Chemicals associated with plastic packaging: Inventory and hazards

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PeerJ Preprints | https://doi.org/10.7287/peerj.preprints.27036v1 | CC BY 4.0 Open Access | rec: 13 Jul 2018, publ: 13 Jul 2018

Abstract

Global plastics production has reached 380 million metric tons in 2015, with around 40% used for packaging. Plastic packaging is diverse and made of multiple polymers and numerous additives, along with other components, such as adhesives or coatings. Further, packaging can contain residues from substances used during manufacturing, such as solvents, along with non-intentionally added substances (NIAS), such as impurities, oligomers, or degradation products. To characterize risks from chemicals potentially released during manufacturing, use, disposal, and/or recycling of packaging, comprehensive information on all chemicals involved is needed. Here, we present a database of *Chemicals associated with Plastic Packaging* (CPPdb), which includes chemicals used during manufacturing and/or present in final packaging articles. The CPPdb lists 906 chemicals likely associated with plastic packaging and 3377 substances that are possibly associated. Of the 906 chemicals likely associated with plastic packaging, 63 rank highest for human health hazards and 68 for environmental hazards according to the harmonized hazard classifications assigned by the European Chemicals Agency within the Classification, Labeling and Packaging (CLP) regulation implementing the United Nations' Globally Harmonized System (GHS). Further, 7 of the 906 substances are classified in the European Union as persistent, bioaccumulative, and toxic (PBT), or very persistent, very bioaccumulative (vPvB), and 15 as endocrine disrupting chemicals (EDC). Thirty-four of the 906 chemicals are also recognized as EDC or potential EDC in the recent EDC report by the United Nations Environment Programme. The identified hazardous chemicals are used in plastics as monomers, intermediates, solvents, surfactants, plasticizers, stabilizers, biocides, flame retardants, accelerators, and colorants, among other functions. Our work was challenged by a lack of transparency and incompleteness of publicly available information on both the use and toxicity of numerous substances. The most hazardous chemicals identified here should be assessed in detail as potential candidates for substitution.

Keywords

Plastics; packaging; chemical composition; additive; harmonized hazard data; environment; human health; substitution; non-intentionally added substances (NIAS)

1. Introduction

The use of plastic packaging is on the rise (Smithers Pira, 2018; Van Eygen et al., 2017), explained by the need to reduce food waste or the increased demand due to population growth and market expansion (Andrady and Neal, 2009; Sohail et al., 2018; Thompson et al., 2009b). However, there are also increasing concerns about the harm caused to the environment (North and Halden, 2013) and human health (Halden, 2010). These concerns include littering and accumulation of nondegradable plastics in the environment (Jambeck et al., 2015; Thompson et al., 2009a), generation of secondary microplastics and nanoplastics (Galloway, 2015; Galloway and Lewis, 2016; Revel et al., 2018; Wright and Kelly, 2017), and release of hazardous chemicals during manufacturing and use (Biryol et al., 2017; Caporossi and Papaleo, 2017; Dematteo et al., 2013), as well as following landfilling (Mavakala et al., 2016; Sarigiannis, 2017), incineration (Franchini et al., 2004), or improper disposal leading to pollution of the environment (Gallo et al., 2018; Hahladakis et al., 2018; Hammer et al., 2012; Hermabessiere et al., 2017). In 2015, production of plastics reached 380 million metric tons worldwide, and of these, around 40% were used for packaging (Geyer et al., 2017; PlasticsEurope, 2016). Around 60% of all plastic packaging is used for food and beverages, while the rest covers non-food applications, such as healthcare, cosmetics, consumer, household, apparel, and shipment packaging. To reduce environmental impacts, efforts to drastically increase recycling rates of packaging plastics are currently being undertaken (EU, 2018; European Commission, 2018; Hammer et al., 2012).

Many chemicals used to make plastics, including packaging plastics, are highly hazardous (Lithner et al., 2011) and therefore of significant concern for occupational health (Fucic et al., 2018; Montano, 2014). Moreover, during the subsequent use, disposal, and recycling chemicals present in plastic packaging may transfer into products such as foods or cosmetics, or in the environment (Gallo et al., 2018; Hahladakis et al., 2018; Hermabessiere et al., 2017). With this, plastic packaging is likely to substantially contribute to chemical exposures of the human population and the environment (Biryol et al., 2017; Grob et al., 2006). Recycling can also result in accumulation of hazardous chemicals in secondary materials, negatively affecting their market value and restricting downstream applications (Geueke et al., 2018; Lahl and Zeschmar-Lahl, 2013; Ragossnig and Schneider, 2017). Therefore, a detailed assessment of plastic packaging-associated chemicals may be necessary (Bilitewski et al., 2012b; Bodar et al., 2018; Guzzonato et al., 2017).

Several strategies for assessing and scoring hazardous chemicals in plastics have already been proposed (Lithner et al., 2011; Rossi and Blake, 2014). These studies have so far focused on monomers and a small number of additives used in high concentrations, such as phthalate plasticizers in flexible polyvinyl chloride (PVC). However, to comprehensively inform design, manufacturing, and policy decisions supporting benign alternatives to hazardous chemicals in plastic

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packaging, the identity and amounts of all involved substances should be known. This applies to both the intentionally added substances (IAS), such as monomers used to make the polymer, additives added to the polymer to impart a desired property or function, and other chemicals intentionally used during manufacturing (e.g., solvents or processing aids), as well as the non-intentionally added substances (NIAS), such as impurities, reaction by-products, and breakdown products (Bradley and Coulier, 2007; Nerin et al., 2013). Unfortunately, achieving a comprehensive overview of all substances associated with plastic packaging is not a straightforward task. This is due to two main reasons: First, with regard to IAS, packaging plastics are made of multiple polymer types containing a large variety of chemical additives. Second, the chemical identity of many NIAS present in finished plastic packaging is seldom measured and often remains unknown.

The five polymers most commonly applied in plastic packaging include polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), polystyrene (PS), and PVC (PlasticsEurope, 2016). Many other polymers, including, for example, polycarbonate (PC), polyamides (PA, nylon), acrylics, polylactic acid (PLA), polyurethanes (PU) and even more specialized polymer types, are also applied for specific packaging applications (PlasticsEurope, 2016; Selke and Culter, 2016). A recent study found that the less common polymers still account for over 10% of post-consumer plastic packaging waste collected for recycling (Brouwer et al., 2018).

The major families of plastics additives (listed in order of decreasing total tonnage) are fillers, plasticizers, flame retardants, colorants, stabilizers, lubricants, foaming agents, and antistatic agents. Stabilizers can be further divided into several groups with more specific functions, including antioxidants, antiozonants, heat stabilizers, UV stabilizers, and biostabilizers (biocides) (Harper, 2006). There are also many other types of additives used in lower amounts (Flick, 2002; Zweifel et al., 2009). In addition to single-material based articles, multimaterial multilayers along with laminated structures are frequently used for packaging as well. In such systems, adhesives are often used to hold the construct together, adding another dimension of chemical diversity (Nerin et al., 2018).

Currently, no publicly available information source exists that offers a one-stop, easily accessible overview of all chemicals associated with plastic packaging. The available information is incomplete and scattered across multiple sources. For example, Annex I of Commission Regulation (EU) No 10/2011 (EU, 2011), also called the Union list, is a positive list of monomers and additives authorized for use in plastic food contact materials (FCMs). The Union list is, however, not specific for plastic food packaging, since it covers all food contact plastics in general, i.e., it includes other food contact articles (FCAs) such as cooking utensils or conveyor belts. Moreover, this list is focused on the IAS only and consequently does not cover most NIAS. Importantly, the EU legislation requires that safety of NIAS should be covered by risk assessment of FCMs but does not provide detailed guidance. Further, to the best of our knowledge, no lists comparable to the Union list exist for non-food plastic packaging.

To address the current dearth of information, we compiled a list of chemicals associated with plastic packaging. For this, we relied primarily on the information available from publicly accessible sources, but also explored the suitability of several industry-maintained databases on plastics and plastics additives products for finding and extracting information on the exact chemical composition of materials used in plastic packaging. However, we did not include any commercial, paid-for data sources, in order to ensure that the resulting database of chemicals associated with plastic packaging could be made publicly available. Free access to such a resource is highly desirable, as it can inspire and enable further research, regulatory actions, and packaging design innovations, as well as guide citizen activities aimed to tackle the plastic pollution problem. Further, we preliminarily explored the environmental and human health hazards of these chemicals and identified over a hundred substances of high concern that may require further detailed assessment. Numerous data gaps exist with regard to the use patterns and exposure, but also toxicity of plastic packaging-associated substances. These gaps need to be addressed in the future in order to properly evaluate the risks and explore substitution options.

