

# **Food contact substances and chemicals of concern:**

## **A comparison of inventories**

Birgit Geueke,\* Charlotte C. Wagner,\* Jane Muncke

*Food Packaging Forum, Zurich, Switzerland*

Correspondence details: Food Packaging Forum Foundation, Staffelstrasse 12, 8045 Zurich, Switzerland,

Phone +41 44 515 5255, e-mail: birgit.geueke@fp-forum.org (corresponding author),

jane.muncke@fp-forum.org; charlotte.wagner@fp-forum.org

\*Both authors contributed equally.

### **Disclosure statement**

All authors are employees at the Food Packaging Forum Foundation, a charitable non-profit organization. It is funded largely by donations from the packaging industry, but works independently of donors' special interests. The employer does not restrict the study authors' freedom to design, conduct, interpret, and publish research results in any way.

## **Abstract**

Food contact materials (FCMs) are intended to be in contact with food during production, handling or storage. They are one possible source of food contamination, because chemicals may migrate from the material into the food. More than 6000 FCM substances appear on regulatory or non-regulatory lists. Some of these substances have been linked to chronic diseases, whilst many others lack (sufficient) toxicological evaluation. The aim of this study was the identification of known FCM substances which were also considered to be chemicals of concern (COCs). The investigation was based on the following three FCM lists: (i) the 2013 Pew Charitable Trusts database of direct and indirect food additives legally used in the U.S. (short: Pew), (ii) the current EU-wide positive list for plastic FCMs (short: Union), and (iii) the 2011 non-plastics FCM substances database published by EFSA (short: ESCO). These three lists of food contact substances (Pew, Union, ESCO lists) were compared with the Substitute It Now! (SIN) list 2.1 which includes chemicals fulfilling the criteria listed in article 57 of Regulation (EC) No 1907/2006 (REACH), and the TEDX database on endocrine disrupting chemicals. A total of 175 chemicals used in FCMs were identified as COCs. 54 substances present on the SIN list 2.1 were also found on the Union and/or ESCO lists. 21 of those 54 substances are candidates for Substances of Very High Concern (SVHC), and 6 of these 21 are listed on Annex XIV and intended for phase-out under REACH. In conclusion, COCs used in FCMs were identified and information about their applications, regulatory status and potential hazards was included.

**Keywords:** food contact materials, hazard identification, chemicals of concern, regulation, endocrine disruption, Substances of Very High Concern

## **Introduction**

Chemical exposures have been linked to several chronic diseases, including metabolic and reproductive disorders and cancer (Norman et al. 2013; Sharpe and Irvine 2004). Food contact materials (FCM) have been identified as a major source of chronic exposure to chemicals (Borchers et al. 2010; Grob et al. 2006). FCMs include food packaging, but also any other material or substance intended to come into contact with food during production, processing, transport and storage (e.g. lubricating oils, conveyor belts, cleaning agents, secondary packaging). More than 6000 chemicals are compiled in FCM inventory lists in the EU and the U.S. (ESCO list 2011; Neltner et al. 2013; Neltner et al. 2011; Oldring et al. 2014). These lists do not distinguish between substances actually used in the production of FCMs and substances listed but not used. National or international regulatory frameworks aim at ensuring chemical food safety in the respective countries (Magnuson et al. 2013). In the EU, chemicals used for the production of plastic FCMs are regulated in detail (Commission Regulation (EU) No 10/2011, commonly referred to as Plastics Regulation). However, manufacturers of non-plastic FCMs cannot refer to any EU-wide harmonized and legally binding positive list. Under article 3 of Regulation (EC) No 1935/2004 (commonly referred to as FCM framework regulation), manufacturers have the responsibility to guarantee that their products “do not transfer their constituents to food in quantities which could endanger human health”. For non-plastic FCMs, they must rely on national legislation for specific substances, if existent. In 2012, the European Food Safety Authority’s (EFSA) Scientific Cooperation (ESCO) working group published an inventory with nearly 3000 entries of substances and mixtures used in non-plastic FCMs (ESCO list 2011). This list was established to anticipate emergency situations caused by the detection of any of these substances in food. The list is not legally binding, although some of the included substances may be subject to EU Member State law. In the U.S., chemicals not intentionally

added, but expected to migrate into foods, as well as substances intended to have a technical effect in the food, are regulated as indirect food additives under 21 C.F.R. Parts 174-178. In the past, authorization of indirect food additives was granted following indirect food additive petitions. Today food contact substances (FCS) may also be used legally after notifying the U.S. Food and Drug Administration (USFDA) via the Food Contact Notification system, if their migration into food does not exceed 50 ppb. Substances that are generally recognized as safe (GRAS) (21 C.F.R. Part 178) or that fall under the Threshold of Regulation Exemption (21 C.F.R. §170.39), with migration into food below 0.5 ppb, may be exempted from authorization. A recent publication by the Pew Charitable Trusts estimated that as many as 80% of FCS are insufficiently evaluated regarding their toxicity (Neltner et al. 2013).

Although FCMs are regulated to a certain extent in the EU and the U.S., many regulatory gaps remain to be filled (Muncke 2009; Neltner et al. 2013; Neltner et al. 2011). Furthermore, ongoing scientific discussions show that also authorized chemicals require re-evaluation when new scientific insights regarding toxicity, exposure and metabolism become available. Bisphenol A (BPA) is probably the most prominent example of a regulated compound whose use in FCMs was put into question in the recent years (Brotons et al. 1995). On one hand, hundreds of toxicological studies published adverse effects of BPA targeting a variety of endpoints (EFSA 2014; vom Saal et al. 2007). BPA was reported to act as endocrine disruptor (Soto and Sonnenschein 2010), cause developmental effects and changes in metabolism at low concentrations (Boudalia et al. 2013; Vandenberg et al. 2012), display changes to epigenetic footprints (Kim et al. 2014; Kundakovic and Champagne 2011; Manikkam et al. 2013), and result in enhanced endocrine disrupting properties when added to several chemical mixtures (Isling et al. 2013; Naville et al. 2013; Viñas and Watson 2013). On the other hand, several risk assessment agencies continue to consider the use of BPA at present exposure levels safe (Bisphenol A (BPA))

2010; EFSA 2006; EFSA 2013; EFSA 2014). Albeit, EFSA suggested a reduction of the current tolerable daily intake (TDI) by a factor of 10 to 5 µg/kg bodyweight per day (EFSA 2014) and the USFDA issued a statement expressing some concern about BPA's effects on the brain, behaviour, and prostate gland of foetuses, infants, and children (Bisphenol A (BPA) 2010). Furthermore, EFSA and USFDA are awaiting new research findings on BPA's chronic toxicity in rats currently being carried out by the U.S. National Toxicology Program (NTP), the National Institute of Environmental Health Sciences (NIEHS) and the USFDA (Schug, Heindel, et al. 2013). These results are expected at the earliest in 2015 (Birnbaum et al. 2012). In an exemplary manner, the discussion about BPA indicates that also the use of other substances previously considered safe could become controversial with increasing knowledge about toxicity, exposure, and evolving basic scientific understanding.

In this study, we identified potentially hazardous chemicals listed as food contact substances in the U.S. and the Europe. We investigated these chemicals of concern (COCs) with respect to their application and legal status. Our results (i) show gaps in the regulation of FCMs and (ii) indicate how knowledge from different authorities and organizations could be used to increase chemical safety with the objective of improving public health.

## **Methods.**

### ***General information***

Databases listing COCs were compared with regulatory and non-regulatory FCM lists. It is not known how many of these FCM substances are actually used in the production of FCMs, so all of them were assumed to be used. For the unequivocal identification of a chemical, we compared only the Chemical Abstract Service Registry Numbers (CASRN) of the substance, not the chemical names. These comparisons were either performed using Microsoft Excel 2010 (SIN list

2.1, TEDX list vs. Pew, Union, and ESCO lists) or manually ((SIN 2.1 list  $\cap$  Union and/or ESCO list) vs. SVHC list and Annex XIV). In the following the lists of COCs and the databases compiling FCM substances are described in detail.

- COC lists

- Substitute it now! (SIN) list 2.1

The SIN list 2.1 contains 626 substances and substance groups of very high concern that were identified by the International Chemical Secretariat (ChemSec, Göteborg, Sweden) based on the criteria established in article 57 of Regulation (EC) No 1907/2006 (REACH). Chemicals on the list were characterized as being carcinogenic, mutagenic or toxic to reproduction (CMR), persistent, bioaccumulative and toxic (PBT), very persistent and very bioaccumulative (vPvB), or posing an equivalent environmental or health threat. The last category (“equivalent concern”) includes chemicals with endocrine disrupting properties or substances that are less toxic, but highly bioaccumulative and/or persistent (article 57(f), Regulation (EC) No 1907/2006). The chemicals identified as endocrine disruptors by ChemSec fulfilled the criteria specified by the Danish Centre on Endocrine Disruptors (2012).

