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## Food contact substances and chemicals of concern: a comparison of inventories

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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 that are also considered to be chemicals of concern (COCs). The investigation was based on the following three FCM lists: (1) the 2013 Pew Charitable Trusts database of direct and indirect food additives legally used in the United States (or Pew for short), (2) the current European Union-wide positive list for plastic FCMs (or Union for short), and (3) the 2011 non-plastics FCM substances database published by EFSA (or ESCO for short). 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. Fifty-four substances present on the SIN list 2.1 were also found on the Union and/or ESCO lists. Twenty-one of those 54 substances are candidates for Substances of Very High Concern (SVHC), and six 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 (Sharpe & Irvine 2004; Norman et al. 2013). Food contact materials (FCM) have been identified as a major source of chronic exposure to chemicals (Grob et al. 2006; Borchers et al. 2010). 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 European Union (EU) and the United States (ESCO list 2011; Neltner et al. 2011, 2013; 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 harmonised 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, EFSA’s 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 United States, 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, authorisation of indirect food additives was granted following indirect food additive petitions. Today food contact substances (FCS) may also be used legally after notifying the USFDA via the Food Contact Notification system, if their migration into food does not exceed 50 ppb. Substances that are generally recognised as safe (GRAS) (21 C.F.R. Part 178) or that fall under the Threshold of Regulation Exemption (21 C.F.R. §170.39),

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with migration into food below 0.5 ppb, may be exempted from authorisation. 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 US, many regulatory gaps remain to be filled (Muncke 2009; Neltner et al. 2011, 2013). Furthermore, ongoing scientific discussions show that also authorised 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 (vom Saal et al. 2007; EFSA 2014). BPA was reported to act as endocrine disruptor (Soto & Sonnenschein 2010), cause developmental effects and changes in metabolism at low concentrations (Vandenberg et al. 2012; Boudalia et al. 2014), display changes to epigenetic footprints (Kundakovic & Champagne 2011; Manikkam et al. 2013; Kim et al. 2014), and result in enhanced endocrine-disrupting properties when added to several chemical mixtures (Isling et al. 2013; Naville et al. 2013; Viñas & Watson 2013). On the other hand, several risk assessment agencies continue to consider the use of BPA at present exposure levels safe (EFSA 2006, 2013; Bisphenol A (BPA) 2010; EFSA 2014). Albeit, EFSA suggested a reduction of the current tolerable daily intake (TDI) by a factor of 10 to 5  $\mu\text{g kg}^{-1}$  bodyweight  $\text{day}^{-1}$  (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 US National Toxicology Program (NTP), the National Institute of Environmental Health Sciences (NIEHS) and the USFDA (Schug 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 United States and the Europe. We investigated these chemicals of concern (COCs) with respect to their application and legal status. Our results (1) show gaps in the regulation of FCMs and (2) indicate how knowledge from different authorities and organisations could be used to increase chemical safety with the objective of improving public health.

## Materials and 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 versus Pew, Union, and ESCO lists) or manually (SIN 2.1 list  $\cap$  Union and/or ESCO list) versus 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, Gothenburg, Sweden) based on the criteria established in article 57 of Regulation (EC) No. 1907/2006 (REACH). Chemicals on the list were characterised 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 authorisation 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, USA.
- Databases of FCM substances
  - US food additive list (Pew list)  
In the United States, 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) USEPA's 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 & 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 2 October 2013 and the Union list was exported on 21 October 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 13 January 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 authorised by the EC in the Plastics Regulation. The other 146 substances/mixtures had not completed the authorisation process. Nevertheless, we also included these chemicals in our study. A total of 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). A total of 154 of these substances were listed in the US inventory of food additives, the PEW

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

List	Total number of entries	Number of CASRN entries	List compiled by:	Details	Reference
COCs	802	789	ChemSec	Chemicals of concern according to article 57 of REACH	SIN list 2.1 (2013)
	912	855	The Endocrine Disruption Exchange	Endocrine-disrupting compounds (EDCs)	TEDX list (2013)
	151	173	ECHA	Candidate list of SVHC for authorisation	SVHC list (2014)
FCMs	22	28	ECHA	Authorisation list	Annex XIV (2014)
	7169	5802	The Pew Charitable Trusts	Direct and indirect food additives authorised by the USFDA	Neltner et al. (2013)
	1038	873	European Commission	Positive list of chemicals authorised 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 European Union member states	ESCO list (2011)