2. Materials and Methods

2.1 Compilation of the database "Chemicals associated with plastic packaging" (CPPdb)

An overview of information sources used to compile the database of chemicals associated with plastic packaging (CPPdb) is given in Figure 1 and the workflow is described below. As a first information source we used the Chemicals and Product Categories database (CPCat; http://actor.epa.gov/cpcat) constructed by the U.S. Environmental Protection Agency (EPA) (Dionisio et al., 2015) (Fig. 1A). From this database, we extracted chemicals assigned to categories we deemed to be potentially plastics- and/or packaging-relevant, such as raw materials or monomers used to make plastics, or various types of additives and process regulators (Flick, 2002; Zweifel et al., 2009). Thus, we extracted the CPCat categories such as "plastics," "manufacturing packing plastics," "food packaging" or "fillers," but omitted the categories clearly irrelevant to plastic packaging, such as "building material plastics" or "wood preservatives." The complete list of all CPCat categories extracted for this project is given in the Supplementary File 1. Since many chemicals can be used in multiple applications, most chemicals in the CPCat database are listed in multiple categories. Therefore, in the next step we fused all extracted categories for each extracted unique CAS number. The extracted chemicals were regarded as associated with plastics ("yes" in the respective column in the CPPdb) whenever the extracted categories contained the indication "plastics" or "manufacturing

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plastics," and as associated with "plastic packaging" ("yes" in the respective column in the CPPdb) whenever there were indications for both "plastics" and "packaging."

The second information source consulted for the CPPdb (Fig. 1A) was the "Plastics additives database" by Ernest Flick (2004), which lists around 7000 commercial products being marketed as plastics additives, sorted according to their function in plastics, e.g., stabilizer, antioxidant, filler, or plasticizer (Flick, 2004). Where available, the identity of chemicals associated with the listed products was recorded (withholding the brand name) and corresponding CAS numbers were searched and assigned manually where found. All chemicals referenced in this source were regarded as associated with plastics. The resulting list of chemicals was merged with the CPCat-derived list. For duplicate chemicals (matching by CAS), Flick-derived use/function information was added to CPCat-derived category descriptors and identification as being associated with plastics was assigned if not already given previously based on CPCat data.

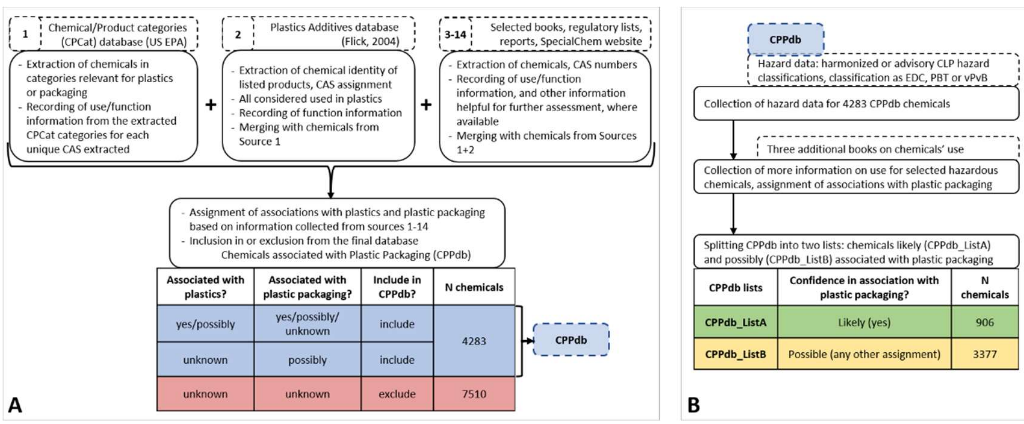

Figure 1. Overview of information sources (dashed-line boxes) and approaches/workflow (solid-line boxes) followed to (A) compile the database of chemicals associated with plastic packaging (CPPdb) and (B) split the full CPPdb into the two lists according to the assigned likely (CPPdb_ListA) or possible (CPPdb_ListB) association with plastic packaging. Abbreviations not explained on the figure: CLP, Classification, Labeling and Packaging; EDC, endocrine disrupting chemical; PBT, persistent, bioaccumulative, toxic; vPvB, very persistent, very bioaccumulative.

Further information sources (see Fig. 1A, sources numbered 3 to 13) that we consulted and integrated into the CPPdb included: (3) the chemicals listed in the book on chemical analytics of plastics and polymers (Bolgar et al., 2016); (4) the list of plastic monomers and selected additives along with some other substances used in plastics manufacturing (Lithner et al., 2011); (5) the chemicals listed on the European Flavours, Additives, and food Contact materials Exposure Task (FACET) list for food contact materials (Oldring et al., 2014); (6-8) three reports on hazardous chemicals associated with plastics (Hansen et al., 2013; Klar et al., 2014; Stenmarck et al., 2017); (9) the list of 1009 food contact substances for which Biryol and colleagues provided high-throughput estimates of their initial concentration in food contact articles made of "plastics, coatings, or

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silicones" (Biryol et al., 2017); (10) the chemicals discussed in two reviews on NIAS (Geueke, 2018; Nerin et al., 2013); (11) the list of extractables from pharmaceutical packaging and devices made of polyolefins, PET, PS, PVC, PA, ethylene-vinyl acetate (EVA), and PU (Jenke, 2009); (12) Annex I of Commission Regulation (EU) No 10/2011, listing plastics monomers and additives permitted for use in plastic food contact materials in the European Union (EU, 2011); and (13) EPA's list of 16 priority polycyclic aromatic hydrocarbons (PAHs) (Keith and Telliard, 1979; Keith, 2015). The latter list was included because some PAHs have been detected as contaminants in plastic packaging made of PS (Li et al., 2017; Rochman et al., 2013). Apart from the chemicals' identity extracted from these sources, we also recorded, as far as available, other relevant information, such as product or polymer types where a given substance has been used or found. The resulting lists of chemicals were merged with the list generated at the previous step. For CAS-matched chemicals, additional information was recorded and identification as being associated with plastics and/or plastic packaging was assigned where appropriate.

The 14th and final information source consulted for the initial compilation of the CPPdb (Fig. 1A) was the SpecialChem website ("The Universal Selection Source of Chemical & Materials," https://www.specialchem.com, accessed November 24, 2017). Some content on this website can be viewed for free upon registration; additional features are provided through paid upgrades, but this option was not used in our research. We performed a search in the subsection on plastics additives (https://polymer-additives.specialchem.com) with the filter "recommended for packaging applications." For the products returned with this search, we extracted chemical identity and assigned CAS numbers manually, where found. The resulting list was fused with the list generated at the previous step. For CAS-matched chemicals, additional identification as being associated with plastics and/or plastic packaging was assigned if not given previously.

All chemicals identified as likely or possibly associated with plastics were kept in the final CPPdb inventory, regardless of whether or not clear indications of their association with plastic packaging were available at this stage (Fig. 1A). This was done because we reasoned that all chemicals associated with plastics could potentially be associated with plastic packaging as well, and we lacked the information necessary to systematically exclude substances that might be applied only in plastics not used for packaging purposes. However, all chemicals for which we could not find at this stage any indication of their association with plastics or plastic packaging were removed from the final CPPdb inventory (Fig. 1A). All CPPdb chemicals were then taken further to the next stage of this project, that is, the exploration of human health and environmental hazards (see Subsection 2.2). For selected hazardous chemicals identified at this later stage, three additional books on chemicals' use (Ash and Ash, 2008; Milne, 2005; Sheftel, 2000) were then consulted to obtain more information regarding their potential use in plastic packaging, and additional identification as being associated with plastic

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packaging was then assigned where justified. After this, depending on a substance's assigned association with plastic packaging, the full CPPdb was split into the CPPdb_ListA and CPPdb_ListB, containing lists of chemicals likely and possibly associated with plastic packaging, respectively (Fig. 1B, see also Subsection 3.1).

2.2 Exploration of CPPdb chemicals' hazards

To explore the environmental and human health hazards of the CPPdb chemicals, we applied, with some modifications, the methodology published by Lithner and colleagues (2011). This approach uses the harmonized hazard classifications assigned by the European Chemical Agency (ECHA) under the European Classification, Labeling and Packaging (CLP) legislation (EU, 2008). The CLP governs the EU implementation of the Globally Harmonized System of Classification and Labeling of Chemicals (GHS), adopted by the United Nations (UN) in 2002 (see http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html, accessed June 5, 2018). Harmonized CLP classifications (hazard category and class) were extracted from the ECHA-provided file "Annex VI to CLP_ATP10" (updated version of Table 3.1 of Annex VI to CLP, 10th Adaptation to Technical Progress (ATP10; in force from Dec 1, 2018), accessed at https://echa.europa.eu/information-on-chemicals/annex-vi-to-clp on Nov 2, 2017). These classifications were matched to the CPPdb chemicals by CAS numbers. Every classification was assigned a numerical hazard grade score according to the previously proposed gradation (Lithner et al., 2011). For example, Carcinogenicity 1A (Carc. 1A) and Carc. 1B received the highest hazard grade score of 10 000, while that of Carc. 2 was 100. Acute Toxicity 1 (Acute Tox. 1) and Acute Tox. 2 both received a hazard grade score of 1000, while grade scores of Acute Tox. 3 and 4 were 100 and 10, respectively. For aquatic toxicity, Aquatic Acute 1 (Aq. Acute 1) classification was assigned a hazard grade score of 100 and Aq. Chronic 1 received a hazard grade score of 1000. A table listing all CLP classifications with corresponding hazard grade scores as adopted in this work is given in the Supplementary File 2. Then, a sum hazard score was calculated for each chemical, separately for environmental and human health hazards. For the former, hazard grade scores assigned in Aq. Acute and Aq. Chronic categories were summed. For the latter, hazard grade scores assigned in all human health-related toxicity categories were summed.