- Candidate List of Substances of Very High Concern (SVHC list) and Annex XIV

Under the REACH legislative process, substances satisfying the criteria laid out in article 57 may be placed on the Candidate List of Substances of Very High Concern that currently comprises 151 substances (SVHC list 2014). Chemicals may be suggested for the SVHC list by Member States or, on request of the European Commission (EC), by the European Chemicals Agency (ECHA). Suppliers and manufactures of any chemical listed as SVHC are obliged to provide customers and consumers with safety information. Since 2009, ECHA recommended a total of 33 SVHCs (Recommendation lists 2014), of which 22 were subsequently placed on Annex XIV by the EC (Annex XIV 2014). Any chemical included in

Annex XIV is intended for phase-out and a sunset date for this phase-out is established upon adoption. The use of these chemicals in areas covered under REACH requires authorization which must be completed before the sunset date.

- The Endocrine Disruption Exchange (TEDX) list

The TEDX list contains 1518 entries based on 906 compounds (TEDX list 2013). Chemicals on the TEDX list are based on at least one verified, accessible, primary scientific citation describing endocrine disrupting effects *in vivo* and/or *in vitro*. The database was set up and is maintained by the Endocrine Disruption Exchange, Paonia, CO, U.S.

- Databases of FCM substances

- U.S. food additive list (Pew list)

In the U.S., the most comprehensive inventory of FCS is the food additive list (Pew list) compiled by The Pew Charitable Trusts (Neltner et al. 2013). This database contains 7201 substances known to be directly or indirectly added to food and included in the following official databases:

(i) USFDA's Priority-based Assessment of Food Additives (PAFA) (direct and indirect additives) database.

(ii) Notifications from different programs (GRAS, FCN, TOR) accessible on the USFDA website.

(iii) U.S. Environmental Protection Agency's (EPA) pesticides. The Pew list contains only pesticides that were also approved for use as food additives (Neltner et al. 2013).

(iv) Flavor and Extract Manufacturers Association's (FEMA) list of GRAS substances.

Indirect additives cover all substances that may become part of the food during packaging, storage or other handling steps. Direct additives are substances intentionally and directly

added to food and include preservatives, nutritional supplements and flavours (Neltner et al. 2011). Substances used in accordance with direct food additives regulation are also considered safe for use as indirect food additives; consequently, direct additives may also be used in FCMs (Baughan and Attwood 2010).

- EU plastics regulation (Union list)

Substances that may be used in plastic FCMs are listed in Annex I of Commission Regulation (EU) No 10/2011 (Union list). It regulates mono- and multilayer plastic articles, plastic layers in direct contact with food, as well as coatings on plastics, gaskets of glass jar closures and substances that may be used in those materials. The positive list in Annex I defines all chemicals allowed for the production of the above mentioned materials and articles (starting substances like monomers and additives). For our work we extracted the complete database published by the EC's Directorate-General for Health and Consumers (Food Contact Materials 2013), well aware that not all 1038 entries in the database had completed the application procedure at the time and that for some the application procedure had been stopped.

- ESCO working group list on non-plastic FCMs (ESCO list)

Most FCM groups other than plastic FCMs are not specifically regulated under EU law. However they may be regulated under Member State law. In 2011, the ESCO working group issued an inventory of substances used in non-plastic FCMs (ESCO Working Group 2011). Its Annex I contains nearly 3000 entries of substances and mixtures used in the manufacture of food contact grade paper and board, printing inks, coatings, rubber, colorants, wood and cork of which some have previously been evaluated by the European Member States (ESCO list 2011).



## ***Procedure***

### *Step 1: Export and formatting of data*

The SIN list 2.1, TEDX, Pew and ESCO lists were all retrieved on October 2, 2013 and the Union list was exported on October 21, 2013. CASRN and chemical names were exported from all five lists and the numbers were truncated by deleting all hyphens and preceding zero. Chemicals with several CASRN in the original files were separated and subsequently handled as individual chemicals. Substances without CASRN were excluded from the comparison.

### *Step 2: Automatic matching of lists*

To determine the presence of COCs in FCMs, the SIN list 2.1 and TEDX list were matched against the Pew, Union and ESCO lists by comparing the presence of truncated CASRN. The Excel 2010 equation

$$=IF(ISNA(MATCH(*cellref*,$*arrayref*$,0)),FALSE,TRUE)$$

was used to query the Pew, Union and ESCO lists for each truncated CASRN listed in the SIN 2.1 list and TEDX list, respectively. The function *cellref* thereby refers to a specific cell in the SIN list 2.1 or the TEDX list containing a CASRN. The function *arrayref* refers to a specified array containing all CASRN listed for a specific FCM list. The formula returned TRUE for those CASRN for which exact matches were registered in the FCM lists and FALSE for those chemicals that could not be matched.

### *Step 3: Manual matching of lists*

Chemicals present on the SIN list 2.1 and used as FCMs in the EU (indicated by their presence on the Union and/or ESCO lists) were manually matched against the SVHC list and Annex XIV of REACH (Annex XIV 2014; SVHC list 2014). Both lists were accessed on January 13, 2014.

## Results

### *Analysis of lists of concern and FCM databases*

The export, quantitative analysis and formatting of all data was performed before we compared the two lists of concern with the three FCM databases. In October 2013, the SIN list 2.1 and the TEDX database contained 802 and 912 different substances, but both lists included chemicals or mixtures of chemicals without CASRN (Table 1). We did not include any substance or mixture without CASRN in our comparison to FCM databases, which reduced the number of investigated COCs by less than 10%. The Union list contained 1038 different chemical entries of which 892 are currently authorized by the EC in the Plastics Regulation. The other 146 substances/mixtures had not completed the authorization process. Nevertheless, we also included these chemicals in our study. 177 of the chemicals on the Union list lacked a CASRN and were not included in the comparison; 12 chemicals were assigned more than one CASRN and each of them was handled as separate entry. The chemicals from the different working sheets of the ESCO list were compiled on one sheet resulting in almost 2994 entries. This number was misleadingly high because many substances were present on several working sheets (e.g. formaldehyde appeared five times). We removed all multiple CASRN entries leading to 1577 unique CASRN included in our study. The 883 entries without CASRN were not further considered. The Pew list included 7169 chemicals, but only 5802 had CASRN. The remaining 1367 substances were assigned to a number with a similar style by the USFDA (Neltner et al. 2013), but it was not possible to automatically differentiate between these two types of numbers in the Pew database. Thus, we included all 7169 chemicals into our study, being aware that 19% of the substances might not be matched correctly.

A quantitative analysis of the overlaps between the lists of concern and the FCM databases resulted in a total of 175 chemicals that appeared on the SIN list 2.1 and/or TEDX list,

as well as on at least one of the three FCM lists (Table S1). 154 of these substances were listed in the U.S. inventory of food additives, the PEW list, and a total of 92 substances were present on the Union and/or ESCO lists (Figure 1A). A similar pattern was observed analyzing the 96 FCM chemicals that appeared only on the SIN list 2.1: 87 and 54 of those compounds were identified in the U.S. and EU lists, respectively (Figure 1B). From the 119 FCM chemicals present on the TEDX list, 100 and 67 were listed on the PEW and the Union and/or ESCO lists, respectively (Figure 1C).

The 154 COCs on the PEW list were approved as indirect food additives (84%), direct food additives (29%), GRAS (17.5%), flavours (17%) and/or colours (2.6%) by the USFDA (Table S1). We counted 21, 14, 14 and 1 entries for direct additives, flavours, GRAS and colours, respectively, but 25 substances were not explicitly listed as indirect food additives. In principle, direct food additives may be used as indirect food additives under certain conditions according to U.S. law (21 C.F.R. §170.39). We were able to identify FCM-relevant applications for 8 of these 25 non-indirect additives, but not for the remaining 17 chemicals (Ash and Ash 2008; ESCO list 2011; Sheftel 2000) (Table S1).

We were interested in the chemicals that appeared on either lists of concern and in the FCM databases, indicating their use in food packaging, processing and handling both in the U.S. and the EU. 40 substances among the previously identified 175 FCM chemicals were present on both the SIN list 2.1 and TEDX list (Table S1) and 14 of these 40 chemicals were also included in each of the three FCM lists. In Table 2, we detailed the main applications in FCMs and the assessment criteria for inclusion on the SIN list 2.1 of these 14 chemicals. All of these chemicals were included in the TEDX list based on their potential endocrine disrupting properties as shown by at least one peer-reviewed study. The incorporation of the chemicals in the SIN list 2.1, on the other hand, was based on the criteria stated in article 57 of REACH. Three phthalates (dibutyl

phthalate (DBP), benzylbutyl phthalate (BBP), and bis(2-ethylhexyl) phthalate (DEHP)), as well as ethylene oxide, 1-chloro-2,3-epoxypropane and boric acid were classified as CMR according to Annex I of Council Directive 67/548/EEC and Annex VI of Regulation (EC) No 1272/2008, respectively. The phthalates are mainly used as plasticisers/additives in plastics, but also in paper and board, printing inks and rubber, whereas the three other chemicals are applied as monomers for the production of various FCMs (Table 2, Table S2). In the EU, all six chemicals are either subject to legally-binding specific migration limits (SMLs) or other restrictions and specifications for their use in the production of plastics (Table S2). The other eight chemicals present on all five lists were included on the SIN list 2.1 because of their presence on the “priority list of substances for further evaluation of their role in endocrine disruption” published by the EC (2007) or because they fulfilled criteria published by the Danish Centre on Endocrine Disruptors (2012). Propylparaben and styrene, two of these 8 endocrine disruptors, do not have SMLs or other restrictions according to the Plastics Regulation (Table S2). However, toxicological and biomonitoring studies showed that most of the 14 chemicals present on all five lists caused further adverse effects as specified in article 57(f) of REACH (Table 2).