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

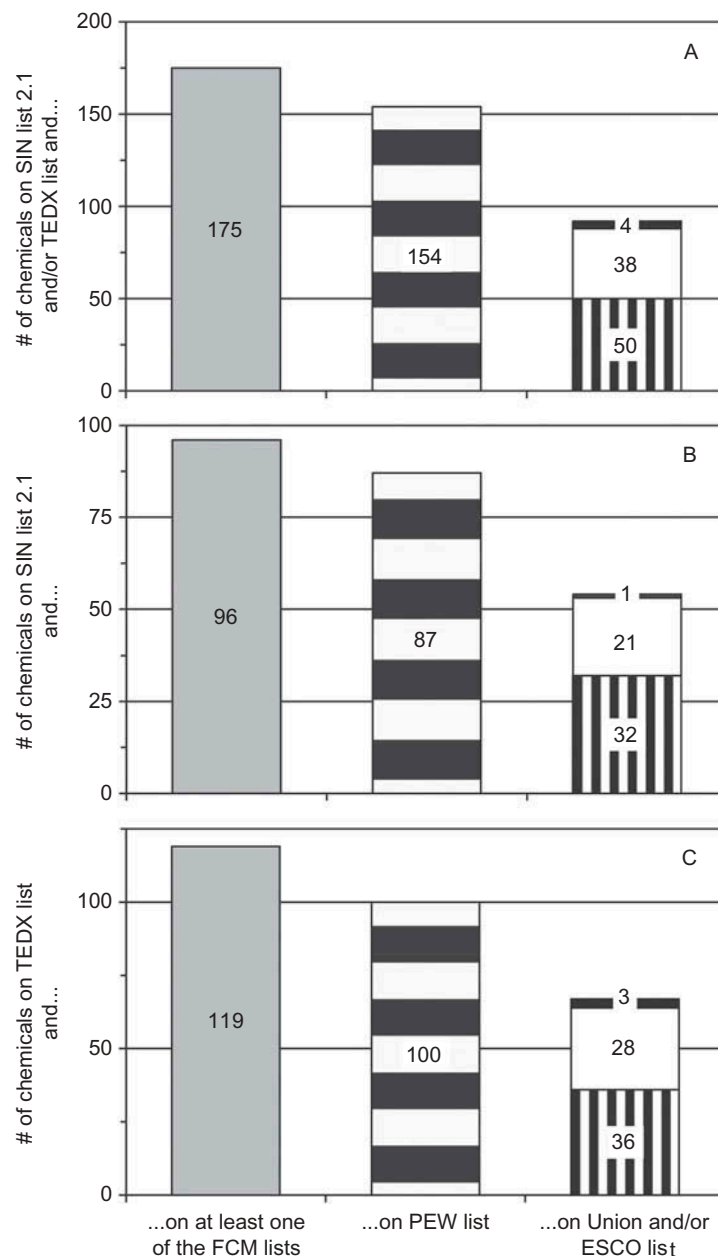


Figure 1. Number of chemicals listed on COC and FCM lists. Grey = chemicals on at least one of the three FCM lists; horizontal stripes = chemicals on the PEW list; vertical stripes = chemicals on the Union and ESCO lists; white = chemicals only on the ESCO list; and black = chemicals only on the Union 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; and (C) chemicals are listed on the TEDX list.

list, and a total of 92 substances were present on the Union and/or ESCO lists (Figure 1A). A similar pattern was observed analysing the 96 FCM chemicals that appeared only on the SIN list 2.1: 87 and 54 of those compounds were identified in the US 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). Only 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 US 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 & Ash 2008; ESCO list 2011; Sheffel 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 US and the EU. Forty 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 (diethyl phthalate (DEHP), 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 (Tables 2 and 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 eight 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 and 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 and Table S2). Fifteen out of 30 CMR substances were also listed on the SVHC list and six 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 harmonised 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 authorisation. The application for authorisation 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 US 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 et al. 2012; Vandenberg 2014) 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 harmonisation in the regulation of chemicals could improve chemical safety.

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

This study focuses on COCs that are inventoried or authorised for the manufacture of FCMs; it does not

