexus (4.1.0)	Mutagenicity in vitro	SAR	Not available	Commercial
Sarah	Sarah Nexus (1.2.0)	Ames mutagenicity	QSAR	Sarah AD	Commercial

AD(I), applicability domain (index); *(Q)SAR*, (quantitative) structure-activity relationship.

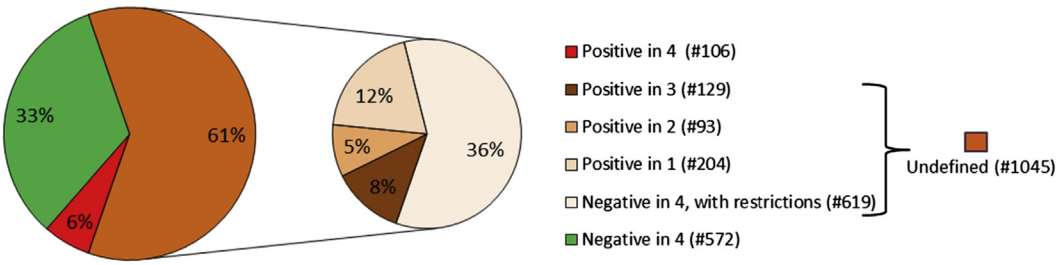

Figure 1 Distribution of the substances according to overall negative (green), positive (red) or undefined (orange) prediction for AMES mutagenicity when combining 4 (Q)SAR tools (pie). The undefined results are subdivided in substances generating a positive outcome in one up to three tools or substances negative in all four but outside domain (stacked bar) (Van Bossuyt et al., 2017).

established by investigating the availability (and quality) of experimental toxicological data within the (Q)SAR tools. Information provided within the models allowed identification of 53 substances for which Ames mutagenicity prediction already has in vitro Ames test results. For the other 53 substances, no experimental data are available in the (Q)SAR systems. An overview of these substances is given in **Table 2**.

Subsequently, their experimental mutagenicity potential should be investigated urgently by consulting the literature and, if necessary, further in vitro and in vivo testing.

Finally, it should be emphasized that genotoxic compounds are not necessarily excluded as starting product for the manufacture of FCMs. For example, in the Annex I of Regulation (EU) No. 10/2011, some genotoxicants are included. Importantly, one of the requirements associated with their use is that no migration into the food occurs. If no migration occurs, the consumer will not be exposed to the genotoxic compound, and consequently, will not be at risk.

Based on the work of Van Bossuyt et al. (2017), it can be concluded that in silico tools can have an important role in the prioritization of substances in terms of potential genotoxicity.

Photo-Initiators as a Case Study

A specific class of substances commonly present in printed paper and board FCMs are the photo-initiators. Mixtures of photo-initiators are commonly used in the formulation of inks, particularly ultraviolet (UV) light-cured inks. After exposure to light, the photo-initiator decomposes into free radicals that trigger the polymerization reaction which causes the ink to cure onto the substrate. Consequently, drying times are much shorter for UV-cured inks than those with conventional solvent or water-based coatings. Nevertheless, residues of unreacted photo-initiators are still able to migrate from the printed food contact material into the food.

This is illustrated by the large number of notifications in the Rapid Alert System for Food and Feed (RASFF). The RASFF was put in place to provide food and feed control authorities with an effective tool to exchange information about serious risks detected in relation to food or feed. This exchange of information helps EU Member States to act more rapidly and in a coordinated manner in response to a health threat caused by food or feed. In the period from 2000 until 2011, 143 notifications corresponded to migration of photo-initiators from food packaging. An overview of RASFF notifications of photo-initiators from 2000 till 2011 is given in **Table 3** (Aparicio and Elizalde, 2015).

Evaluation of the Exposure to Photo-Initiators

Due to the ITX- and benzophenone crises in 2005 and 2009, respectively, these photo-initiators are the most widely studied. Pastorelli et al. (2008) investigated the migration behavior of benzophenone from printed paperboard packages to cakes through different films and showed that not all secondary packaging materials serve as functional barriers. Furthermore, recycled carton board can be used in direct contact with dry food, and often significantly higher levels of contaminants were observed in food packaging materials made from recycled materials (Nicoletta et al., 2013). As a result, photo-initiators can also be present in recycled materials, even though the packaging itself has not been printed with UV-cured inks, due to incomplete removal of the photo-initiators during the recycling process (Anderson and Castle, 2003; Brauer and Funke, 2008).