### ***Assessment of FCM chemicals on the SIN list 2.1***

The SIN list 2.1 is of particular relevance for the identification of COCs used in FCMs, as it is based on legally defined criteria for SVHC which are more stringent than the criteria necessary for being placed on the TEDX list. As mentioned above, 54 chemicals present on the SIN list 2.1 were also listed on the Union and/or ESCO lists (Figure 1B, Table S2). Thirty of these substances entered the SIN list 2.1 due to their CMR properties in accordance with EU law, 10 chemicals were endocrine disruptors as listed by the EC (2007), and the further 14 chemicals were judged by ChemSec to fulfil the criteria specified in article 57 of REACH (Figure 2, Table S2). 15 out of

30 CMR substances were also listed on the SVHC list and 6 of those entered the Annex XIV of REACH. None of the EDCs was placed on either the SVHC list or Annex XIV. Five out of 14 substances with different adverse effects according to article 57(f) of REACH were listed as SVHC, but did not enter Annex XIV (Figure 2). The six CMR substances included in Annex XIV encompass four phthalates (diisobutyl phthalate, DBP, BBP and DEHP), 4,4'-methylene-dianiline (MDA) and tris(2-chloro-ethyl) phosphate (TCEP) (Table 3). 4,4'-methylenebis[2-chloroaniline] (MOCA) is going to be added to Annex XIV once the scrutiny process by the European Parliament and Council of Ministers is completed. Whereas the use of DBP, BBP, DEHP and TCEP in plastic FCMs is regulated by the Plastics Regulation, their application in non-plastic FCMs is not harmonized in the EU. Rather, national measures apply to the substances (Table 3) (ESCO list 2011). Under REACH the use of the three phthalates DBP, BBP and DEHP in the packaging of medicinal products was exempted from authorization. The application for authorization regarding further uses is currently ongoing. The remaining two substances diisobutyl phthalate (DiBP) and MDA are examples of chemicals that are not regulated under the Union list and have only been addressed by specific national regulations or recommendations for the production of non-plastic FCMs.

## **Discussion**

At least 175 chemicals with hazardous properties appear to be used in FCMs in the U.S. and the EU. All 119 FCM chemicals that were present on the TEDX list are suspected endocrine disruptors and 92 of the 96 FCM substances from the SIN list 2.1 were classified as EDCs and/or CMR. These chemicals might act at very low doses (often without a measurable toxicological threshold) (Vandenberg 2014; Vandenberg et al. 2012) and their toxicity can be increased in the presence of other chemicals with the same mode of action (Kortenkamp et al. 2007). Currently,

we cannot predict how many of the chemicals possibly used in FCMs are still to enter any COC list because many of these substances lack sufficient toxicological data for a definite evaluation (Neltner et al. 2013). Nevertheless, our results show that improved data management and harmonization in the regulation of chemicals could improve chemical safety.

### ***What are the methodological limitations?***

This study focuses on COCs that are inventoried or authorized for the manufacture of FCMs; it does not describe a chemical's actual use, actual concentration in an FCM or its migration behavior. The aim of the work was the identification of hazardous chemicals used in FCMs. This study does not provide the basis for a risk assessment, because substance-specific exposure and hazard characterization were not addressed.

The two European FCM lists cover many, but not all groups of FCM materials. The ESCO and the Union lists are an inventory and a positive list, respectively. They do not contain impurities, break-down or side products, although these so-called non-intentionally added substances (NIAS) might also migrate from FCMs into food (Food Standards Agency 2007; Nerin et al. 2013). Furthermore, other groups of FCMs such as metal and alloys, adhesives and glass were not covered, because no specific European legislation exists for these materials and they are not part of the ESCO list. European regulations issuing specific substances or materials (e.g. ceramics, epoxy derivatives and regenerated cellulose) were also not included in the study, because we focused on more comprehensive lists including only intentionally added substances. Council Directive 84/500/EEC sets limits for the migration of lead and cadmium, two possible contaminants of ceramics. These two heavy metals pose a high hazard to human health and are also listed on the SIN list 2.1, the SVHC and TEDX lists. Commission Regulation (EC) No 1895/2005 authorizes the use of bisphenol A diglycidyl ether (BADGE, CASRN 1675-54-3) and

certain of its derivatives in FCMs. BADGE is the only of these substances also listed on the Union, ESCO and TEDX lists. Annex I of Commission Directive 2007/42/EC contains a positive list of substances authorized for use in regenerated cellulose materials. Missing CASRN did not allow an automatic comparison, but random samples showed that most of these chemicals were also listed on at least one of the FCM lists.

All FCM and COC lists also contained chemicals without CASRN and included chemical mixtures or structurally uncharacterized chemicals. Therefore, not all chemicals present on the lists were covered by our search strategy. In the case of the Pew and ESCO lists, this amounts to an exclusion of 19% and 36% of entries, respectively (Table 1). CASRN are usually unambiguously assigned to a certain chemical or mixture of chemicals, but different forms of a molecule receive unique CASRN (e.g. salts and the corresponding free acid, substances with different degrees of hydration). In such a case, the potential hazard of chemicals could be very similar, but the automatic inquiry would not result in a match. We manually identified one example that was missed by our computer-aided CASRN search: Perfluorooctanoic acid (PFOA, CASRN 335-67-1) is listed on the SIN list 2.1 and the SVHC list due to its carcinogenic and reprotoxic effects and its persistence in the environment, but not on any FCM list. However, the corresponding ammonium salt of PFOA (CASRN 3825-26-1) is listed on the ESCO and Union lists, but not on any of the COC lists. It remains unknown whether other similar examples exist. Only a targeted, manual expert search of thousands of compounds could result in a comprehensive analysis. To facilitate the search amongst the chemicals in FCM and COC databases in future, it would be desirable to provide CASRN for all compounds and to further characterize mixtures. All closely related chemical structures of a substance should be included to avoid missing matches, like in the case of PFOA and its ammonium salt. The SIN list 2.1 is one example where already many closely related structures were listed in substance groups.

***Is the number of COCs used in FCMs synonymous with a greater risk to public health?***

Our analysis showed that in absolute numbers there are significantly more COCs in the Pew list than in the ESCO or the Union list (154 vs. 88 and 54, respectively). However, the pool of FCM substances listed in the Pew list for the U.S. is much larger than the number of FCM substances listed in the EU (Table 1). Thus, in relative terms the Pew list only contains 2.7% COCs, whereas Union and ESCO lists contain 6.2 and 5.7% COCs, respectively. At the same time it has to be considered that the COCs listed on the Union list have all been toxicologically evaluated and have partially been assigned SMLs. At migration levels below the SML, a chemical's use is deemed safe by the EC. Many substances appearing on the ESCO list are also present on the Union list. Accordingly, the risk posed by these chemicals has been evaluated. Their application in plastics, but not in other FCMs, is restricted (Table S2). Further, some COCs on the ESCO list have been evaluated by national authorities in the framework of Member State legislation (Table S2), but the use of other FCS (e.g. diethyl phthalate, CASRN 84-66-2, ethoxylated nonylphenol, CASRN 9016-45-9 and 26027-38-3) has not yet been evaluated (Table S2). In the U.S., on the other hand, only 28.6% of the substances listed on the Pew list have been evaluated based on published feeding studies and it was concluded that around 75% of authorized indirect additives lack sufficient data (Neltner et al. 2013). A further consideration is that the total number of FCM substances used in the EU which were included in our study may be an underestimate. The recently published European Flavours, Additives, and food Contact materials Exposure Tool (FACET) lists 6475 substances used in FCMs in Europe (Oldring et al. 2014). This number is significantly higher compared to the roughly 3500 entries from EU lists included in our analysis (Table 1). Thus, the mere absolute or relative number of COCs identified as FCMs does not allow the deduction of an elevated risk to the consumer in the U.S. compared to the EU, or *vice versa*.



Such a comprehensive risk assessment can only be achieved when detailed hazard characterization and exposure data for each individual substance is available.