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	Monomer for plastics (e.g. polyethylene oxide, polyethylene terephthalate)	Classified CMR <sup>c</sup>
80-05-7	Bisphenol A	Monomer for printing inks and rubber Defoamer in paper and board Monomer for plastics (polycarbonate) Monomer for resins (e.g. epoxy, phenolic, ethoxylene and ion exchange) Monomer and additive for printing inks	Possible reprotoxic chemical (R3) and categorised as an endocrine disruptor (category 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 Classified CMR <sup>c</sup>
84-74-2	Dibutyl phthalate (DBP)	Additive in plastics (plasticiser in, for example, polyvinyl chloride, polymethyl metacrylate, polyvinyl acetate and cellulose esters) Additive/plasticiser in paper and board, printing inks, adhesives, slimicides and cellophane	Classified CMR <sup>c</sup>
85-68-7	Benzylbutyl phthalate (BBP)	Additive in plastics (plasticiser in, for example, polyvinyl chloride, polyacrylates, polyvinyl acetate and nitrocellulose) Additive/plasticiser in paper and board, printing inks, acrylic coatings, adhesives and rubber	Classified CMR <sup>c</sup>
94-13-3	Propylparaben	Additive in plastics and printing inks	Endocrine disruptor with estrogenic and anti-androgen activity, affecting sperm function and prenatal development among others. Detected in biomonitoring studies and human urine and milk. Categorised as an endocrine disruptor in the European Commission EDC database
98-54-4	4-tert-Butylphenol	Monomer for plastics Plasticiser for cellulose acetate Adjuvant for polycarbonate Synthetic rubber manufacture Printing inks	Endocrine disruptor and toxic to reproduction. Widely found in the environment
100-42-5	Styrene	Monomer for different materials (e.g. styrene-butadiene rubber, acrylonitrile-butadiene-styrene polymer, styrene-acrylonitrile copolymer resin, printing inks) Cross-linking agent Solvent	Styrene is an endocrine disruptor (category 1). Reprotoxic as well as carcinogenic and mutagenic effects have been reported. It is highly toxic to aquatic species
106-89-8	1-Chloro-2,3-epoxypropane	Monomer for different materials (e.g. epoxy resins, elastomers, plasticisers, stabilisers, printing inks)	Classified CMR <sup>c</sup>
108-46-3	1,3-Dihydroxy-benzene	Monomer for plastics Plasticiser, stabiliser, rubber production, resins Flavouring agent	Endocrine disruptor affecting thyroid function as well as estrogen and glucose metabolism. Categorised as an endocrine disruptor in the European Commission EDC database

(continued)



Table 2. Continued.

CASRN	Chemical	FCM application <sup>a</sup>	Assessment for inclusion on SIN list 2.1 <sup>b</sup>
117-81-7	<i>Bis</i> (2-ethylhexyl) phthalate (DEHP)	Additive in plastics (e.g. plasticiser in PVC and its copolymers, cellulose nitrate and polystyrene) Additive in food packaging adhesives Defoamer in food-contact paper and board Lubricant Additive/plasticiser in paper and board, printing inks and rubber	Classified CMR <sup>c</sup>
119-61-9	Benzophenone	Additive in plastics UV curing agent and photoinitiator Polymerisation inhibitor for styrene	Carcinogenic effects have been reported. Potentially persistent, found in the environment. Derivates are potential endocrine disruptors
131-57-7	Benzophenone-3; oxybenzone	Additive in plastics and printing inks UV absorbing agent Used in the production of plastic surface coatings and polymers	Endocrine disruptor with estrogenic, anti-androgen and thyroid activity, affecting several body functions including development and immune function. Found in biomonitoring studies and in human milk and urine. Categorised as an endocrine disruptor in the European Commission EDC database Classified CMR <sup>d</sup>
10043-35-3	Boric acid	Additive and monomer in plastics (e.g. nylon) Component of paper, glass, ceramics and cork and wood	
25013-16-5	<i>tert</i> -Butyl-hydroxyanisole (BHA)	Additive in plastics, coatings and printing inks Antioxidant and preservative	Endocrine disruptor with estrogenic, thyroid and anti-androgen activity, affecting several body functions including development and reproduction. It is categorised as an endocrine disruptor in the European Commission EDC database

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.

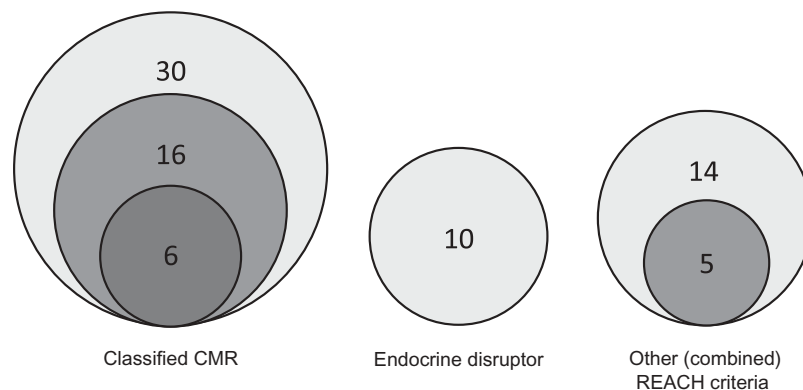


Figure 2. Toxicological classification of 54 chemicals listed on the SIN list 2.1 and on the Union and/or ESCO lists. The chemicals were classified according to their final assessment criteria for inclusion on the SIN list 2.1 as CMRs (according to Annex 1 of Council Directive 67/548/EEC or Annex VI 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; and dark grey = number of these chemicals also listed on Annex XIV of REACH.

describe a chemical's actual use, actual concentration in an FCM or its migration behaviour. 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 characterisation were not addressed.