In 2007, a market survey was conducted by Rothenbacher et al. (2007) to evaluate the occurrence of ITX on the German market. In this study, the packaging material of 137 food products was screened for the presence of ITX. In case of positive findings, the food itself was tested for ITX. In 26% of the packages, ITX was found and a significant migration was observed in 27 foods (20%). More recently, Bradley et al. (2013) demonstrated the migration of typical printing ink compounds into food in a UK survey. The presence of benzophenone (BP), 4-phenylbenzophenone (PBZ), methyl-2-benzoylbenzoate, 1-hydroxycyclohexyl phenyl ketone (HCPK), 2,2-dimethoxy-2-phenylacetophenone (DMPA), 4-(4-methylphenylthio)benzophenone, ethyl-4-dimethylaminobenzoate (EDMAB) and 2-ethylhexyl-4-dimethylaminobenzoate (EDB) was confirmed in both the food and the packaging material (Bradley et al., 2013).

Table 2 Overview of substances, listed for use in printed paper and board FCM, predicted positive for Ames mutagenicity in 4 (Q)SAR tools and requiring experimental testing (Van Bossuyt et al., 2017)

CAS No.	*Name*
82-38-2	Solvent red 111
136-84-5	2-Imidazolidinone, 1,3-bis(hydroxymethyl)-
624-65-7	Propyne, 3-chloro-
938-18-1	Benzoyl chloride, 2,4,6-trimethyl-
1208-52-2	2,4′-Diaminodiphenylmethane
1606-83-3	2-Propanol, 1,1′-(2-butynylenedioxy)bis[3-chloro-
1719-57-9	Silane, chloro(chloromethyl)dimethyl-
1742-95-6	Naphthalimide, 4-amino-
2095-03-6	Oxirane, 2,2′-[methylenebis(4,1-phenyleneoxymethylene)]bis-
2238-07-5	Ether, bis(2,3-epoxypropyl)
2478-20-8	Solvent Yellow 44
2530-83-8	[3-(2,3-Epoxypropoxy)propyl]trimethoxysilane
2602-34-8	Oxirane, 2-[[3-(triethoxysilyl)propoxy]methyl]-
2897-60-1	Silane, [3-(2,3-epoxypropoxy)propyl]diethoxymethyl-
3049-71-6	Pigment red 178
3126-95-2	Oxirane, (propoxymethyl)-
3176-79-2	Solvent red 25
3271-22-5	2,4-Dimethoxy-6-(1-pyrenyl)-1,3,5-triazine
3454-29-3	Trimethylolpropane triglycidyl ether
4378-61-4	Pigment red 168
4482-25-1	1,3-Benzenediamine-4,4′-[(4-methyl-1,3-phenylene) bis(azo)] bis[6-methyl-
5026-74-4	2-Oxiranemethanamine, N-[4-(oxiranylmethoxy)phenyl]-N-(oxiranylmethyl)-
6410-38-4	Pigment red 9
6448-95-9	Pigment red 22
6471-50-7	Pigment red 14
6539-67-9	Reactive Yellow 3
6655-84-1	Pigment red 17
7328-97-4	Ethane, 1,1,2,2-tetrakis[p-(2,3-epoxypropoxy)phenyl]-
12,225-06-8	Pigment red 176
12,236-64-5	Pigment orange 38
13,236-02-7	Propane, 1,2,3-tris(2,3-epoxypropoxy)-
14,228-73-0	Cyclohexane, 1,4-bis[(2,3-epoxypropoxy)methyl]-
16,096-30-3	Oxirane, 2,2′-[(1-methyl-1,2-ethanediyl) bis(oxymethylene)]bis-
16,096-31-4	Oxirane, 2,2′-[1,6-hexanediylbis(oxymethylene)]bis-
16,403-84-2	Pigment red 268
25,188-42-5	Direct red 81
28,804-47-9	Toluenesulfonic acid, methyl ester
31,482-56-1	Disperse orange 25
36,215-07-3	Propane, 1-chloro-3-methoxy-
36,968-27-1	Pigment red 266
39,817-09-9	Bisphenol F diglycidyl ether
50,593-68-5	1H-Indazole, 3-chloro-6-nitro-
52,373-93-0	2,3-Anthracenedicarbonitrile, 1-amino-4-(ethylamino)-9,10-dihydro-9,10-dioxo-
56,396-10-2	Pigment red 213
59,487-23-9	Pigment red 187
61,847-48-1	Pigment red 188
1951-98-251920-12-8	Pigment red 185
62,570-50-7	2-Anthracenecarbonitrile, 1-amino-4-(ethylamino)-9,10-dihydro-9,10-dioxo-
67,990-05-0	Pigment red 269
68,227-78-1	Pigment red 147
68,516-75-6	Pigment Brown 41
68,818-86-0	Anthracene, 9,10-diethoxy-
74,336-59-7	Pigment orange 67

Table 3 RASFF notifications on photo-initiators in the period 2000–11 (Aparicio and Elizalde, 2015)