***What do the findings mean for regulators and manufacturers?***

Under EU law, all manufacturers of FCMs are bound by article 3 of the framework regulation. Article 3 requires that substances may not migrate at levels endangering human health (Regulation (EC) No 1935/2004). Manufacturers of SVHCs for plastic FCMs are in addition bound by the Union list, and can thus rely on the risk assessments carried out under Commission Regulation EC 10/2011. Manufacturers of non-plastic FCMs, on the other hand, cannot depend on a specific regulation to guarantee that their product does not endanger human health. Instead, they have to independently carry out a risk assessment in order to ensure that their product complies with article 3. For this purpose, companies may refer to risk assessment guidelines established in other legislative frameworks. For example, many manufacturers reference the migration limit of 0.01 mg/kg according to article 13(3) of Commission Regulation (EU) No 10/2011 for their risk assessment of non-plastic FCMs.

REACH aims to register, evaluate, authorize and eventually restrict the use of hazardous chemicals used in consumer products, thereby improving public health. It is part of a larger effort to harmonize the regulation of chemicals and thus should not be seen as completely separate of other areas of EU chemicals legislation. The regulation applies to environmental impacts of FCMs, and the area of human health effects was only exempted under the assumption that this issue is already sufficiently covered by FCM-specific legislation. Further, the criteria defined in article 57 of REACH, on which also the SIN list 2.1 is based, are scientifically established and legally recognized. As such, we consider these criteria to be also relevant to FCMs, especially when other specific regulations are missing. Chemicals considered SVHCs by the ECHA and the

EC have been evaluated for their environmental and public health impact, even if this impact excludes public health risks arising from FCMs. In short, there is an established scientific and/or societal consensus that SVHCs are hazardous chemicals, and that there is a need to reduce the general population's exposure to these chemicals. We thus question whether a manufacturer can fulfil his obligations under article 3 of the framework regulation without supplying a comprehensive risk assessment, if a substance used in FCMs has been declared a SVHC by another EU authority. Our analysis showed that this applies to the examples of DIBP and MDA, which require authorization under REACH due to their Annex XIV status and are also used in the production of non-plastic FCMs without a specific, binding EU legislation (Table 3). As Annex XIV is intended to be gradually extended, in the future an increasing number of non-plastic FCM substances may be legally identified as hazardous and require authorization for their application in consumer products.

To support the idea of safer materials, manufacturers may perform toxicological tests already during the development of a new chemical or material. While currently not required by regulatory authorities, tests for endocrine disrupting properties should also be included to support safer FCMs. To achieve highest confidence in a novel chemical's non-hazardousness regarding endocrine disrupting effects, tests described as Tiered Protocol for Endocrine Disruption (TiPED) could be one valuable option (Schug, Abagyan, et al. 2013).

## **Conclusions**

With the aim of increased harmonization between different legal bodies and certainty for manufacturers, it appears necessary to consider that substances declared SVHCs under REACH are also restricted under the FCM regulation. Until such harmonization is achieved, manufacturers may self-reliantly attempt to avoid the use of potentially hazardous substances in

FCMs and fill existing data gaps to ensure their product's safety. The research and development phase of new products is best suited to test for hazard properties while simultaneously maximising technical functionality. In general, a prioritization of chemicals based on their production volume and suitable toxicological screening programs could help to fill the most urgent data gaps. From a consumer perspective, it is certainly unexpected and undesirable to find COCs being intentionally used in FCMs, and thus it seems appropriate to replace substances case-by-case with inherently safer alternatives.

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Table 1. Summary of four databases listing chemicals of concern (COC) and three food contact material (FCM) lists.

List		Total entries	CASNR entries	List compiled by	Details	Reference
COCs	SIN 2.1	802	789	ChemSec	Chemicals of concern according to article 57 of REACH	(SIN list 2.1 2013)
	TEDX	912	855	The Endocrine Disruption Exchange	Endocrine disrupting compounds (EDCs)	(TEDX list 2013)
	SVHC	151	173	ECHA	Candidate list of substances of very high concern for authorisation	(SVHC list 2014)
	Annex XIV	22	28	ECHA	Authorisation list	(Annex XIV 2014)
FCMs	Pew	7169	5802	The Pew Charitable Trusts	Direct and indirect food additives authorized by the USFDA	(Neltner et al. 2013)
	Union	1038	873	EC	Positive list of chemicals authorized for use in the production of plastics	(Commission Regulation (EU) No 10/2011)
	ESCO	2994 / 2460 <sup>a</sup>	1577	EFSA	Non-plastic FCM inventory based on national legislation of EU Member States	(ESCO list 2011)

Notes: <sup>a</sup>After removal of multiple CASRN entries (1577 unique CASRN and 883 entries without CASRN)

Table 2. Chemicals present on the SIN list 2.1, TEDX, Pew, Union and ESCO lists, their application in FCMs and toxicological assessment for inclusion on the SIN list 2.1.

CASRN	Chemical	FCM Application <sup>a</sup>	Assessment for inclusion on SIN list 2.1 <sup>b</sup>
75-21-8	Ethylene oxide	<ul style="list-style-type: none"> <li>• Monomer for plastics (e.g. polyethylene oxide, polyethylene terephthalate)</li> <li>• Monomer for printing inks and rubber</li> <li>• Defoamer in paper and board</li> </ul>	<ul style="list-style-type: none"> <li>• Classified CMR.<sup>c</sup></li> </ul>
80-05-7	Bisphenol A	<ul style="list-style-type: none"> <li>• Monomer for plastics (polycarbonate)</li> <li>• Monomer for resins (e.g. epoxy, phenolic, ethoxylene and ion-exchange)</li> <li>• Monomer and additive for printing inks</li> </ul>	<ul style="list-style-type: none"> <li>• Possible reprotoxic chemical (R3) and categorized as an endocrine disruptor (cat 1). Associated with reproductive dysfunction, increased cancer risk, including breast and prostate, and a range of other chronic or irreversible health problems, often from very low levels of exposure. Commonly detected in humans.</li> </ul>
84-74-2	Dibutyl phthalate (DBP)	<ul style="list-style-type: none"> <li>• Additive in plastics (plasticiser in e.g. polyvinyl chloride, polymethyl methacrylate, polyvinyl acetate and cellulose esters)</li> <li>• Additive/plasticiser in paper and board, printing inks, adhesives, slumicides and cellophane</li> </ul>	<ul style="list-style-type: none"> <li>• Classified CMR.<sup>c</sup></li> </ul>
85-68-7	Benzylbutyl phthalate (BBP)	<ul style="list-style-type: none"> <li>• Additive in plastics (plasticiser in e.g. polyvinyl chloride, polyacrylates, polyvinyl acetate and nitrocellulose)</li> <li>• Additive/plasticiser in paper and board, printing inks, acrylic coatings, adhesives and rubber</li> </ul>	<ul style="list-style-type: none"> <li>• Classified CMR.<sup>c</sup></li> </ul>
94-13-3	Propylparaben	<ul style="list-style-type: none"> <li>• Additive in plastics and printing inks</li> </ul>	<ul style="list-style-type: none"> <li>• Endocrine disruptor with estrogenic and antiandrogen activity, affecting sperm function and prenatal development among others. Detected in biomonitoring studies and human urine and milk. Categorized as an endocrine disruptor in the EU Commission EDC database.</li> </ul>
98-54-4	4-tert-Butylphenol	<ul style="list-style-type: none"> <li>• Monomer for plastics</li> <li>• Plasticiser for cellulose acetate</li> <li>• Adjuvant for polycarbonate</li> <li>• Synthetic rubber manufacture</li> <li>• Printing inks</li> </ul>	<ul style="list-style-type: none"> <li>• Endocrine disruptor and toxic to reproduction. Widely found in the environment.</li> </ul>
100-42-5	Styrene	<ul style="list-style-type: none"> <li>• Monomer for different materials (e.g. styrene-butadiene rubber, acrylonitrile-butadiene-styrene polymer, styrene-acrylonitrile copolymer resin, printing inks)</li> <li>• Cross-linking agent</li> <li>• Solvent</li> </ul>	<ul style="list-style-type: none"> <li>• Styrene is an endocrine disruptor (cat 1). Reprotoxic as well as carcinogenic and mutagenic effects have been reported. It is highly toxic to aquatic species.</li> </ul>
106-89-8	1-Chloro-2,3-epoxypropane	<ul style="list-style-type: none"> <li>• Monomer for different materials (e.g. epoxy resins, elastomers, plasticisers, stabilizers, printing inks)</li> </ul>	<ul style="list-style-type: none"> <li>• Classified CMR.<sup>c</sup></li> </ul>
108-46-3	1,3-Dihydroxybenzene	<ul style="list-style-type: none"> <li>• Monomer for plastics</li> <li>• Plasticiser, stabilizer, rubber production, resins</li> <li>• Flavouring agent</li> </ul>	<ul style="list-style-type: none"> <li>• Endocrine disruptor affecting thyroid function as well as estrogen and glucose metabolism. Categorized as an endocrine disruptor in the EU Commission EDC database.</li> </ul>
117-81-7	Bis(2-ethyl-hexyl) phthalate (DEHP)	<ul style="list-style-type: none"> <li>• Additive in plastics (e.g. plasticiser in PVC and its copolymers, cellulose nitrate and polystyrene)</li> <li>• Additive in food packaging adhesives</li> <li>• Defoamer in food-contact paper and board</li> <li>• Lubricant</li> <li>• Additive/plasticiser in paper and board, printing inks and rubber</li> </ul>	<ul style="list-style-type: none"> <li>• Classified CMR.<sup>c</sup></li> </ul>
119-61-9	Benzophenone	<ul style="list-style-type: none"> <li>• Additive in plastics</li> <li>• UV curing agent and photoinitiator</li> <li>• Polymerization inhibitor for styrene</li> </ul>	<ul style="list-style-type: none"> <li>• Carcinogenic effects have been reported. Potentially persistent, found in the environment. Derivates are potential endocrine disruptors.</li> </ul>
131-57-7	Benzophenone-3; Oxybenzone	<ul style="list-style-type: none"> <li>• Additive in plastics and printing inks</li> <li>• UV absorbing agent</li> <li>• Used in the production of plastic surface coatings and polymers</li> </ul>	<ul style="list-style-type: none"> <li>• Endocrine disruptor with estrogenic, antiandrogen and thyroid activity, affecting several body functions including development and immune function. Found in biomonitoring studies and in human milk and urine. Categorized as an endocrine disruptor in the EU Commission EDC database.</li> </ul>