Since many chemicals in the CPPdb did not have any harmonized CLP classifications assigned by ECHA, we also extracted advisory CLP classifications for human health hazards as assigned by the Danish Environmental Protection Agency (Danish EPA) in the online database at http://mst.dk/kemi/kemikalier/stoflister-og-databaser/vejledende-liste-til-selvklassificering-af-farlige-stoffer/clp/, accessed March 28, 2018. Each advisory CLP classification was then assigned the same hazard grade score as that assigned to a matching harmonized CLP classification, and sum

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hazard scores were calculated as described above for harmonized CLP classifications. We did not examine advisory CLP classifications for environmental hazards, because updated classifications for the Aq. Chronic category were not available at the time.

In addition to the hazard categories currently covered by the CLP system, we also considered whether the substance is classified as persistent, bioaccumulative, and toxic (PBT), or very persistent, very bioaccumulative (vPvB), or endocrine disrupting chemical (EDC). This type of information was searched and added for the CPPdb chemicals by consulting sources such as PBT and vPvB status of a substance in the EU (https://echa.europa.eu/information-on-chemicals/pbt-vpvb-assessments-under-the-previous-eu-chemicals-legislation, accessed December 7, 2017), EDC classifications assigned by December 2017 within the Registration, Evaluation, Authorization and restriction of Chemicals (REACH) regulation in the EU (EU, 2006), recognition as an EDC or a potential EDC listed in the recent report by the United Nations Environment Programme (UNEP) on EDCs (UNEP, 2018), the Substitute It Now! (SIN) list maintained by the non-governmental organization (NGO) International Chemical Secretariat (ChemSec; http://chemsec.org/business-tool/sin-list/, accessed November 24, 2017) and ChemSec's identification of REACH-relevant EDCs (ChemSec, 2015), and The Endocrine Disruption Exchange (TEDX) list of potential EDCs (https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/, accessed November 24, 2017), maintained by the U.S. NGO TEDX.

To complete the CPPdb with information which could be useful for further assessment, we also documented additional aspects, for example, a substance's production tonnage band in the EU as documented in its REACH registration dossier (resource accessed September 11, 2017, database containing information from 62200 dossiers on 16402 unique substances), a substance's presence in the U.S. Toxic Substances Control Act inventory (accessed January 16, 2018), or whether it is included in a biomonitoring program in the U.S. (Centers for Disease Control and Prevention (CDC), 2018), performed with the blood and urine samples collected within the National Health and Nutrition Examination Survey (NHANES) (Sobus et al., 2015), or similar programs in Canada, i.e., within Canada Health Measures Survey (Haines et al., 2017), or Germany (Kolossa-Gehring et al., 2017). With regard to the regulatory status, we recorded a substance's inclusion on the Candidate, Authorization, or Restriction lists (status December 2017) within REACH (EU, 2006), on the California Proposition 65 list in the U.S. (http://oehha.ca.gov/proposition-65/proposition-65-list, accessed March 16, 2018, and in the Occupational Chemical Database maintained by the U.S. Occupational Safety and Health Administration (OSHA) (http://www.osha.ogv/chemicaldata/, accessed November 25, 2017. A detailed description of all information sources used for populating different columns in the CPPdb is given in the "READ ME" worksheet of the Supplementary File 3 presenting the CPPdb.

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3. Results

3.1 The CPPdb and its information content

To populate the CPPdb we relied on 14 publicly available information sources and followed the strategy described in the subsection 2.1 and summarized in the Figure 1A. Based on this, we identified and included in the CPPdb 4283 substances that are likely or possibly associated with plastic packaging, both in terms of use during the manufacturing and/or presence in the final products. Additional 7510 substances, most of them originally retrieved from our first source, the CPCat database, were excluded from the CPPdb list at that stage, because the 14 initial information sources did not contain any indication of these substances' use in plastics and/or plastic packaging (Fig. 1A).

The 4283 substances included in the CPPdb cover raw materials and chemicals used in plastics manufacturing, such as monomers, polymerization aids, solvents or catalysts, along with additives such as pigments, fillers, antioxidants, stabilizers, plasticizers, antistatic agents, slip agents and others (Zweifel et al., 2009). We also added several well-known NIAS such as impurities or degradation products of some polymers and stabilizers (Nerin et al., 2013). However, the coverage of NIAS was knowingly incomplete. Many more substances have been reported to be present in different plastics (Bradley and Coulier, 2007), but data characterizing their complete chemical identity, hazard, and exposure are often lacking (Muncke et al., 2017).

When compiling the CPPdb, we sought to determine the substance's relevance specifically for plastic packaging, whenever any such indications could be found in the original 14 data sources. However, information on the substance's association with plastic packaging was even scarcer than that on the substance's association with plastics in general. For example, the CPCat database does contain a category "manufacturing packing plastics," but this category includes only 79 substances, although many more chemicals are likely used (Biryol et al., 2017; EU, 2011; Muncke et al., 2017; Oldring et al., 2014). Most other data sources, while indicating that a given chemical is used in plastics in general, often did not further specify the types of polymers, products, or applications using this chemical. Thus, based on the 14 initial information sources, the likely association with plastic packaging could be assigned for only a few hundred CPPdb substances. Therefore, for a subset of substances we considered the most important, we consulted three additional literature sources on chemical uses (Ash and Ash, 2008; Milne, 2005; Sheftel, 2000) in order to further explore their potential association with plastic packaging. These substances were those identified to be of the highest environmental and/or human health hazard based on harmonized and/or advisory CLP classifications (see below), and/or classified in the EU as EDC, PBT, or vPvB substance, or included in biomonitoring programs in the U.S., Canada or Germany (Fig. 1B).

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In the end, we were able to identify 906 substances to be likely associated with plastic packaging in terms of being used during the manufacture of plastic packaging or being present in the final packaging articles. These substances are listed on the CPPdb_ListA (Fig. 1B). All remaining substances (3377 chemicals), jointly considered as possibly associated with plastic packaging, are listed on the CPPdb_ListB (Fig. 1B). This list includes substances for which only 'possible' association with plastic packaging could be assigned, or no information regarding the association with plastic packaging was available in the information sources referenced above, with or without the three additional books on chemicals' use. Since these three last sources were checked only for selected chemicals, it is possible that some of the chemicals on the CPPdb_ListB are in fact also 'likely' associated with plastic packaging, but this could not be assigned based on the information collected. Note, although a few substances on the CPPdb_ListB are currently banned in Europe or in the U.S., they have been kept on the list because their relevance to plastic packaging worldwide could not be excluded. The two CPPdb lists can be found in the Supplementary File 3 or accessed at the DOI 10.5281/zenodo.1287773. Additionally, the CPPdb lists will be uploaded into the Chemical Hazard Data Commons resource, maintained by the non-governmental organization (NGO) Healthy Building Network (HBN) (https://commons.healthymaterials.net/home, accessed June 5, 2018).

3.2 Exploration of CPPdb chemicals' hazards, identification of the most hazardous substances

To explore the hazards of the CPPdb chemicals with the goal to identify the most hazardous substances, we consulted both the harmonized CLP classifications (i.e. ECHA-assigned) and the advisory CLP classifications assigned by the Danish EPA based on *in silico* models. In addition, we considered EU-accepted classifications as an EDC, PBT, or vPvB substance, and recognition as an EDC or a potential EDC in the 2018 UNEP report on EDCs (UNEP, 2018). The UNEP report recognizes three stakeholders and consequently the EDC assessments that they performed as "robust," namely the REACH EDC classifications, the ChemSec's assessments for SIN list, and the assessments by the Danish Centre for Endocrine Disruptors. The "thorough scientific assessments" performed by these stakeholders were carried out based on the definition of an EDC or a potential EDC given by the World Health Organization (WHO)/International Program on Chemical Safety (IPCS) in 2002 (WHO/IPCS, 2002). Further, the UNEP report differentiates between chemicals identified as EDCs or potential EDCs with the involvement of "multiple stakeholders" (this group includes REACH EDC classifications only) and "at least one stakeholder" (this group includes EDC identifications by ChemSec and/or Danish Centre for Endocrine Disruptors). For 60% of the 4283 CPPdb substances no hazard data were available in the sources we reviewed. A detailed breakdown of the number of chemicals having at least one of the reviewed hazard classifications is given in Table 1. To select the most hazardous substances as candidates for further assessment and potential substitution with

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regard to their use in plastic packaging, we next focused on the substances identified as likely associated with plastic packaging (CPPdb_ListA), as discussed in the next subsections.