Photo-initiators	*Abbreviation*	*RASFF notifications (year)*
Benzophenone	BP	5 (2009), 5 (2010), 3 (2011)
4-Methylbenzophenone	MBP	5 (2009)
α-Hydroxycyclohexylphenylketone	HCPK	1 (2009), 1 (2010), 3 (2011)
Methyl-2-benzoylbenzoate	/	1 (2009), 2 (2011)
2-Isopropylthioxanthone	ITX	61 (2005), 56 (2006), 1 (2009), 1 (2010)
2-Hydroxy-2-methylpropiophenone	/	1 (2009)
4-Phenylbenzophenone	PBZ	1 (2009)
2-Methyl-4′-(methylthio)-2-morpholinopropiophenone	/	1 (2009), 2 (2010), 3 (2011)
Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide	/	1 (2009)
Ethyl-4-dimethylaminobenzoate	EDMAB	2 (2010), 3 (2011)
2,4-Diethylthioxanthone	/	2 (2010), 3 (2010)

In a German surveillance study from 2008 to 2011, 99 food products were screened for the presence of photo-initiators and amine synergists (Jung et al., 2013). Ninety nine food samples were analyzed and photo-initiators and/or amine synergists were detected in 33 samples. For 12 of the 23 food samples in which benzophenone (BP) was quantified, the SML of 0.6 mg kg^{-1} (as mentioned in the Swiss Ordinance on Materials and Articles in Contact with Food) was exceeded. Some products also violated the SML listed in the Swiss Ordinance on Materials and Articles in Contact with Food (Swiss Confederation, 2005) for ethyl-4-dimethylaminobenzoate (EDMAB), 2-ethylhexyl-4-(dimethylamino)-benzoate (EDB), methylbenzophenone (MBP) and methyl-*o*-benzoylbenzoate.

Finally, a market survey was conducted in Belgium by Van den Houwe et al (Van den Houwe et al., 2016). investigating 97 dry foods purchased on the Belgian market for the presence of 17 photo-initiators. An overview of the photo-initiators included in this study is given in **Fig. 2** and **Table 4**.

Table 4 also mentions the SML, if available, of the photo-initiators included in this study. It should be noted that the SML for Ethyl-4-dimethylaminobenzoate (EDMAB) and 2-Hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (HMMP) were under re-evaluation. However, the Swiss Ordinance on Materials and Articles in Contact with Food was recently updated (first of May 2017) and the evaluation of the substances has been completed; an SML of 0.05 mg kg^{-1} was allocated to both EDMAB and HMMP. Since the samples of the market survey, conducted by Van den Houwe et al. (2016) were purchased in 2014, the previous version of the Swiss Ordinance was still applicable. Therefore, these substances were considered as non-evaluated for the current risk assessment, but the update of the Swiss Ordinance will be taken into account in the discussion of the results.

The dry foods of the market survey conducted by Van den Houwe et al. (2016) were analyzed using a method described by Gallart-Ayala et al. (2011). that was modified in order to be less time-consuming and more easily transferable to different laboratories. The dry food was extracted with acetonitrile by vortex extraction. Afterward, Carrez I (i.e., zinc sulfate heptahydrate) and Carrez II (i.e., potassium hexacyanoferrate(II) trihydrate) were added to precipitate fatty residues. After centrifugation, the extract was analyzed by liquid chromatography in combination with tandem mass spectrometry (LC-MS/MS). The method has been validated in-house in terms of linearity, recovery, precision, specificity, limit of detection and limit of quantification and was subsequently used for the analysis of the dry food of the market survey. An overview of the samples included in the market survey is given in **Table 5**.

In 89% of the samples, at least one photo-initiator was detected. The photo-initiators BP, EDMA and DMPA were most frequently found, while some photo-initiators (CPTX, DEAB, DMBP, HCPK, HMBP and MK) were never detected (Van den Houwe et al., 2016). The results are greatly consistent with the German market survey performed by Jung et al. (2013). The presence of BP, DMPA and EDMAB photo-initiators cannot be related to the type of dry food, the choice in brand or house brand, nor the presence of a secondary packaging material. Most samples resulted in concentrations lower than 10 μg kg^{-1} for DMPA and EDMAB. Nevertheless, two out of three rice samples of brand X contained higher amounts of EDMAB and DMPA (Y1: 9 μg kg^{-1} EDMAB, 242 μg kg^{-1} DMPA; Y2: 204 μg kg^{-1} EDMAB, 818 μg kg^{-1} DMPA). BP was detected in 68 (out of 97) samples with concentrations ranging from below LOQ (i.e., 23 samples) to 0.02 mg kg^{-1}. One rice sample (brand Y) contained a significant concentration of BP (0.262 mg kg^{-1}), most probably due to incomplete removal during the recycling process as was already demonstrated by Anderson and Castle (2003). Since the sample was analyzed approximately 1 year before expiration date and because migration is mainly a diffusion controlled process, this was further investigated. Twelve products of brand Y were purchased and the concentration of benzophenone was checked every month, till the expiration date. The results are given in **Fig. 3** and demonstrate that the migration equilibrium had probably settled already 1 year before the expiration date for the rice sample of brand Y.