10043-35-3	Boric acid	<ul style="list-style-type: none"> <li>• Additive and monomer in plastics (e.g. nylon)</li> <li>• Component of paper, glass, ceramics and cork and wood</li> </ul>	<ul style="list-style-type: none"> <li>• Classified CMR.<sup>d</sup></li> </ul>
25013-16-5	tert-Butyl-hydroxyanisole (BHA)	<ul style="list-style-type: none"> <li>• Additive in plastics, coatings and printing inks</li> <li>• Antioxidant and preservative</li> </ul>	<ul style="list-style-type: none"> <li>• Endocrine disruptor with estrogenic, thyroid and antiandrogen activity, affecting several body functions including development and reproduction. It is categorized as an endocrine disruptor in the EU Commission EDC database.</li> </ul>

Notes: <sup>a</sup>Sources (Ash and Ash 2008; Commission Regulation (EU) No 10/2011; ESCO list 2011; Food Contact Materials 2013; Sheftel 2000)

<sup>b</sup>Source: (SIN list 2.1 2013)

<sup>c</sup>According to Annex I of Council Directive 67/548/EEC

<sup>d</sup>According to Annex VI of Regulation (EC) No 1272/2008

Table 3. Chemicals listed on Annex XIV and the Union and/or ESCO lists including their authorized, restricted and further known uses. All six chemicals are classified CMRs according to Annex I of Council Directive 67/548/EEC or Annex VI of Regulation (EC) No 1272/2008.

CASRN	Chemical	Union list (SML/restrictions and specifications)	ESCO list (FCM: SML/restriction and specification (country))	Further FCM applications <sup>a</sup>
84-69-5	Diisobutyl phthalate (DIBP)	<ul style="list-style-type: none"> <li>• Not listed.</li> </ul>	<ul style="list-style-type: none"> <li>• Paper and board: SML = 1 mg/kg alone or with DBP (NL)</li> <li>• Coatings: SML = 1 mg/kg alone or with DBP (NL)</li> </ul>	<ul style="list-style-type: none"> <li>• Plasticiser in e.g. PVC</li> <li>• Component of adhesives, coatings, paper, cellophane, rubber articles</li> </ul>
84-74-2	Dibutyl phthalate (DBP)	<ul style="list-style-type: none"> <li>• SML = 0.3 mg/kg, SML (T) = 60 mg/kg</li> <li>• Only to be used as plasticiser in repeated use materials and articles contacting non-fatty foods and technical support agent in polyolefins (up to 0.05% in the final product).</li> </ul>	<ul style="list-style-type: none"> <li>• Paper and board: SML = 1 mg/kg alone or with DIBP (NL)</li> <li>• Printing inks: SML = 0.3 mg/kg; SML (T) = 60 mg/kg (CH)</li> <li>• Rubber: SML = 3 mg/kg (F); SML = 15 mg/kg (NL); maximum use level 5%, cumulative for all phthalates and not for fatty foods (I)</li> </ul>	<ul style="list-style-type: none"> <li>• See Table 2.</li> </ul>
85-68-7	Benzyl butyl phthalate (BBP)	<ul style="list-style-type: none"> <li>• SML = 30 mg/kg, SML (T) = 60 mg/kg</li> <li>• Only to be used as plasticiser in repeated use materials and articles, plasticiser in single-use materials and articles contacting non-fatty foods (except for infant formula and further specified food for babies and young children) and technical support agent (up to 0.1% in the final product).</li> </ul>	<ul style="list-style-type: none"> <li>• Paper and board: not exceeding 1% in starting substance, no SML (NL)</li> <li>• Printing inks: SML = 30 mg/kg, SML (T) = 60 mg/kg (CH)</li> <li>• Rubber: SML = 3 mg/kg (F); SML = 15 mg/kg (NL); maximum use level 5%, cumulative for all phthalates and not for fatty foods (I)</li> </ul>	<ul style="list-style-type: none"> <li>• See Table 2.</li> </ul>
101-77-9	4,4'-Methylene-dianiline (MDA)	<ul style="list-style-type: none"> <li>• Not listed.</li> </ul>	<ul style="list-style-type: none"> <li>• Printing inks: SML = ND (DL = 0.01 mg/kg) (CH)</li> </ul>	<ul style="list-style-type: none"> <li>• Additive in synthetic rubbers, dyes and polyamide resins.</li> <li>• Curing agent of epoxy and polyurethane resins.</li> <li>• Monomer of polydiisocyanates.</li> </ul>
115-96-8	Tris(2-chloro-ethyl) phosphate (TCEP)	<ul style="list-style-type: none"> <li>• SML = ND</li> <li>• Additive</li> </ul>	<ul style="list-style-type: none"> <li>• Printing inks: SML = ND (DL = 0.02 mg/kg) (CH)</li> </ul>	<ul style="list-style-type: none"> <li>• Plasticiser in cellulose derivatives, polyesters, polyacrylates and polyurethanes.</li> <li>• Flame retardant.</li> </ul>
117-81-7	Bis(2-ethyl-hexyl) phthalate (DEHP)	<ul style="list-style-type: none"> <li>• SML = 1.5 mg/kg; SML (T) = 60 mg/kg</li> <li>• Only to be used as plasticiser in repeated use materials and articles contacting non-fatty foods and technical support agent (up to 0.1% in the final product).</li> </ul>	<ul style="list-style-type: none"> <li>• Paper and board: SML = 40 mg/kg (NL)</li> <li>• Rubber: SML = 1.5 mg/kg (F); SML = 40 mg/kg (NL); maximum use level 5%, cumulative for all phthalates and not for fatty foods (I)</li> <li>• Printing inks (CH)</li> </ul>	<ul style="list-style-type: none"> <li>• See Table 2.</li> </ul>

Notes: SML – specific migration limit; SML (T) – group-specific migration limit; ND – substance should not be detectable; DL – detection limit

<sup>a</sup>Sources: (Ash and Ash 2008; Sheftel 2000)

**Figure titles.**

Figure 1. Number of chemicals listed on COC and FCM lists. Grey – chemicals on at least one of the three FCM lists; horizontal stripes – chemicals on the PEW list; vertical stripes – chemicals on the Union AND ESCO lists; white – chemicals ONLY on the ESCO list; black – chemicals ONLY on the Union list. (A) Chemicals are listed on the SIN list 2.1 and/or the TEDX list. (B) Chemicals are listed on the SIN list 2.1. (C) Chemicals are listed on the TEDX list.

Figure 2. Toxicological classification of 54 chemicals listed on the SIN list 2.1 and on the Union and/or ESCO lists. The chemicals were classified according to their final assessment criteria for inclusion on the SIN list 2.1 as CMRs (according to Annex 1 of Council Directive 67/548/EEC or Annex VI of Regulation (EC) No 1272/2008), endocrine disruptors (according to the EC (2007)) or fulfilling other criteria according to article 57 of REACH. Light grey – Number of chemicals listed on the SIN list 2.1; medium grey – number of these chemicals also listed on the SVHC list; dark grey – number of these chemicals also listed on Annex XIV of REACH.