Table 1. Availability of hazard information for CPPdb chemicals in the sources consulted

Group		CPPdb full, i.e., ListA + ListB	Association with plastic packaging	
			Likely CPPdb_ListA	Possible CPPdb_ListB
Total		4283	906	3377
Harmonized CLP for environmental hazards		332 (7.8%)	121 (13.4%)	211 (6.2%)
sum hazard score	1100	173	68	105
	200	1	1	0
	100	96	30	66
	10	62	22	40
	0, i.e., no classifications	3951 (92.2%)	785 (86.6%)	3166 (93.8%)
Harmonized CLP for human health hazards		718 (16.8%)	245 (27.0%)	473 (14.0%)
sum hazard score	10 000 – 32 100 (34 210)*	205	63	142
	1000 – 3210	200	67	133
	100 – 400	182	70	112
	10 – 50	131	45	86
	0, i.e., no classifications	3565 (83.2%)	661 (73.0%)	2904 (86.0%)
Advisory CLP for human health hazards		950 (22.2%)	202 (22.3%)	748 (22.1%)
sum hazard score	1000 – 2110 (2220)	304	102	202
	100 – 300 (200)	264	59	205
	10 – 20	382	41	341
	0, i.e., no classifications	3333 (77.8%)	704 (77.7%)	2629 (77.9%)
EDC classification, REACH		17 (0.4%)	15 (1.7%)	2 (0.06%)
EDC identification, UNEP report, 'multiple'		16 (0.4%)	14 (1.5%)	2 (0.06%)
EDC identification, UNEP report, 'at least one'		25 (0.6%)	20 (2.2%)	5 (0.15%)
PBT and/or vPvB classification, EU		31 (0.7%)	7 (0.8%)	24 (0.7%)
None of the above classifications		2568 (60.0%)	433 (47.6%)	2135 (63.2%)

*The number in brackets shows the upper border value for this range on the CPPdb_ListB, if different from CPPdb_ListA.

3.2.1 Identification of the most hazardous substances based on harmonized CLP and EU classifications

The sum hazard scores derived based on harmonized CLP classifications for environmental or human health hazards were used to sort the lists of chemicals from highest to lowest sum hazard scores, corresponding to higher and lower hazards, respectively. In addition to harmonized CLP-based ranking, substances classified within the EU as EDC, PBT, or vPvB, and recognized as EDCs or potential EDCs in the UNEP report (2018) were also considered to be highly hazardous for human health and/or the environment. A detailed breakdown of the number of substances with each classification and within several sum hazard score ranges is given in Table 1. Based on these sources,

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we identified 148 substances as the most hazardous ones among the 906 substances on the CPPdb_ListA, i.e., likely associated with plastic packaging; 24 of these substances had more than one of the reviewed hazard classifications in the chosen ‘most hazardous’ range (Fig. 2). These 148 substances are listed in the Supplementary File 4. Among the 3377 substances on the CPPdb_ListB, i.e., possibly associated with plastic packaging, 214 substances were identified as the most hazardous based on the same criteria, with 57 substances showing an overlap between different classifications in the ‘most hazardous’ range.

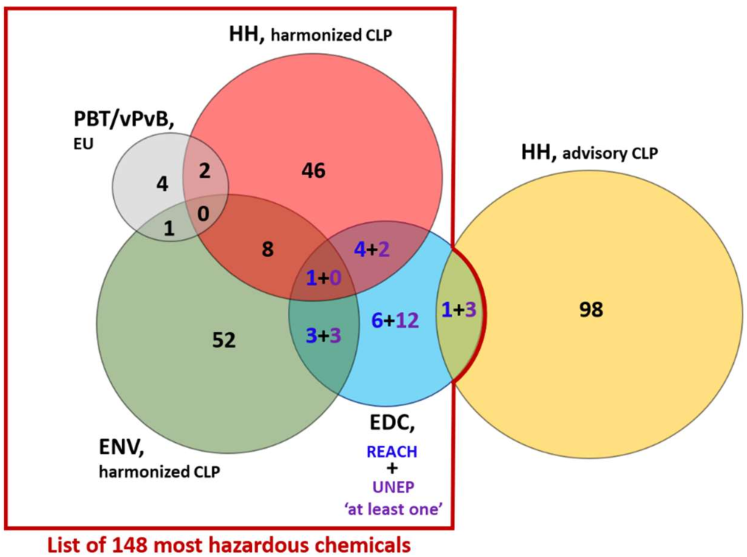

Figure 2. Overlap between the groups of the most hazardous substances likely associated with plastic packaging (i.e., on the CPPdb_ListA), identified according to (i) environmental (ENV) hazards based on harmonized Classification, Labeling and Packaging (CLP) classifications (green circle, list “ENV, harmonized CLP,” 68 substances in total); (ii) human health (HH) hazards based on harmonized CLP classifications (red circle, list “HH, harmonized CLP,” 63 substances in total); (iii) classification in the European Union (EU) as a substance with persistent, bioaccumulative, and toxic (PBT) properties and/or very persistent, very bioaccumulative (vPvB) properties (gray circle, list “PBT and/or vPvB, EU,” 7 substances in total); (iv) classification as an endocrine disrupting chemical (EDC) within Registration, Evaluation, Authorization and restriction of CHemicals (REACH) legislation in the EU [font color blue] or recognition in the 2018 United Nations Environment Programme (UNEP) report as an EDC or a potential EDC identified by at least one robust stakeholder following a thorough scientific assessment based on a definition of an EDC or a potential EDC postulated by the World Health Organization (WHO)/International Program on Chemical Safety (IPCS) in 2002 [font color purple] (blue circle, list “EDC, REACH + UNEP ‘at least one’,” 35 substances in total; *n.b.*, all but one REACH-classified EDC is also recognized in the UNEP report as an EDC or a potential EDC identified with involvement of multiple stakeholders); and (v) HH hazards based on advisory CLP classifications (yellow circle, list “HH, advisory CLP,” 102 substances in total). The red frame encloses the substances included in the final list of 148 most hazardous chemicals likely associated with plastic packaging. The 98 substances identified as ‘most hazardous’ for HH based only on advisory CLP classifications are not included in this final list. Sizes of the circles are not exactly to scale.

For environmental hazards, there were only 4 different sum hazard score values (Table 1), because only two relevant categories, Aq. Acute and Aq. Chronic, were available to calculate this score. Sixty-eight substances on the CPPdb_ListA had the highest sum hazard score for environmental hazards (1100) and were thus considered to be of the highest environmental hazard based on harmonized CLP classifications.

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For human health hazards, there were 80 different sum hazard score values based on harmonized CLP classifications (ranging from 32 100 to 10) within the CPPdb_ListA (Table 1). Here, 63 substances on the CPPdb_ListA with sum hazard scores equal to or higher than 10 000 were considered to have the highest human health hazard based on harmonized CLP classifications (Table 1). This range was chosen because the substances that would be included within it are certain to have at least one classification with the highest hazard grade score of 10 000, given to the most severe CLP classifications only, namely the 1A and 1B hazard classes in the carcinogenicity (Carc.), mutagenicity (Muta.), and reproductive toxicity (Repr.) categories, reflective of the so-called CMR properties (Lithner et al., 2011).

Fifteen CPPdb_ListA substances have been identified as substances of very high concern (SVHC) within REACH for their endocrine disrupting properties with regard to human health and/or the environment, either as an individual substance or belonging to a group of related substances. Fourteen of these 15 substances are also listed in the UNEP report (2018) as EDCs or potential EDCs identified after a thorough scientific assessment with involvement of multiple stakeholders (with the exception of BPA, see above). The fifteenth chemical, not inventoried by the UNEP report but classified as an EDC within REACH, is bisphenol A (BPA, CAS 80-05-7). This chemical was not included in the UNEP report because it was officially classified as an EDCs only after the final drafting of the UNEP report in July 2017. Twenty additional substances on the CPPdb_ListA are listed in the UNEP report (2018) as EDCs or potential EDCs identified after a thorough scientific assessment by at least one robust stakeholder. Further 7 substances on the CPPdb_ListA have been classified as having PBT and/or vPvB properties in Europe. Among the two latter categories, three substances have both PBT and vPvB classifications.

3.2.2 Identification of the substances most hazardous for human health based on advisory CLP classifications

Similar to the approach taken with harmonized CLP classifications, the sum hazard scores derived based on advisory CLP classifications were used to sort the chemical lists from the highest to the lowest hazard. Based on this ranking, 102 CPPdb_ListA substances having sum hazard score values equal to or higher than 1000 were considered to exhibit the highest human health hazard. This cut-off was chosen because it covered all CMR-classified substances along with a Skin Sensitization 1 classification, also regarded as a crucial human health-related hazard (Lithner et al., 2011). Overall, CPPdb_ListA chemicals had 15 sum hazard score values calculated based on advisory CLP classifications for human health hazards, ranging from 2110 to 10 (Table 1). Thus, the maximal sum hazard scores in this case were much lower than those calculated based on the harmonized CLP classifications. This is because the most severe hazard classifications—those reflective of the CMR properties—are never assigned when only *in silico* estimations of toxicity are considered. Therefore,

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modeling-based advisory CLP classifications by default cannot rise above “possible” or “predicted” status. Among the 102 most hazardous substances identified based on advisory CLP classifications, 4 chemicals have been identified as EDCs by REACH and/or UNEP report (2018) (Fig. 2).

3.2.3 Distribution of CLP hazard categories among the most hazardous substances

The 68 CPPdb_ListA substances identified as the most hazardous for the environment according to harmonized CLP data are assigned in the highest hazard class for both acute and chronic aquatic toxicity (Aq. Acute 1 and Aq. Chronic 1). Among the 63 most hazardous CPPdb_ListA substances identified based on harmonized CLP classifications for human health hazards, CMR properties were represented most often, followed by acute toxicity after oral intake or inhalation, specific target organ toxicity after a single or repeated exposure (STOT SE and STOT RE categories), and skin sensitization (Fig. 3A). Other hazard categories, such as acute toxicity after dermal exposure, skin irritation or corrosion, eye damage or irritation, were also assigned often, but these have much less weight (lower numerical hazard grade score) and therefore contributed the least to the overall sum hazard score for human health hazards. On the contrary, among the most hazardous chemicals identified based on the advisory CLP classifications for human health hazards, classifications in the CMR-related categories were assigned relatively rarely, while classifications for skin sensitization were the most frequent (Fig. 3B).