Finally, it can be concluded that 11 photo-initiators are still present in dry food sold on the Belgian market. An overview of these substances and the highest concentration detected is given in **Table 6**. A preliminary risk assessment for these photo-initiators should be conducted.

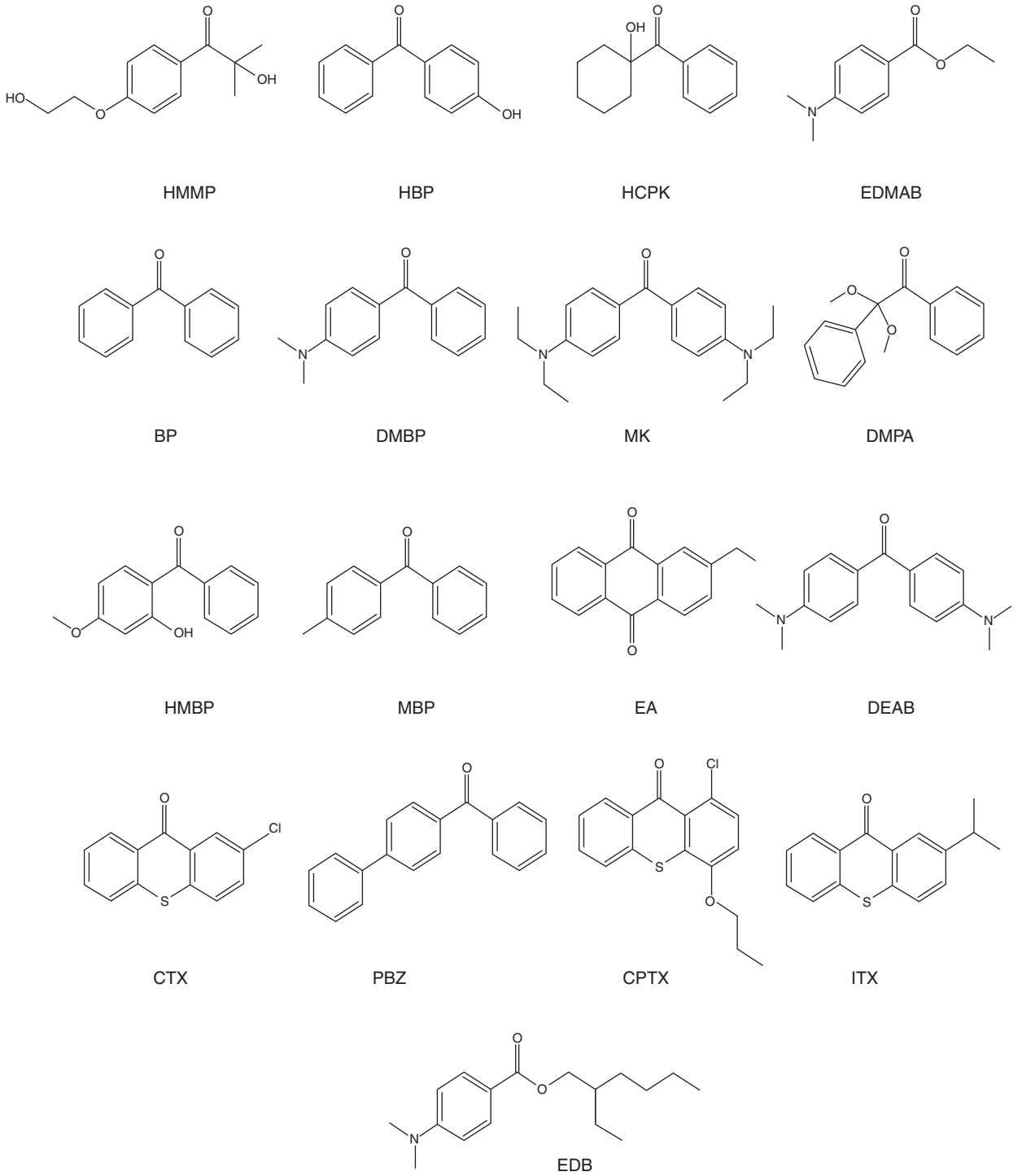

Figure 2 Chemical structures of the investigated photo-initiators.

Risk Assessment of the Detected Photo-Initiators

The market survey conducted by Van den Houwe illustrated that both photo-initiators that were evaluated in an FCM context and non-evaluated photo-initiators are present in dry food. Therefore, a dual strategy was applied for the risk assessment depending on whether or not the photo-initiator was evaluated in an FCM-context.