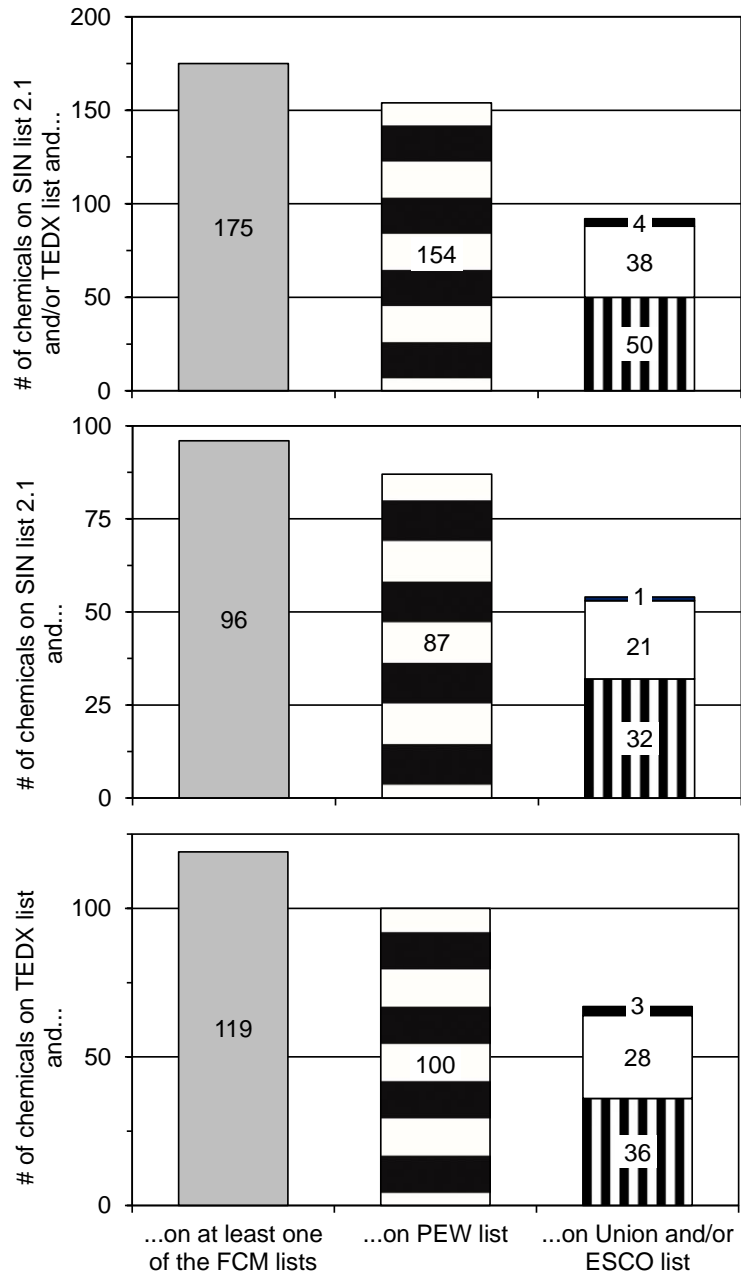


Figure 1

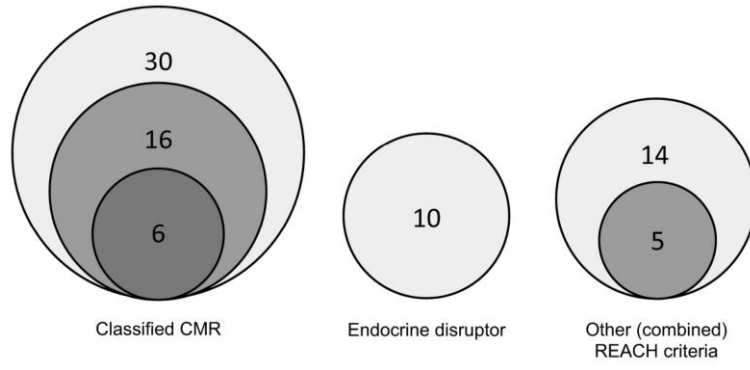


Figure 2



## Supplemental online material

**Table S1.** 175 chemicals present on the SIN list 2.1, the TEDX, Union, ESCO and/or Pew lists. The FDA approval for chemicals present on the Pew list were shown according to the agency's designation as listed in [1]. A truncated format was used for the CASRN ((X)<sub>n</sub>XXX instead of (X)<sub>n</sub>-XX-X).

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
50000	Formaldehyde	+		+	+	+	D	I					
51036	Piperonylbutoxide		+			+		I					
56235	Carbon tetrachloride		+		+	+		I					
56359	Tributyltin oxide (TBTO)	+	+		+	+		I					
56360	Tributyltin acetate		+			+		I					
57578	Propiolactone	+				+		I					
58082	Caffeine		+			+	D		F	G			Not known.
59507	4-Chloro-3-methylphenol		+		+	+		I					
60822	Phloretin		+			+	D		F	G			Not known.
62533	Aniline	+				+		I					
64675	Diethyl sulphate	+				+		I					
65850	Benzoic acid		+	+	+	+		I	F	G			
68122	N,N-Dimethylformamide	+	+			+		I					
71432	Benzene	+	+		+	+	D	I					
71487	Cobalt acetate	+				+		I					
74317	Diphenyl-p-phenylenediamine		+			+		I					
75014	Chloroethylene	+		+	+	+		I					
75092	Dichloromethane		+			+	D	I			C		

**Table S1 - continued**

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
75127	Formamide	+				+		I					
75150	Carbon disulfide		+			+		I					
75218	Ethylene oxide	+	+	+	+	+	D	I	F	G			
75569	Methyloxirane	+		+	+	+	D	I					
77407	Bisphenol B		+			+		I					
77587	Dibutyltin (dilaurate)	+			+	+		I					
77781	Dimethyl sulphate	+				+		I					
78795	Isoprene	+		+	+	+		I					
79016	Trichloroethylene	+				+	D	I	F				
79061	Acrylamide	+		+	+	+		I					
79469	2-Nitropropane	+				+		I					
80057	Bisphenol A	+	+	+	+	+		I					
80091	Bisphenol S		+	+		+		I					
80466	4-tert-Pentylphenol		+			+		I					
81141	Musk ketone		+			+	D		F				Not known.
84617	Dicyclohexyl phthalate (DCHP)	+	+		+	+		I					
84628	Diphenyl phthalate		+			+		I					
84662	Diethyl phthalate (DEP)	+	+		+	+		I				P	
84695	Diisobutyl phthalate	+	+		+	+		I					
84742	Dibutyl phthalate (DBP)	+	+	+	+	+		I					
84753	Dihexyl phthalate (DHP)	+	+			+		I					
85687	Benzyl butyl phthalate (BBP)	+	+	+	+	+		I					
87865	Pentachlorophenol (PCP)	+	+			+		I					
88040	4-Chloro-3,5-dimethylphenol		+			+		I					

**Table S1 - continued**

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
90437	2-Phenylphenol		+		+	+	D	I		G			
91225	Quinoline	+				+	D		F	G			Not known.
91532	Ethoxyquin		+			+	D	I					
92524	Biphenyl		+		+	+			F				Fungistat in FCM [2]; in wrapping paper for citrus fruits [3].
92693	4-Phenylphenol		+			+		I					
92886	4,4'-Biphenol		+	+									
92933	4-Nitrobiphenyl	+				+		I					
94133	Propylparaben	+	+	+	+	+	D	I	F	G		P	
94188	Benzyl paraben		+		+								
94268	Butylparaben	+	+			+	D		F	G			Not known.
95807	4-Methyl-m-phenylenediamine	+			+	+		I					
96093	Styrene oxide	+	+			+		I					
96184	1,2,3-Trichloropropane	+				+		I					
96457	Ethylene thiourea	+	+		+								
97234	Dichlorophen		+	+	+	+		I					
98293	4-tert-Butylpyrocatechol		+			+		I					
98544	4-tert-Butylphenol	+	+	+	+	+	D	I	F	G			
99763	Methylparaben		+	+	+	+	D	I	F	G		P	
99934	4-Hydroxyacetophenone		+			+	D		F	G			Not known.
99967	4-Hydroxybenzoic acid		+	+	+	+	D		F	G			Printing inks [3].
100425	Styrene	+	+	+	+	+	D	I	F	G			
101144	4,4'-Methylenebis[2-chloroaniline]	+			+								
101779	4,4'-Methylenedianiline (MDA)	+			+	+		I					