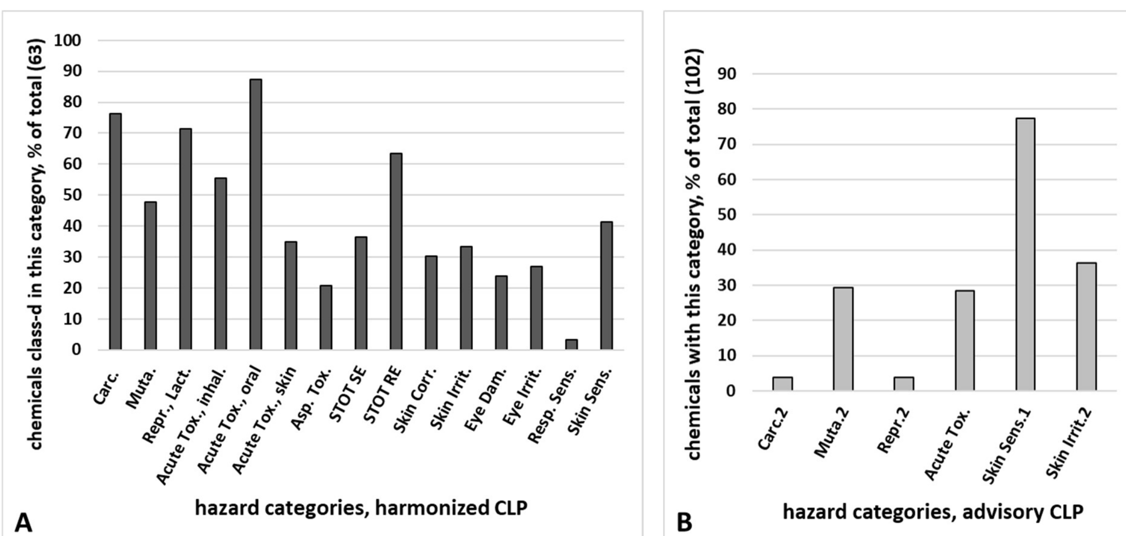

Figure 3. Distribution of hazard categories among the most hazardous substances identified based on harmonized classification, labeling and packaging (CLP) classifications for human health hazards (A, 63 substances in total) or advisory CLP classifications for human health hazards (B, 102 substances in total). Hazard categories given without numbers include all classes within the given category. Hazard categories given with numbers include on the respective class. Abbreviations: Carc.: Carcinogenicity, Muta.: Mutagenicity, Repr.: Reproductive Toxicity, Lact.: Lactation toxicity, Acute Tox., inhal.: Acute Toxicity, inhalation; Acute Tox., oral: Acute Toxicity, oral; Acute Tox., skin: Acute Toxicity, dermal; Asp. Tox.: Aspiration Toxicity; STOT SE: Specific Target Organ Toxicity Single Exposure; STOT RE: Specific Target Organ Toxicity Repeated Exposure; Skin Corr.: Skin Corrosion; Skin Irrit.: Skin Irritation; Eye Dam.: Eye Damage; Eye Irrit.: Eye Irritation; Resp. Sens.: Respiratory Sensitization; Skin Sens.: Skin Sensitization.

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3.2.4 Distribution of functions among the most hazardous substances

Table 2 presents an overview of the main functions performed in plastics by the most hazardous chemicals likely associated with plastic packaging, identified as described in the subsection 3.2.1, along with the specific hazards and sum hazard scores calculated for each substance. This table also shows the specific hazards and sum hazard scores calculated for each substance. The functions represented most often were (in the order of decreasing number of substances in a group): Monomers and intermediates, solvents, surfactants and their degradants, stabilizers, plasticizers, biocides, fire retardants, accelerators, and colorants (Table 2).

The overview in Table 2 is intended to be illustrative only and is by no means comprehensive. For clarity, we chose to show only one, presumably main, function for each chemical, although some substances could perform several different functions in plastics. Further, to avoid overcrowding, we excluded the 22 substances containing one or more of the 4 heavy metals considered most hazardous according to the European Directive 94/62/EC on packaging and packaging waste (EU, 1994), i.e., cadmium, lead, mercury, and hexavalent chromium. Therefore, only 126 out of the 148 most hazardous substances identified in 3.2.1 are listed in Table 2. Among the 22 excluded metal-containing substances, all except one (cadmium sulfide, CAS 1306-23-6) are classified into the top category for environmental hazards (sum hazard score 1100), and some are also highly hazardous to human health due to CMR properties (see Supplementary File 4).

Table 2. Main performance functions and chemical groups represented among the 111 most hazardous chemicals likely associated with plastic packaging (CPPdb_ListA), identified based on selected harmonized hazard data(*).

function	chemical group	CAS	name	Sum hazard scores, harmonized CLP(**)		EDC, PBT/vPvB(***)
				ENV	HH	
accelerators	dithiocarbamate	14324-55-1	zinc bis(diethyldithiocarbamate)	1100	1040	-
		136-23-2	zinc bis(dibutyldithiocarbamate)	1100	1030	-
	thiazole and thiuram	97-77-8	disulfiram	1100	1110	-
		120-78-5	di(benzothiazol-2-yl) disulphide	1100	1000	-
		149-30-4	2-mercaptobenzothiazole	1100	1000	-
biocides	carbamate	137-30-4	ziram	1100	2220	EDC (UNEP)
		55406-53-6	3-iodo-2-propynyl-N-butyl carbamate	1100	2210	-
		137-26-8	thiram	1100	1140	EDC (UNEP)
	phenolics	3380-34-5	triclosan	1100	20	EDC (UNEP)
		97-23-4	dichlorophen	1100	20	-
	organo metallic	76-87-9	fentin hydroxide	1100	2520	-
		900-95-8	fentin acetate	1100	2520	-
		1338-02-9	naphthenic acids, copper salts	1100	10	
		155925-27-2	silver sodium hydrogen zirconium phosphate	1100	-	
	parabens	99-76-3	methyl 4-hydroxybenzoate	-	-	EDC (UNEP)
		120-47-8	ethyl 4-hydroxybenzoate	-	-	EDC (UNEP)
		94-13-3	propyl 4-hydroxybenzoate	-	-	EDC (UNEP)
colorants	dye, azo	101-77-9	4,4-methylenedianiline	100	13100	-
		95-80-7	4-methyl-m-phenylenediamine	100	12310	-
		1937-37-7	disodium 4-amino-3-[[4-[(2,4-diaminophenyl)azo][1,1-biphenyl]-4-yl]azo]-5-hydroxy-6-(phenylazo)naphthalene-2,7-disulphonate	-	10100	-

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		573-58-0	disodium 3,3-[[1,1-biphenyl]-4,4-diylbis(azo)]bis(4-aminonaphthalene-1-sulphonate)	-	10100	-
	pigment, Co	71-48-7	cobalt(II) diacetate	1100	23000	-
fire retardants	boron	10043-35-3	boric acid	-	10000	-
		12179-04-3	sodium tetraborate, pentahydrate	-	10000	-
		1303-96-4	sodium borate, decahydrate	-	10000	-
		1330-43-4	sodium tetraborate, anhydrous	-	10000	-
	organo phosphate	115-96-8	tris(2-chloroethyl) phosphate	100	10110	-
		115-86-6	triphenyl phosphate	-	-	EDC (UNEP)
		25155-23-1	trixylyl phosphate	-	10000	-
	other	117-08-8	tetrachlorophthalic anhydride	1100	2100	-
		79-94-7	2,2',6,6'-tetrabromobisphenol A	1100	-	-
foaming agents	simple hydrocarbon	75-28-5	isobutane	-	20000	-
monomers and intermediates	acrylic	29590-42-9	isooctyl acrylate	1100	30	-
		107-13-1	acrylonitrile	100	11420	-
		106-91-2	glycidyl methacrylate	-	23320	-
		79-06-1	acrylamide	-	22240	-
	amine	108-45-2	m-phenylenediamine	1100	2310	-
		151-56-4	aziridine	100	23100	-
		111-41-1	2-((2-aminoethyl)amino)ethanol	-	11100	-
	bisphenol	80-05-7	bisphenol A	-	11110	EDC ENV, EDC HH (REACH)
		620-92-8	bisphenol F	-	-	EDC (UNEP)
		80-09-1	bisphenol S	-	-	EDC (UNEP)
	other hydrocarbons	91-20-3	naphthalene	1100	110	-
		92-52-4	biphenyl	1100	30	-
		75-56-9	propylene oxide	-	20230	-
		96-18-4	1,2,3-trichloropropane	-	20030	-
		106-97-8	butane	-	20000	-
		106-99-0	1,3-butadiene	-	20000	-
		50-00-0	formaldehyde	-	12400	-
		106-89-8	epichlorohydrin	-	11400	-
		126-99-8	2-chlorobuta-1,3-diene	-	10150	-
		96-09-3	(epoxyethyl)benzene	-	10020	-
		75-01-4	chloroethylene	-	10000	-
	zinc	7646-85-7	zinc chloride	1100	110	-
		7733-02-0	zinc sulphate	1100	110	-
		7440-66-6	zinc	1100	-	-
		7779-90-0	trizinc bis(orthophosphate)	1100	-	-
plasticizers	chlorinated paraffin	85535-84-8	alkanes, C10-13, chloro	1100	100	PBT, vPvB
		85535-85-9	medium-chain chlorinated paraffins, >17 carbon atoms	1100	100	-
	phthalate	85-68-7	benzyl butyl phthalate	1100	10000	EDC HH (REACH); EDC (UNEP)
		131-17-9	diallyl phthalate	1100	10	-
		84-74-2	dibutyl phthalate	100	10000	EDC HH (REACH); EDC (UNEP)
		117-81-7	bis(2-ethylhexyl) phthalate	-	10000	EDC ENV, EDC HH (REACH); EDC (UNEP)
		84-69-5	diisobutyl phthalate	-	10000	EDC HH (REACH); EDC (UNEP)
		117-82-8	dimethoxyethyl phthalate	-	10000	-
		68515-42-4	1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters	-	10000	-
		71888-89-6	diisoheptyl phthalate	-	10000	-
		84-61-7	dicyclohexyl phthalate	-	11000	EDC (UNEP)
		84-75-3	dihexyl phthalate	-	10000	EDC (UNEP)
		84-66-2	diethyl phthalate	-	-	EDC (UNEP)
		117-84-0	dioctyl phthalate	-	-	EDC (UNEP)
		3648-40-0	diundecyl phthalate	-	-	EDC (UNEP)
		26761-40-0	di-isodecyl phthalate	-	-	EDC (UNEP)
solvents	limonene	138-86-3	dipentene	1100	1010	-