It should be noted that only the substances that were detected in the market survey were included in the risk assessment. Consequently, CPTX, DEAB, DMBP, HCPK, HMBP and MK were not considered for the risk assessment.

Table 4 Overview of the photo-initiators in the Belgian market survey and their SML, if available (Van den Houwe et al., 2016)

Photo-initiators	*Abbreviation*	*CAS No.*	*SML (mg kg^{-1})*
2-Chlorothioxanthen-9-one	CTX	86-39-5	/
2-Isopropyl thioxanthone	ITX	5495-84-1	0.05[a]
1-Chloro-4-propoxythioxanthone	CPTX	142770-42-1	/
4,4′-bis(diethylamino)benzophenone	DEAB	90-93-7	/
Michler's ketone	MK	90-94-8	/
Benzophenone	BP	119-61-9	0.6[b]
4-Methylbenzophenone	MBP	134-84-9	0.05[a]
4-Dimethylaminobenzophenone	DMBP	530-44-9	/
4-Phenylbenzophenone	PBZ	2128-93-0	/
Ethyl-4-dimethylaminobenzoate	EDMAB	10,287-53-3	0.05[a,c]
2-Ethylanthraquinone	EA	84-51-5	/
α-Hydroxycyclohexylphenylketone	HCPK	947-19-3	/
2-Hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone	HMMP	106797-53-9	0.05[a,c]
2,2-Dimethoxy-2-phenylacetophenone	DMPA	24,650-42-8	/
2-Ethylhexyl 4-dimethylaminobenzoate	EDB	21,245-02-3	2.4[a]
2-Hydroxy-4-methoxy benzophenone	HMBP	131-57-7	6[a,b,d]
4-Hydroxybenzophenone	HBP	1137-42-4	/

[a]Swiss Ordinance on Materials and Articles in Contact with Food (Swiss Confederation, 2005).
[b]Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food. (European Union, 2011).
[c]Under re-evaluation.
[d]The SML is expressed as the sum of all hydroxybenzophenone derivatives.

Table 5 Overview of the number of dry foods included in the Belgian market (Van den Houwe et al., 2016)

	Cereals	*Bread crumbs*	*Pasta*	*Rice*	*Total*
Brand	32	7	11	14	*64*
House brand	17	3	4	9	*33*
Total	*49*	*10*	*15*	*23*	*97*

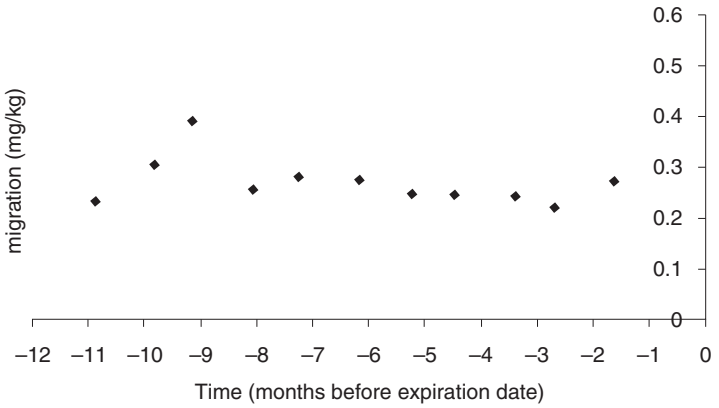

Figure 3 Migration of benzophenone until expiration date (Van den Houwe et al., 2016).

Four out of 11 detected photo-initiators were included in Annex I of Regulation (EU) No 10/2011 on plastic FCM (European Union, 2011) and/or in Annex six of the Swiss Ordinance on Materials and Articles in Contact with Food (Swiss Confederation, 2005). For all four substances, an SML was available and consequently, the concentration detected in the dry food was compared to its respective SML. The SML indicates the maximum amount of a substance allowed to migrate into food and can vary from 'not detectable' to 60 mg kg^{-1}. An overview of the evaluated substance, their SML and the highest concentration detected in dry food in the market survey is presented in Table 7.