**Table S1 - continued**

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
103162	4-Benzyloxyphenol		+			+		I					
103231	Di(2-ethylhexyl)adipate		+	+	+	+		I					
104405	4-Nonylphenol	+	+			+		I					
106445	p-Cresol		+	+	+	+	D	I	F	G			
106898	1-Chloro-2,3-epoxypropane	+	+	+	+	+		I					
106990	Buta-1,3-diene	+		+	+	+		I					
107062	1,2-Dichloroethane	+				+	D	I					
107131	Acrylonitrile	+		+	+	+		I				P	
107211	Ethylene glycol		+	+	+	+		I					
107302	Chloromethyl methyl ether	+				+	D						Not known.
108054	Vinyl acetate		+	+	+	+	D	I					
108463	1,3-Dihydroxybenzene	+	+	+	+	+	D	I	F	G			
108781	Melamine		+	+	+	+		I					
108883	Toluene		+		+	+		I					
108952	Phenol		+	+	+	+	D	I	F	G			
109864	2-Methoxyethanol	+	+		+	+		I					
110543	n-Hexane	+	+			+	D	I					
110805	2-Ethoxyethanol	+			+	+		I			C		
111159	2-Ethoxyethyl acetate	+				+		I					
111411	2-(2-Aminoethyl-amino)ethanol	+		+	+	+		I					
115866	Triphenyl phosphate		+			+		I					
115968	Tris(2-chloroethyl)-phosphate (TCEP)	+		+	+								
117817	Bis(2-ethylhexyl) phthalate (DEHP)	+	+	+	+	+		I				P	
117840	Diethyl phthalate		+		+	+		I					

**Table S1 - continued**

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
118558	Phenyl salicylate		+			+	D	I		G			
118752	Chloranil		+			+		I					
119619	Benzophenone	+	+	+	+	+	D	I	F	G			
120478	Ethyl paraben		+	+	+	+		I					
120809	Catechol		+	+	+								
122601	2,3-Epoxypropyl phenyl ether	+				+		I					
123079	4-Ethylphenol		+			+	D		F	G			Not known.
123319	Hydroquinone		+	+	+	+		I					
123773	Diazene-1,2-dicarboxamide	+			+	+	D	I					
126001	Diphenolic acid		+			+		I					
126998	2-Chlorobuta-1,3-diene	+	+		+	+		I					
127184	Perchloroethylene	+	+			+		I					
131566	2,4-Dihydroxybenzophenon	+	+	+	+								
131577	Benzophenone-3; Oxybenzone	+	+	+	+	+		I					
135193	2-Naphthol		+			+		I					
136367	Resorcinol monobenzoate		+			+		I					
137268	Thiram	+	+		+	+		I					
137304	Ziram		+		+	+		I					
137428	Sodium methyl-dithiocarbamate	+	+		+								
140669	4-(1,1,3,3-Tetra-methylbutyl)phenol	+	+		+	+	D						Printing inks [3].
142596	Nabam		+			+	D						Slimicide in FCM [2].
149575	2-Ethylhexanoic acid		+		+								
151564	Ethyleneimine	+		+	+	+		I					

**Table S1 - continued**

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
302012	Hydrazine	+				+	D						Polymerization catalyst, foaming agent [4].
520332	Hesperetin		+			+	D		F	G			Not known.
611994	4,4'-Dihydroxy-benzophenone	+	+	+	+								
620177	3-Ethylphenol		+			+		I					
620928	Bisphenol F		+	+	+								
630080	Carbon monoxide	+		+		+		I					
645567	4-n-Propylphenol		+			+	D		F	G			Not known.
683181	Dibutyltin dichloride	+	+			+		I					
872504	N-Methyl-2-pyrrolidone	+		+	+	+		I					
1131608	4-Cyclohexylphenol		+			+		I					
1303964	Disodium tetraborate decahydrate	+				+		I					
1309644	Antimony trioxide	+		+	+								
1330207	Xylene		+		+	+		I					
1330434	Disodium tetraborate, anhydrous	+		+	+	+							Preservative in paper and board; printing inks [3].
1332214	Asbestos	+				+		I					
1344087	Sodium polysulfide (Na <sub>2</sub> (S <sub>x</sub> ))		+		+	+		I					
1461229	Tributyltin chloride	+	+			+		I					
1675543	Bisphenol A diglycidyl ether		+	+	+								
1806264	4-Octylphenol		+			+		I					
2451629	Tris(2,3-epoxypropyl) isocyanurate	+				+		I					
3033770	2,3-Epoxypropyl-trimethylammonium chloride	+				+		I					
3380345	Triclosan	+	+	+	+								

**Table S1 - continued**

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
3825261	Perfluorooctanoic acid, ammonium salt		+	+	+								
7235407	β-Carotene		+			+			G	C			Not known.
7429905	Aluminum		+		+	+		I					
7439965	Manganese		+			+		I					
7440224	Silver (nanoparticles)		+		+								
7601890	Sodium perchlorate		+	+									
7632044	Sodium peroxometaborate	+			+	+		I					
7664417	Ammonia		+	+	+	+		I					
7681494	Sodium fluoride		+			+		I					
7758012	Potassium bromate	+				+	D						Not known.
7758987	Copper sulfate		+			+			G	C			Not known.
7775113	Sodium chromate	+				+		I					
7778509	Potassium dichromate	+				+		I					
7778747	Potassium perchlorate		+			+		I					
7783064	Hydrogen sulfide		+			+	D		F	G			Not known.
8009038	Petrolatum	+			+	+	D	I					
8016259	Hops extract		+			+	D		F				Not known.
8030306	Naphtha	+				+	D						Adhesive and defoamer in FCM [2].
8032324	Ligroine	+				+		I					
9002931	4-(1,1,3,3-Tetramethylbutyl)- phenyl-polyethylene glycol	+				+	D						Adhesive in FCM [2].
9016459	Nonylphenol, ethoxylated	+			+	+		I					
10043013	Aluminum sulfate		+			+	D			G			Not known.
10043353	Boric acid	+	+	+	+	+		I					
10049044	Chlorine dioxide		+		+	+	D	I					

**Table S1 - continued**

CASRN	Chemical name	SIN 2.1	TEDX	Union	ESCO	Pew	FDA approval						Application of non-indirect food additives in FCM
							Direct	Indirect	Flavour	GRAS	Colour	Prior sanct.	
10380286	Oxine-copper		+			+		I					
10605217	Carbendazim		+		+								
12001284	Crocidolite	+				+		I					
12001295	Chrysotile	+				+		I					
12122677	Zineb	+	+			+		I					
13171001	ADBI; Celestoide		+			+	D		F	G			Not known.
21245023	2-Octyl-(4-dimethyl-amino)benzoic acid		+		+								
25013165	tert-Butylhydroxyanisole (BHA)	+	+	+	+	+	D	I	F	G		P	
25154523	Nonylphenol	+				+		I					
25167833	2,3,4,5-Tetrachlorophenol		+			+		I					
26027383	4-Nonylphenol, ethoxylated	+			+	+		I					
26761400	Diisodecyl phthalate		+	+	+	+		I					
27193288	(1,1,3,3-tetramethyl-butyl)phenol	+				+		I					
28553120	Diisononyl phthalate (DINP)	+		+	+	+		I					
52918635	Deltamethrin		+		+								
63449398	Chlorinated paraffins (CPs)	+				+		I					
68515480	Diisononyl phthalate (DINP)	+	+	+	+								
Σ	175	96	119	54	88	154	45	129	26	27	4	6	

1. Neltner TG, Alger HM, Leonard JE, et al. 2013. Data gaps in toxicity testing of chemicals allowed in food in the United States. *Reprod Toxicol.* 42:85-94.
2. Ash M, and Ash I. 2008. Handbook of food packaging chemicals and materials. Synapse Information Resources, Inc., Endicott, NY.
3. EFSA. 2012. Report of ESCO WG on non-plastic Food Contact Materials - Annex I, Supporting Publications.
4. Sheftel VO. 2000. Indirect food additives and polymers - Migration and toxicology. Lewis publishers, Boca Raton.



**Table S1 - continued**

**Table S2.** 54 Chemicals from the SIN list 2.1 that were present on the Union and/or ESCO lists. Chemicals on the SIN list 2.1 were classified as carcinogenic, mutagenic or toxic for reproduction (CMR), as endocrine disrupters (ED) or according to further criteria referring to article 57 of REACH. The presence on the SVHC list and Annex XIV is shown. Any restrictions, specifications, specific migration limits (SMLs) of all food contact substances and applications of non-plastic food contact substances were shown. A truncated format was used for the CASRN ((X)<sub>n</sub>XXX instead of (X)<sub>n</sub>-XX-X).