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		5989-27-5	(R)-p-mentha-1,8-diene	1100	1010	-
	naphtha-related	8052-41-3	stoddard solvent	-	21100	-
		64741-65-7	naphtha (petroleum), heavy alkylate	-	20100	-
		64741-66-8	naphtha (petroleum), light alkylate	-	20100	-
		64742-49-0	naphtha (petroleum), hydrotreated light	-	20100	-
		64742-95-6	solvent naphtha (petroleum), light arom.	-	20100	-
		8030-30-6	naphtha	-	20100	-
		64742-46-7	distillates (petroleum), hydrotreated middle	-	10000	-
		64742-52-5	distillates (petroleum), hydrotreated heavy naphthenic	-	10000	-
		64742-54-7	distillates (petroleum), hydrotreated heavy paraffinic	-	10000	-
		8009-03-8	petrolatum	-	10000	-
	pure hydrocarbons	110-82-7	cyclohexane	1100	120	-
		142-82-5	heptane	1100	120	-
		79-01-6	trichloroethylene	10	11030	-
		71-43-2	benzene	-	21120	-
		109-86-4	2-methoxyethanol	-	10030	-
		68-12-2	dimethylformamide	-	10030	-
stabilizers	tin	683-18-1	dibutyltin dichloride	1100	13210	-
		77-58-7	dibutyltin dilaurate	-	12000	-
		15571-58-1	2-ethylhexyl 10-ethyl-4,4-dioctyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate	-	10000	-
	organic phosphite	26523-78-4	tris(nonylphenyl) phosphite	1100	1000	-
		101-02-0	triphenyl phosphite	1100	20	-
	hindered phenol	128-37-0	butylated hydroxytoluene (BHT)	-	-	EDC (UNEP)
		25013-16-5	butylated hydroxyanisole (BHA)	-	-	EDC (UNEP)
	benzophenone	131-56-6	2,4-dihydroxybenzophenone	-	-	EDC (UNEP)
		131-55-5	2,2',4,4'-tetrahydroxybenzophenone	-	-	EDC (UNEP)
		131-57-7	2-hydroxy-4-methoxybenzophenone	-	-	EDC (UNEP)
	benzotriazol	36437-37-3	2-(2H-benzotriazol-2-yl)-4-(tert-butyl)-6-(sec-butyl)phenol	-	-	vPvB
		3864-99-1	Phenol, 2-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1,-dimethylethyl)-	-	-	vPvB
		25973-55-1	2-(2'-hydroxy-3,5'-di-t-amylphenyl)benzotriazole	-	-	PBT, vPvB
		3846-71-7	2-benzotriazol-2-yl-4,6-di-tert-butylphenol	-	-	PBT, vPvB
	other	2451-62-9	1,3,5-tris(oxiranylmethyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	10	11400	-
		122-39-4	diphenylamine	1100	400	-
		1314-13-2	zinc oxide	1100	-	-
surfactants and their degradation products	NP, OP, and NP-related	84852-15-3	phenol, 4-nonyl-, branched	1100	210	EDC ENV (REACH); EDC (UNEP)
		25154-52-3	nonylphenol	1100	210	Same as above
		140-66-9	4-tert-Octylphenol	1100	110	Same as above
		104-40-5	p-nonylphenol	-	-	Same as above
		127087-87-0	4-nonylphenol, branched, ethoxylated	-	-	Same as above
		26027-38-3	nonoxynol-1	-	-	Same as above
		37205-87-1	Isononylphenol ethoxylate	-	-	Same as above
		7311-27-5	2-[2-[2-[2-(4-nonylphenoxy)ethoxy]ethoxy]ethoxy]ethanol	-	-	Same as above
		68412-54-4	nonylphenol, branched, ethoxylated	-	-	Same as above
		9016-45-9	nonylphenol, ethoxylated	-	-	Same as above
	amine and N-containing	61788-46-3	amines, coco alkyl	1100	320	-
		112-90-3	(Z)-octadec-9-enylamine	1100	320	-
		61788-45-2	amines, hydrogenated tallow alkyl	1100	310	-
		61790-33-8	amines, tallow alkyl	1100	310	-
		2687-96-9	N-dodecyl-2-pyrrolidone	1100	1100	-
		107-64-2	dimethyldioctadecylammonium chloride	1100	100	-
	PFAS	335-67-1	perfluorooctanoic acid	100	11320	PBT
		3825-26-1	ammonium pentadecafluorooctanoate	100	11320	PBT

(*) Harmonized hazard data reviewed included: (i) harmonized classification, labeling and packaging (CLP) classifications for environmental hazards (ENV) and human health (HH) hazards; (ii) classification as endocrine disrupting chemical (EDC) for ENV or HH effects within Registration, Evaluation, Authorization and restriction of Chemicals (REACH) legislation or recognition in the 2018 report by the United Nations Environment Programme (UNEP) as EDC or potential EDC identified with involvement of multiple stakeholders (corresponds to all but one REACH-identified EDCs) or at least one robust stakeholder following a thorough scientific assessment based on a definition of an

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EDC or a potential EDC postulated by the World Health Organization (WHO)/International Program on Chemical Safety (IPCS) in 2002; and (iii) classification in the European Union (EU) as a substance with persistent, bioaccumulative, and toxic (PBT) and/or very persistent, very bioaccumulative (vPvB) properties.

(**) Red background highlights properties exhibited by the most hazardous substances selected according to (sum hazard score ENV)=1100 and/or (sum hazard score HH)≥10,000; yellow background highlights ranges 100≤(sum hazard score ENV)<1000 and 1000≤(sum hazard score HH)<10,000; blue background highlights ranges (sum hazard score ENV)<100 and (sum hazard score HH)<1000; gray background: no classifications found.

(***) Red background identifies the most hazardous substances selected based on the classification/identification as EDC, PBT, or vPvB substance; gray background: no classifications/identifications found.

4. Discussion

This study aimed to (i) compile a comprehensive and publicly accessible database of chemicals used or found in plastic packaging, (ii) provide hazard information for these chemicals with regard to human health and the environment, and (iii) identify the most hazardous substances in need of further assessment as potential candidates for substitution. Achieving the study's aims was significantly hindered by substantial information and data gaps on chemical use, levels of chemicals in finished plastic packaging products, and hazards of chemicals associated with plastic packaging.

4.1 Challenges and information requirements

Two major challenges hamper the identification of chemicals associated with plastic packaging: (i) The lack of publicly accessible comprehensive registries for chemicals used in plastic packaging, and (ii) use restrictions for commercial data sources. This also impacted on the verification of a substance's current use in plastic packaging. Multiple commerce-oriented online-accessible inventories exist, such as global product databases or smaller repositories maintained by individual companies producing plastics and plastics additives. However, such sources usually give little information on the chemical composition of formulated products, concentrating almost exclusively on physical properties such as material performance or compatibility of different products. Furthermore, industry sources tend to limit their users in accessing and retrieving chemicals-related information (whichever is available) for multiple products or product categories simultaneously. Instead, users can view or extract information for only a few products at a time. In addition, users are often requested to demonstrate a commercial interest in order to be allowed to retrieve detailed chemical information or continue any data-mining on the website. Thus, even though commercial websites and companies clearly could be or are in possession of potentially detailed chemicals-related information, they strongly limit access to this information for non-commercial, academic research purposes. On the other hand, information contained in publicly accessible sources that offer a comparatively easy retrieval of data, such as the CPCat database (Dionisio et al., 2015), is often incomplete or insufficiently detailed. Filling the data gaps by collecting and recording information scattered across multiple literature sources such as research manuscripts, books, or reports is highly

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time-consuming and not achievable within the scope of one project. Furthermore, information collected from such sources could still prove to be incomplete, incorrect, or outdated. For example, several publications summarizing marketing information for plastics additives do provide some use statistics, but only for groups of additives and not for individual chemicals or specific applications (Levy et al., 2001; PlasticsEurope, 2016).