Table 6 Overview of the photo-initiators detected during the Belgian market survey and their highest concentration

Photo-initiator	*Highest concentration detected (mg kg^{-1})*
2-Chloro-9H-thioxanthen-9-one (CTX)	<0.010[a]
2-Isopropyl-9H-thioxanthen-9-one (ITX)	<0.010[a]
Benzophenone (BP)	0.262
4-Methyl benzophenone (MBP)	<0.010[a]
4-Phenylbenzophenone (PBZ)	<0.010[a]
Ethyl-4-dimethylaminobenzoate (EDMAB)	0.242
2-Ethylanthraquinone (EA)	<0.010[a]
2-Hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (HMMP)	<0.010[a]
2,2-Dimethoxy-2-phenyl acetophenone (DMPA)	0.818
2-Ethylhexyl-4-dimethylaminobenzoate (EDB)	<0.010[a]
4-Hydroxybenzophenone (HBP)	<0.010[a]

[a]Limit of quantification is 0.010 mg kg^{-1}

Table 7 Overview of the evaluated substances, their respective SML and the highest concentration detected in dry food in the market survey

Photo-initiator	*Highest concentration detected (mg kg^{-1})*	*SML (mg kg^{-1})*
2-Isopropyl-9H-thioxanthen-9-one (ITX)	<0.010	0.05
Benzophenone (BP)	0.262	0.6
4-Methyl benzophenone (MBP)	<0.010	0.05
2-Ethylhexyl-4-dimethylaminobenzoate (EDB)	<0.010	2.4

For all photo-initiators, the concentrations in the food were always below the corresponding SML. Consequently, no adverse health effects are expected due to migration of these substances into dry food.

Substances that have not been evaluated in an FCM-context should be assessed according to internationally recognized scientific principles of risk assessment (Article 19 of Regulation (EU) 10/2011). The Threshold of Toxicological Concern (TTC) approach is such a tool. This concept was developed by Kroes et al. (2005) and has further been modified and improved by Munro et al. (2008) during the early years of this millennium. TTC provides a predictive risk assessment tool for substances that have not been subjected to toxicity testing. It is designed as a decision tree based on structural alerts for genotoxicity, neurotoxicity and Cramer classification. As a result, a human exposure threshold was established below which there is considered to be a very low probability of an appreciable risk to human health. An overview of the generic scheme for the application of the TTC approach as proposed by EFSA is given in **Fig. 4** (EFSA, 2012b):

In this approach, certain structural groups of substances are first excluded such as high potency carcinogens (i.e., aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines), inorganic substances, metals and organometallics, proteins, steroids, substances that are known to bioaccumulate, nanomaterials and radioactive substances. Next, compounds with a structural alert for genotoxicity are assessed using a threshold of 0.15 μg person^{-1} day^{-1} (e.g., 0.0025 μg kg^{-1} body weight (bw) day^{-1}), below which the lifetime risk of developing cancer is considered to be negligible. For organophosphates and N-methyl carbamates, a threshold of 18 μg person^{-1} day^{-1} (e.g., 0.3 μg kg^{-1} bw day^{-1}) has been proposed. Finally, for the remaining substances, thresholds have been set according to the Cramer classification ranging from 90 μg kg^{-1} day^{-1} (e.g., 1.5 μg kg^{-1} bw day^{-1}) for Cramer class II and II to 1800 μg person day^{-1} (e.g., 30 μg kg^{-1} bw day^{-1}) for substances present in Cramer class I. For any substance taken through the decision tree process, the substance will either be expected not to be a safety concern based on the conservative TTC exposure thresholds, or the risk assessment requires more detailed information (EFSA, 2012b).

Since this approach is solely based on the structural chemical characteristics and estimated exposure, it can be used to assess health concerns of chemicals with limited or no specific toxicity data (EFSA, 2012b). Both in the US and Europe, the usefulness of the TTC approach as a pragmatic risk assessment or prioritization tool has been established in different domains, including that of FCMs (US FDA, 1993; EFSA, 2016).

However, the TTC approach cannot be used when compound-specific assessment and toxicity data are available or are required under existing regulations. Therefore, before applying the TTC-approach, a literature search was performed to check whether these substances had been evaluated by a European authority in another context than their use in FCMs. Data were collected from opinions formulated by the European Food Safety Authority (EFSA) (consultation of OpenToxFood through the 'Global Portal to Information on Chemical Substances (eChemPortal)'), the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health and Environmental Risks (SCHER). Risk assessment reports formulated by a European member state in