CASRN	Chemical name	SIN list 2.1			REACH		Union list			ESCO list			
		CMR	ED	Art. 57 REACH	SVHC list	Annex XIV		Restrictions and specifications	SML [mg/kg] Group SML (T) [mg/kg]		Application	Restrictions and specifications	SML [mg/kg] Group SML (T) [mg/kg]
50000	Formaldehyde			+ <sup>4</sup>			+		(T) 15	+	Cork and wood, paper and board, printing inks, rubber		(T) 15
56359	Tributyltin oxide (TBTO)			+ <sup>4</sup>	+					+	Cork and wood		0.01
71432	Benzene	+ <sup>1</sup>								+	Coatings		0.05
75014	Chloroethylene	+ <sup>1</sup>					+	1 mg/kg in final product	ND	+	Printing inks, rubber	1 mg/kg in final product	ND (DL = 0.01)
75218	Ethylene oxide	+ <sup>1</sup>					+	1 mg/kg in final product	ND	+	Printing inks, rubber	1 mg/kg in final product	
75569	Methyloxirane	+ <sup>1</sup>			+		+	1 mg/kg in final product	ND	+	Printing inks, rubber	1 mg/kg in final product	
77587	Dibutyltin (dilaurate)	+ <sup>2</sup>								+	Coatings, silicones		0.1 for Sn; (T) 0.05
78795	Isoprene	+ <sup>1</sup>					+	1 mg/kg in final product	ND	+	Printing inks, rubber	1 mg/kg in final product	ND (DL = 0.02)
79061	Acrylamide	+ <sup>1</sup>			+		+		ND	+	Paper and board, printing inks, rubber		ND (DL = 0.01); 12
80057	Bisphenol A			+ <sup>4</sup>			+	Not to be used for infant feeding bottles.	0.6	+	Printing inks		0.6
84617	Dicyclohexyl phthalate (DCHP)		+ <sup>3</sup>							+	Coatings, paper and board, printing inks, rubber		6; 30
84662	Diethyl phthalate (DEP)		+ <sup>3</sup>							+	Rubber		
84695	Diisobutyl phthalate	+ <sup>2</sup>			+	+				+	Coatings, paper and board		(T) 1
84742	Dibutyl phthalate (DBP)	+ <sup>1</sup>			+	+	+	Restricted use <sup>5</sup>	0.3; (T) 60	+	Paper and board, printing inks, rubber		1; 3; 15
85687	Benzyl butyl phthalate (BBP)	+ <sup>1</sup>			+	+	+	Restricted use <sup>6</sup>	30; (T) 60	+	Paper and board, printing inks, rubber		6

Table S1 - continued

CASRN	Chemical name	SIN list 2.1			REACH		Union list			ESCO list			
		CMR	ED	Art. 57 REACH	SVHC list	Annex XIV		Restrictions and specifications	SML [mg/kg]		Application	Restrictions and specifications	SML [mg/kg]
94133	Propylparaben		+ <sup>3</sup>				+			+	Printing inks		
95807	4-Methyl-m-phenylenediamine	+ <sup>1</sup>			+					+	Rubber		
96457	Ethylene thiourea	+ <sup>1</sup>			+					+	Rubber		0.05
98544	4-tert-Butylphenol			+ <sup>4</sup>			+		0.05	+	Printing inks		0.05
100425	Styrene			+ <sup>4</sup>			+			+	Printing inks, rubber		
101144	4,4'-Methylene-bis[2-chloroaniline]	+ <sup>1</sup>			+					+	Rubber		
101779	4,4'-Methylene-dianiline (MDA)	+ <sup>1</sup>			+	+				+	Printing inks		ND (DL = 0.01)
106898	1-Chloro-2,3-epoxypropane	+ <sup>1</sup>					+	1 mg/kg in final product	ND	+	Paper and board, printing inks, rubber	1 mg/kg in final product	ND (DL = 0.01)
106990	Buta-1,3-diene	+ <sup>1</sup>					+	1 mg/kg in final product	ND	+	Printing inks, rubber	1 mg/kg in final product	ND (DL = 0.02)
107131	Acrylonitrile	+ <sup>1</sup>					+			+	Printing inks, rubber	1 mg/kg in final product	ND (DL = 0.01); 0.01
108463	1,3-Dihydroxybenzene		+ <sup>3</sup>				+		2.4	+	Printing inks, rubber		
109864	2-Methoxyethanol	+ <sup>1</sup>			+					+	Printing inks		
110805	2-Ethoxyethanol	+ <sup>1</sup>			+					+	Printing inks		(T) 3
111411	2-(2-Aminoethyl-amino)ethanol	+ <sup>2</sup>					+	For indirect food contact only.	0.05	+	Printing inks		
115968	Tris(2-chloro-ethyl)phosphate (TCEP)	+ <sup>2</sup>			+	+	+		ND	+	Printing inks		ND (DL = 0.02)
117817	Bis(2-ethylhexyl) phthalate (DEHP)	+ <sup>1</sup>			+	+	+	Restricted use <sup>5</sup>	1.5; (T) 60	+	Paper and board, printing inks, rubber		1.5; 40
119619	Benzophenone			+ <sup>4</sup>			+		0.6	+	Printing inks		(T) 0.6
123773	Diazene-1,2-dicarboxamide			+ <sup>4</sup>	+					+	Rubber		
126998	2-Chlorobuta-1,3-diene	+ <sup>1</sup>								+	Rubber	1 mg/kg in final product	ND (DL = 0.02)
131566	2,4-Dihydroxybenzophenon		+ <sup>3</sup>				+		(T) 6	+	Printing inks		(T) 6
131577	Benzophenone-3; Oxybenzone		+ <sup>3</sup>				+		(T) 6	+	Printing inks		(T) 6

**Table S1 - continued**

CASRN	Chemical name	SIN list 2.1			REACH		Union list		SML [mg/kg]	Group SML (T) [mg/kg]	ESCO list		SML [mg/kg]	Group SML (T) [mg/kg]
		CMR	ED	Art. 57 REACH	SVHC list	Annex XIV	Restrictions and specifications	Application			Restrictions and specifications			
137268	Thiram		+ <sup>3</sup>							+	Coatings, paper and board, rubber		ND; (T) 1	
137428	Sodium methyl-dithiocarbamate		+ <sup>3</sup>							+	Paper and board		ND	
140669	4-(1,1,3,3-Tetramethylbutyl)-phenol			+ <sup>4</sup>	+					+	Printing inks		ND	
151564	Ethyleneimine	+ <sup>1</sup>					+			+	Printing inks		ND (DL = 0.01)	
611994	4,4'-Dihydroxy-benzophenone		+ <sup>3</sup>				+		(T) 6	+	Printing inks		(T) 6	
630080	Carbon monoxide	+ <sup>1</sup>					+							
872504	N-Methyl-2-pyrrolidone	+ <sup>2</sup>			+		+		60	+	Printing inks			
1309644	Antimony trioxide			+ <sup>4</sup>			+		0.04	+	Printing inks		0.04 for Sb	
1330434	Disodium tetraborate, anhydrous	+ <sup>2</sup>			+		+		(T) 6	+	Paper and board, printing inks		(T) 6	
3380345	Triclosan			+ <sup>4</sup>			+	Provisional list <sup>7</sup>		+	Printing inks			
7632044	Sodium peroxometaborate	+ <sup>2</sup>								+	Paper and board		1	
8009038	Petrolatum	+ <sup>2</sup>								+	Coatings, rubber			
9016459	Nonylphenol, ethoxylated			+ <sup>4</sup>	+					+	Paper and board			
10043353	Boric acid	+ <sup>2</sup>			+		+		(T) 6	+	Cork and wood, printing inks		1; (T) 6	
25013165	tert-Butylhydroxy-anisole (BHA)		+ <sup>3</sup>				+		30	+	Coatings, printing inks		30; (T) 0.6	
26027383	4-Nonylphenol, ethoxylated			+ <sup>4</sup>	+					+	Paper and board			
28553120	Diisononyl phthalate (DINP)			+ <sup>4</sup>			+	Restricted use <sup>6</sup>	(T) 9; (T) 60	+	Rubber		1.8	
68515480	Diisononyl phthalate (DINP)			+ <sup>4</sup>			+	Restricted use <sup>6</sup>	(T) 9; (T) 60	+	Printing inks		T 9	
Σ	54	30	10	14	21	6	33			53				

<sup>1</sup> Classified CMR (Class I & II) according to Annex 1 of Directive 67/548/EEC

<sup>2</sup> Classified CMR according to Annex VI of Regulation 1272/2008

<sup>3</sup> Endocrine disrupter in the European Commission EDC database ([http://ec.europa.eu/environment/archives/docum/pdf/bkh\\_main.pdf](http://ec.europa.eu/environment/archives/docum/pdf/bkh_main.pdf))

## Table S1 - *continued*

<sup>4</sup> According to criteria defined by article 57, REACH

<sup>5</sup> Only to be used: as plasticizer in • repeated use materials and articles; • technical support agent up to defined concentrations.

<sup>6</sup> Only to be used as plasticizer in • repeated use materials and articles; • technical support agent up to defined concentrations; • plasticizer in single-use materials and articles for non-fatty foods (exception: formula, cereal-based and baby food for infants and young children).

<sup>7</sup> Triclosan is on the Provisional list ([http://ec.europa.eu/food/food/chemicalsafety/foodcontact/docs/080410\\_provisional\\_list\\_7\\_211009.pdf](http://ec.europa.eu/food/food/chemicalsafety/foodcontact/docs/080410_provisional_list_7_211009.pdf)) according to articles 6 and 7 of the Commission Regulation (EU) No. 10/2011.