Consequently, in the course of this study we were able to assign with some certainty the likely association with plastic packaging to less than a quarter (906 substances) of the 4283 chemicals included in the CPPdb. For the remaining 3377 CPPdb substances, no final conclusions regarding their association with plastic packaging could be drawn. Moreover, when compiling the CPPdb, we excluded 7510 more substances originally retrieved from the CPCat database, because no indication of their use in plastics was found in the 14 initial information sources we have consulted (Fig. 1A). However, some of these chemicals could still prove to be used in plastic packaging upon closer examination. Adhesives, coatings, and inks represent product categories exhibiting particularly severe information gaps with regard to their constituent chemicals' use in plastic packaging.

In agreement with earlier studies (Bilitewski et al., 2012a; Rossi and Blake, 2014), our work demonstrated a significant lack of detailed information concerning use of chemicals in plastics manufacturing and the chemicals' presence in final products, especially for some additives and the often unpredictable NIAS (Nerin et al., 2013; van Oers et al., 2011). This lack of publicly accessible information is prominent even for those products that are in direct contact with foods and therefore can be assumed to directly contribute to population-wide human exposure (Muncke et al., 2017). More transparency regarding the exact chemical composition of marketed products might improve the situation in the future, but currently the ability to perform accurate risk assessment, i.e., incorporating an exposure component, is rather limited. Therefore, hazard-based assessment remains the approach of choice when dealing with large numbers of chemicals potentially present in consumer products.

Significant data gaps also exist for hazard information. For example, less than a third of the chemicals likely associated with plastic packaging had harmonized hazard classifications in the consulted sources (see Table 1). However, over two hundred plastic packaging-associated chemicals lacking a harmonized CLP classification had advisory CLP classifications assigned by the Danish EPA based on quantitative structure-activity relationship (QSAR) models. Thus, these chemicals might be hazardous as well, but are not yet officially classified as such, possibly due to the fact that confirming the predicted hazardous properties requires experimental toxicity testing data which are usually lacking. This example shows that a comprehensive hazard assessment should include data sources other than the harmonized hazard classifications.

For instance, hazard or risk assessments, conducted based on peer-reviewed literature and then made publicly available, could serve to inform and guide substitution efforts. An example of such an initiative is the SIN list (http://chemsec.org/sin-list/) maintained by the NGO *ChemSec*. However, there are significant obstacles to such an approach, such as funding limitations, or issues related to primary research communication and study quality (Agerstrand et al., 2017), but also integration and regulatory acceptance of alternative toxicity assessment methods, such as *in silico* predictions or *in vitro* tests (Piersma et al., 2018). Furthermore, peer-reviewed literature also tends to be biased towards the better-known substances, and switching the academic attention to the next group of 'emerging' substances tends to have a lengthy lag period (Bao et al., 2015; Li et al., 2018). Despite these challenges, peer-reviewed literature deserves to be given proper consideration in hazard assessment and prioritization studies (Kaltenhäuser et al., 2017; Myers et al., 2010). Increasingly, this is being done using a systematic review methodology, originally developed in the medical field, and now being gradually implemented for toxicological assessments as well (Birnbaum et al., 2013; Hoffmann et al., 2017; Morgan et al., 2016; Vandenberg et al., 2016).

Efficient communication and collaboration are also of crucial importance for ensuring the success of current efforts aimed at identification of hazardous chemicals and promoting their substitution with safer alternatives. One resource developed to facilitate the exchange of information on the use patterns and hazards of chemicals is the Chemical Hazards Data Commons (https://healthybuilding.net/content/data-commons/). This resource brings together the information from multiple lists and resources on hazardous chemicals and provides features supporting communication between different stakeholders. The CPPdb lists will be uploaded to this resource to enable collaborations and open dialogue to support further refinement of the inventory of plastic packaging-associated chemicals, as well as understanding the associated hazards and supporting the search for safer alternatives.

With regard to the generation of new data on the health hazards of plastic packaging-associated chemicals, the focus of toxicity testing may need to shift from assessing individual substances towards looking at the mixtures of chemicals present in a finished packaging article (Muncke, 2014). The advantage would be the ability to evaluate the effects of unknown NIAS, and account for mixture toxicity of multiple substances. Thus, the overall chemical extracts or migrates from a given packaging article could be tested for multiple types of toxicity using cell-based *in vitro* systems (Groh and Muncke, 2017; Severin et al., 2017). Besides the ability to increase the testing throughput, use of *in vitro* systems also allows achieving insights into additional effects and toxicity mechanisms not yet accounted for by the hazard categories covered in the harmonized hazard classification systems and traditional toxicity tests, such as neurobehavioral disorders (Maffini and Neltner, 2014), gut-related

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ailments (Groh et al., 2017), metabolic disruption (Heindel et al., 2017), and endocrine disruption (Wagner, 2016).

4.2 Overview of the most hazardous chemicals associated with plastic packaging

The discussion below will focus on the most hazardous chemicals identified based on the harmonized CLP classifications for environmental and human health hazards, as well as EU-accepted EDC and PBT/vPvB classifications, and recognition as an EDC or potential EDC in the UNEP report on EDCs (2018). One major limitation of this study is its reliance on harmonized hazard data which was available for less than a half of all substances included in the CPPdb. Consequently, the performed ranking could identify only the already known hazardous chemicals, while other chemicals with equal or more severe hazard properties may be overlooked due to the absence of harmonized hazard data.

Over 20 chemicals used as monomers and intermediates in plastics production, and roughly the same number of substances likely used as solvents, were among the most hazardous plastic packaging-associated substances identified in this work. Environmental and human health hazards of plastics monomers and solvents frequently used in plastics manufacturing have been addressed before (Lithner et al., 2011). When judged based on their monomers, some polymers used in packaging, including PS, PVC, PC, and PU (the latter used often in adhesives), are regarded as highly hazardous, while polyolefins and PLA are considered to be of lower hazard (Rossi and Blake, 2014). However, uncompounded polymers are rarely used in final applications, as various additives are usually added to modify polymer properties. If hazardous, these substances can lend hazard properties to even a seemingly safe polymeric material. Indeed, we observed that the majority of plastic packaging-associated substances identified as the most hazardous for environmental and human health were in fact plastics additives representing diverse chemical groups used for a variety of functions.

A particularly prominent group of hazardous additives consisted of substances containing metals, including cadmium, chromium, lead, mercury, cobalt, tin, and zinc. Apart from frequent classifications for aquatic toxicity, some of these chemicals also ranked high with regard to human health hazards, mostly because of CMR properties. Cadmium- and zinc-containing substances have been used as stabilizers in PVC and some other plastics (zinc is safer but less efficient than cadmium), while mercury-containing chemicals can be applied as catalysts in the production of some plastics and rubbers. Many metal-containing substances are also used as colorants, and some as antimicrobials and accelerators (Zweifel et al., 2009). The use and presence of the four most hazardous metals—cadmium, hexavalent chromium, lead, and mercury—in packaging is regulated in the EU (EU, 1994) and 19 U.S. states. However, despite the regulations, toxic metals, especially cadmium, have been detected at levels exceeding the regulatory limits in some PVC packaging

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samples obtained from U.S. retailers (Toxics in Packaging Clearinghouse, 2017; van Putten, 2011). Notably, most of the non-compliant packaging items identified in the U.S. appeared to be imported, often from China. Indeed, in other parts of the world, especially in developing countries, the use and presence of heavy metals in plastic packaging is either not regulated, or regulated insufficiently, or regulations are not properly enforced. For example, PE bags in Uganda contain cadmium, chromium, cobalt, and lead, found to contaminate food cooked in these bags (Musoke et al., 2015), while in Brazil lead was detected in some HDPE packaging samples (Kiyataka et al., 2014). Plastics beached on the shores of a fresh water lake in Europe (Filella and Turner, 2018) or the Pacific ocean (Munier and Bendell, 2018), most often composed of PVC, polyolefins, and PS, were also found to contain multiple heavy metals, including cadmium, mercury, and lead. Although plastics fragments are known to absorb metals present in the environment (Munier and Bendell, 2018), it was also suggested that some of the detected metals could in fact be "legacy" chemicals contained in the non-degraded plastics originating from the times before regulatory restrictions (Filella and Turner, 2018).