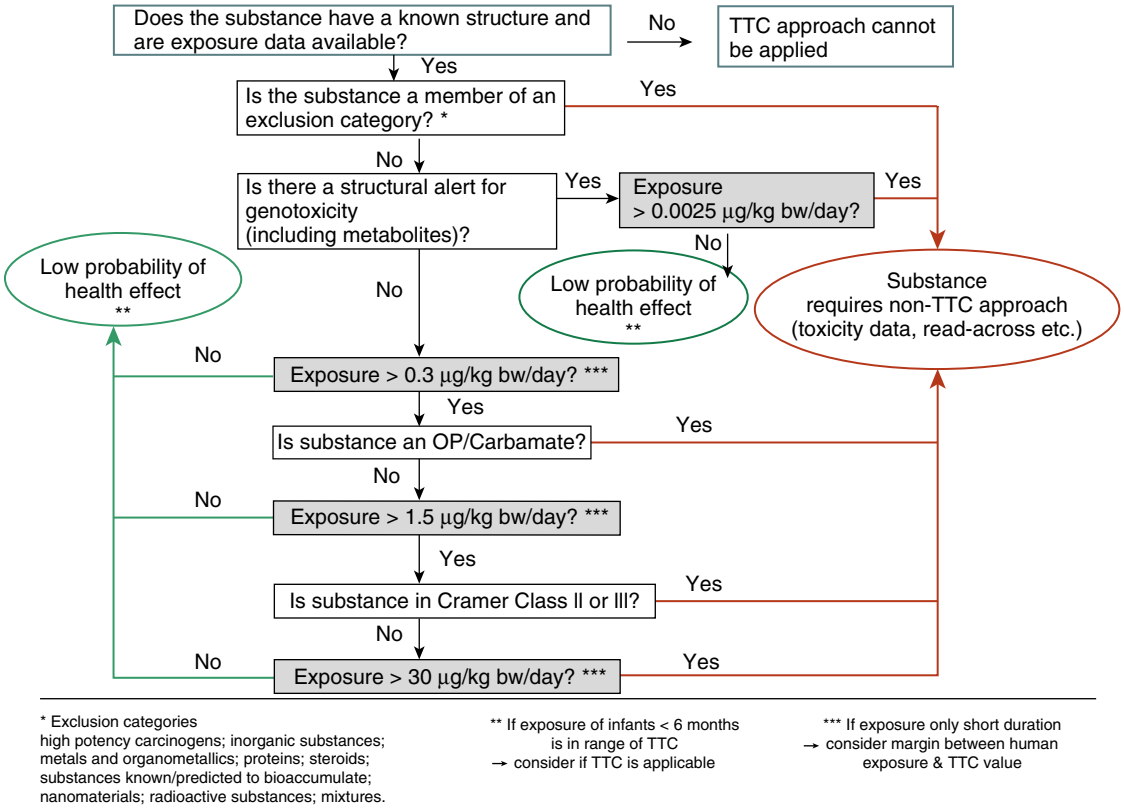

Figure 4 Generic scheme for the application of the TTC approach (EFSA, 2012b).

the context of the Biocidal Product Regulation (EU) 528/2012, the Regulation (EU) 1907/2006 for the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (European Union, 2006b) or the previous Council Regulation (EEC) 793/931 on the evaluation and control of the risks of existing substances were also considered (ECHA). No evaluation was found for any of the substances. However, some inconclusive information was available for 4-hydroxybenzophenone. In 1992, the Scientific Committee on Food (SCF) established a group TDI for benzophenone and 4-hydroxybenzophenone of 0.01 mg kg^{-1} bw (SCF, 1992). The evaluation of the SCF was solely based on a metabolism study and on a 90-day oral rat study on benzophenone. Afterward, the Panel on food contact materials, enzymes, flavorings and processing aids (CEF) of EFSA re-evaluated benzophenone based on toxicological studies published after the adoption of the SCF opinion in 1992. However, no toxicological studies on 4-hydroxybenzophenone were found in the literature. Therefore, it was considered that although 4-hydroxybenzophenone is one of the two important metabolites of benzophenone, it does not justify the inclusion of 4-hydroxybenzophenone in the same TDI as benzophenone (EFSA, 2009b). Consequently, the toxicological information regarding 4-hydroxybenzophenone was considered insufficient for the risk assessment.

Therefore, the TTC approach was applied and exposure of the non-evaluated photo-initiators was determined by multiplying the highest concentration found in the Belgian market survey with the conventional assumption that a person of 60 kg consumes daily 1 kg of food packed in the contaminated FCM. The obtained exposure for the non-evaluated photo-initiators that were detected in the Belgian market survey is given in **Table 8**.

Table 8 Overview of the exposure to the non-evaluated photo-initiators and their corresponding TTC thresholds

Photo-initiator	*Highest concentration detected (mg kg^{-1})*	*Exposure (µg day^{-1})*	*TTC threshold (µg day^{-1})*
2-Chloro-9H-thioxanthen-9-one (CTX)	<0.010	<10	90
4-Phenylbenzophenone (PBZ)	<0.010	<10	90
Ethyl-4-dimethylaminobenzoate (EDMAB)	0.234	234	0.15
2-Ethylanthraquinone (EA)	<0.010	<10	0.15
2-Hydroxy-4′-(2-hydroxyethoxy)-2-methylpropiophenone (HMMP)	<0.010	<10	90
2,2-Dimethoxy-2-phenyl acetophenone (DMPA)	0.753	753	90
4-Hydroxybenzophenone (HBP)	<0.010	<10	90