The two European FCM lists cover many, but not all groups of FCM materials. The ESCO and the Union list are an inventory and a positive list, respectively. They do not contain impurities, breakdown 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 authorises 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 authorised 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 uncharacterised 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 characterise 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.

Table 3. Chemicals listed on Annex XIV and the Union and/or ESCO lists including their authorised, 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)	Not listed	Paper and board: SML = 1 mg kg <sup>-1</sup> alone or with DBP (NL) Coatings: SML = 1 mg kg <sup>-1</sup> alone or with DBP (NL) Paper and board: SML = 1 mg kg <sup>-1</sup> alone or with DIBP (NL) Printing inks: SML = 0.3 mg kg <sup>-1</sup> ; SML (T) = 60 mg kg <sup>-1</sup> (CH) Rubber: SML = 3 mg kg <sup>-1</sup> (F); SML = 15 mg kg <sup>-1</sup> (NL); maximum use level 5%, cumulative for all phthalates and not for fatty foods (I) Paper and board: not exceeding 1% in starting substance, no SML (NL) Printing inks: SML = 30 mg kg <sup>-1</sup> , SML (T) = 60 mg kg <sup>-1</sup> (CH) Rubber: SML = 3 mg kg <sup>-1</sup> (F); SML = 15 mg kg <sup>-1</sup> (NL); maximum use level 5%, cumulative for all phthalates and not for fatty foods (I)	Plasticiser in, for example, PVC Component of adhesives, coatings, paper, cellophane, rubber articles See Table 2 See Table 2
84-74-2	Dibutyl phthalate (DBP)	SML = 0.3 mg kg <sup>-1</sup> , SML (T) = 60 mg kg <sup>-1</sup> 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)		
85-68-7	Benzyl butyl phthalate (BBP)	SML = 30 mg kg <sup>-1</sup> , SML (T) = 60 mg kg <sup>-1</sup> 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)		
101-77-9	4,4'-Methylene-dianiline (MDA)	Not listed	Printing inks: SML = n.d. (DL = 0.01 mg kg <sup>-1</sup> ) (CH)	Additive in synthetic rubbers, dyes and polyamide resins Curing agent of epoxy and polyurethane resins Monomer of polydiisocyanates Plasticiser in cellulose derivatives, polyesters, polyacrylates and polyurethanes Flame retardant See Table 2
115-96-8	Tris(2-chloro-ethyl) phosphate (TCEP)	SML = n.d. Additive	Printing inks: SML = n.d. (DL = 0.02 mg kg <sup>-1</sup> ) (CH)	
117-81-7	Bis(2-ethylhexyl) phthalate (DEHP)	SML = 1.5 mg kg <sup>-1</sup> , SML (T) = 60 mg kg <sup>-1</sup> 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)	Paper and board: SML = 40 mg kg <sup>-1</sup> (NL) Rubber: SML = 1.5 mg kg <sup>-1</sup> (F); SML = 40 mg kg <sup>-1</sup> (NL); maximum use level 5%, cumulative for all phthalates and not for fatty foods (I) Printing inks (CH)	

Notes: SML, specific migration limit; SML (T), group-specific migration limit; n.d., substance should not be detectable; DL, detection limit.

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

***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 versus 88 and 54, respectively). However, the pool of FCM substances listed in the Pew list for the US 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 US, 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 authorised 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 US compared to the EU, or *vice versa*. Such a comprehensive risk assessment can only be achieved when detailed hazard characterisation 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 (EU) No. 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<sup>-1</sup> 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, authorise and eventually restrict the use of hazardous chemicals used in consumer products, thereby improving public health. It is part of a larger effort to harmonise 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 recognised. 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 authorisation 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 authorisation 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 et al. 2013).

## Conclusions

With the aim of increased harmonisation 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 harmonisation 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 prioritisation 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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## Supplemental data

Supplemental data for this article can be accessed here: <http://dx.doi.org/10.1080/19440049.2014.931600>.

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