Next, it was verified whether the substances belonged to any of the groups that are excluded for application of the TTC approach. Since none of the compounds fulfilled the exclusion criteria, the first step of the TTC decision tree was applied, i.e., investigation of the presence of structural alerts (SAs) for genotoxic carcinogenicity by using the carcinogenicity (genotox and nongenotox) and mutagenicity rulebase by Instituto Superiore di Sanità (ISS) of the in silico rule-based program Toxtree version 2.6.0 (Benigni et al., 2008). Two of the substances, i.e., 2-ethylanthraquinone (EA) and benzoic acid, Ethyl-4-dimethylaminobenzoate (EDMAB) showed SAs for genotoxic carcinogenicity and were therefore assigned the TTC value of 0.0025 μg kg^{-1} bw day^{-1} (i.e., 0.15 μg day^{-1} for a person weighing 60 kg). For EDMAB, the estimated exposure exceeded the TTC value, and consequently a risk for human health following daily ingestion of this substance cannot be excluded. Furthermore, this substance was recently evaluated and an SML of 0.05 mg kg^{-1} was allocated, which is much lower compared to the concentration of 0.234 mg kg^{-1} that was found in food. Consequently, the presence of this photo-initiator in dry food should be monitored and its origin investigated.

For the substances that did not have SAs for genotoxic carcinogenicity, chemical structures were analyzed in order to decide whether they belonged to the groups of organophosphates or carbamates. As this was not the case, the Cramer rules (with extensions) of the in silico software Toxtree was applied to assign the substances to one of the three Cramer Classes. All compounds were assigned to Cramer Class III, corresponding to a TTC value of 1.5 μg kg^{-1} bw day^{-1}. While most photo-initiators did not exceed this TTC value, this was clearly the case for 2,2-dimethoxy-2-phenylacetophenone (DMPA). The estimated exposure exceeded the respective TTC value and consequently exposure to this photo-initiator might pose a risk to human health.

However, it is important to note that the TTC approach is a rather conservative method and the TTC values may thus be much lower than the actual TDI. The potential risks associated with the migration of each of these substances were therefore further investigated by collecting more information on the substances in the database of the European Chemicals Agency (ECHA). For substances that have been registered under REACH, toxicological data should be available in this ECHA database. Despite the fact that this toxicological information has been introduced by the registrant and should therefore be considered with caution, the data can often provide an indication as to whether the estimated exposure to the substance exceeding the TTC value poses a risk to human health (Mertens et al., 2016). However, out of the two photo-initiators exceeding their TTC value, only DMPA has been registered under REACH. Furthermore, the data available for DMPA in the ECHA database were based on a read-across approach which was insufficiently described, and therefore the data were not useful for the present study.

In conclusion, more toxicological data are urgently needed to investigate the potential health risks associated with the migration of these photo-initiators for which the estimated exposure exceeded the respective TTC value.

Conclusion

Printed paper and board are an important source of contaminants that can pose a risk to human health. Due to the lack of an appropriate harmonized European legislation, thousands of substances can be present in printed paper and board without any toxicological evaluation. This is illustrated by different databases that have been constructed and strategies that have been developed in order to prioritize these non-evaluated substances (Van Bossuyt et al., 2016; Geueke et al., 2014). One of the possibilities that has been proven to be successful is the use of in silico tools for the prediction of the potential mutagenicity of the substances.

A specific class of substances related to printed paper and board are the photo-initiators. They have already received a lot of attention due to different food crises that led to withdrawal of the food from the market. In this article, a more profound risk assessment for these photo-initiators was performed. First, the exposure to these substances was evaluated by means of a market survey conducted by Van den Houwe et al. (2016). Seventeen selected photo-initiators were monitored in 97 dry foods purchased on the Belgian market. Afterward, the migration of the photo-initiators with an allocated SML was compared to their respective SMLs and all these results were found to be compliant. For the photo-initiators without an allocated SML, a literature study was conducted in order to verify if their toxicity was evaluated in a non-FCM context. Since this was not the case, the Threshold of Toxicological Concern approach was applied for the evaluation of their hazard. As a result, the estimated exposure exceeded the respective TTC value for the photo-initiators DMPA and EDMAB and consequently exposure to these photo-initiators might pose a risk to human health. The potential risks associated with these photo-initiators were therefore further investigated using the ECHA-database. However, the data were not useful for the risk assessment and therefore it can be concluded that more toxicological data are urgently needed to investigate the potential health risks associated with the migration of these photo-initiators.

Finally, it can be concluded that there is an urgent need for a strategy to deal with the thousands of non-evaluated substances that might be present in printer paper and board. The results of the present study have illustrated that the TTC approach, in particular in combination with additional toxicological information, could be an important tool to prioritize large number of substances migrating from FCMs.

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