Surfactants and their degradation products form another large group of highly hazardous substances likely associated with plastic packaging. Surfactants are used in a variety of applications in plastics, for example, as wetting or antistatic agents. Some surfactants can also be used as dispersion agents in biocidal or colorant formulations. Both biocidal and coloring chemicals are also well represented among the hazardous substances likely associated with plastic packaging. Most biocides are classified as environmental hazards, but also have some classifications for human health hazards. Commodity plastics used in packaging applications are usually based on polymers that are not biodegradable and therefore resistant to the attack by microorganisms. Biocides added to such plastics, if any, are intended to prevent microbial degradation of some of the additives, thus their amounts are usually small. However, in PVC plastics, which can contain close to 50% by weight of phthalate plasticizers (Freire et al., 2006; Kawakami et al., 2011), known to be susceptible to microbial attack (Latorre et al., 2012), application of biocides can also be more significant. In addition, biocides are intentionally used to impart antimicrobial properties in the products belonging to a growing family of functional, smart, or active, packaging (Larson and Klibanov, 2013; Malhotra et al., 2015; Nguyen Van Long et al., 2016). Furthermore, biocides can be added to biodegradable plastics to protect the product from premature degradation (Fink, 2014), however, information on the types and amounts of biocides used in biodegradable plastics is rather scarce (Harrison et al., 2018; Lambert and Wagner, 2017). This area requires more research.

Apart from the substances showing a high hazard score based on the harmonized CLP classifications, substances possessing endocrine disrupting, PBT, or vPvB properties are also considered hazardous and therefore of immediate concern (Halden, 2010; Muncke et al., 2014; North and Halden, 2013). To identify the EDCs among the chemicals associated with plastic

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packaging, we relied on the substance's identification as an EDC within the REACH legislation (EU, 2008) along with a recognition as an EDC or potential EDC in the UNEP report on EDCs (2018). Based on the REACH EDC classification source (also recognized in the UNEP report as EDCs assessed with involvement of multiple stakeholders), 15 substances likely associated with plastic packaging were identified as EDCs. Only 8 of these substances also had a high CLP-based sum hazard score for environmental or human health hazards. Thus, without an additional consideration of endocrine disrupting properties, 7 of these 15 chemicals would not have been ranked as hazardous. Similarly, of the 20 additional chemicals recognized in the UNEP report (2018) as EDCs or potential EDCs identified by at least one robust stakeholder, 15 chemicals would not have been ranked as hazardous if the endocrine disrupting properties were not considered. In this regard, it is important to point out that some chemicals that have been suggested as substitutes for the recognized hazardous substances happen to be structurally similar to the original offenders, suggesting that they could have similar hazardous properties. This notion proved to be particularly true with regard to endocrine disruption. For example, BPA, a monomer in some PC plastics and epoxy coatings, has recently been classified as an EDC under REACH, in addition to several harmonized CLP classifications for human health hazards this chemical already had. To replace BPA in some applications, other bisphenols are now used as alternatives, for example, bisphenol S (BPS, CAS 80-09-1) and bisphenol F (BPF, CAS 620-92-8). However, since the endocrine activities displayed by these (and other) bisphenols are similar to those of BPA (Goldringer et al., 2015; Rochester and Bolden, 2015), the safety of such substitutions may be questioned (Rosenmai et al., 2014). Indeed, these substances are already recognized in the UNEP report (2018) as EDCs or potential EDCs identified by at least one robust stakeholder, however, the REACH classification is apparently lagging behind. Similar considerations concern the ortho-phthalate group, as some phthalates are classified as EDCs within REACH, while others, many of them recognized in the UNEP report (2018), lack such a classification to date.

Several other groups of plastic packaging-associated chemicals that have not yet been identified as EDCs within the REACH regulation, but are recognized in the UNEP report (2018), include parabens used as preservatives (Berger et al., 2015), benzophenones used as UV stabilizers (Cwiek-Ludwicka and Ludwicki, 2014; Simon et al., 2016), and two hindered phenols used as antioxidants, butylated hydroxytoluene (BHT, CAS 128-37-0) and butylated hydroxyanisole (BHA, CAS 25013-16-5). Among these groups, the two latter substances are used most extensively in high production volume commodity plastics such as polyolefins (Tolinski, 2009). Both BHT and BHA are estrogenic *in vitro* (Miller et al., 2001; Pop et al., 2018), and several other endocrine-related effects have been observed as well (Rajamani et al., 2017). *In vivo*, variable alterations have been reported, requiring further research to better understand their significance (Pop et al., 2013).

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The PBT and/or vPvB substances associated with plastic packaging include the group of four benzotriazole stabilizers, two of them classified as PBT and two as vPvB substances. These chemicals were shown to accumulate in fish and birds, with patterns of bioaccumulation suggested to depend on food sources and the presence of different plastics within those food sources (Lu et al., 2018). The two other PBT-classified chemicals belong to the family of per-and polyfluoroalkyl substances (PFAS). Many other PFAS show capacity for persistence, and possibly bioaccumulation and toxicity as well (Blum et al., 2015; Cousins et al., 2016; Scheringer et al., 2014; Wang et al., 2015), however, not all of them have been classified or identified as SVHCs in the EU for these properties yet (Brendel et al., 2018). Similarly, chlorinated paraffins with the carbon chain length of 10-13 (short-chain) have a PBT classification, but not the same type of chemicals with longer carbon chains (Glüge et al., 2018). These examples and those discussed above for groups of structurally similar chemicals showing comparable endocrine disrupting properties underscore the importance of assessing and classifying substances by looking at the groups formed according to structural and/or functional similarity and not only one-by-one at individual substances (Blum, 2016). Currently, tools are being developed allowing to weed-out structurally similar chemicals with likely similar toxicity when searching for alternatives, for example, the SINimilarity tool developed by ChemSec (http://sinimilarity.chemsec.org). Regulatory agencies are also increasingly applying grouping-based approaches (OECD, 2014; Schultz et al., 2015) to perform hazard and risk assessments for certain types of chemicals, for example, pesticides (Boobis et al., 2008; EFSA, 2014) and food flavorings (Schrankel, 2004), and there are plans to extend the application of this approach to cover more chemicals in the future (ECHA, 2018; Kienzler et al., 2016; Swedish Chemicals Agency (KEMI), 2015).

Apart from intentionally used substances and well characterized break-down products of plastics additives, important environmental or human health hazards may also be associated with (other) NIAS. These include a multitude of substances not yet completely identified (Bradley and Coulier, 2007; Paseiro-Cerrato et al., 2016; Vera et al., 2018), but also some better known chemicals that may nonetheless be difficult to manage, such as impurities and contaminants. For example, PAHs are often found in the PS polymer or in some additives, e.g., carbon black (Li et al., 2017), and 'legacy' chemicals such as flame retardants have been detected in recycled plastics (Andra et al., 2012; Filella and Turner, 2018; Leslie et al., 2016; Pivnenko et al., 2017; Rani et al., 2014; Samsonek and Puype, 2013). Many of these chemicals are classified as carcinogenic or have other highly hazardous properties, while others have never been tested. Though it can be difficult to control these impurities in the first place, their presence in plastics should not be simply disregarded but rather seen as an additional aspect to be considered when making decisions on the (future) use of a particular polymer for a specific application. Paying attention to impurities and contaminants is also important when evaluating the potential health effects of increasing levels of recycled content in

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products (Geueke et al., 2018). Awareness of contamination may incentivize modification of the manufacturing or recycling processes, substitution of hazardous additives, or even reconsideration of the likely contaminated plastics types for use in packaging applications as a whole.

Some of the substances highlighted above are already regulated to some extent in the EU or U.S., but regulations worldwide may vary widely. For substances regulated within REACH, use in Europe may be on the decline. However, REACH only partially regulates food packaging products in the EU, as these are covered instead by a separate food contact legislation (EU, 2004, 2011). Consequently, such products are not subject to some of the regulations enacted within REACH. For example, some phthalates restricted within REACH are still authorized for use in food contact and thus could still be used in food packaging (an ongoing EFSA-led assessment of several phthalates has not been concluded yet). Many more chemicals are pending REACH classification or have not yet been evaluated under REACH. Furthermore, REACH regulation only applies to products marketed in the EU, but plastic packaging is produced and consumed globally, and distribution of environmental pollutants does not observe country borders (Gallo et al., 2018). Therefore, sharing information on (hazardous) chemicals in these products is highly relevant worldwide, and concerted actions are needed to tackle the associated health problems. We expect that the publication of the CPPdb on Chemical Hazards Data Commons resource will enable continuation of the work initiated here. Urgent collaborative efforts, ideally involving many different stakeholders including industry, are required to decrease the uncertainty with regard to chemical composition of packaging plastics, and the chemical industry has already signaled its intent for information sharing across sectors (Stringer, 2018). This will enable improved understanding, assessment, and management of the environmental and human health risks posed by plastic packaging-associated chemicals.

5. Conclusions

In this study we compiled a database, the CPPdb, listing hundreds of substances that are likely or possibly associated with plastic packaging. The CPPdb contains substances used in manufacturing and/or present in final plastic packaging articles, including selected NIAS. Some of the substances in the CPPdb are known to be hazardous for environmental and/or human health, with harmonized hazard classification data available. For some of the key hazardous chemicals identified in this study, more detailed analyses should be performed in the future, including an assessment of the availability of alternatives. However, we faced numerous data gaps that hinder a comprehensive hazard and risk assessment of chemicals in plastic packaging. First, there is a substantial shortage of, or lack of access to, information on how specific chemicals are used, or which chemicals are used in what application and in what quantities, and at which levels they are present in finished plastic packaging. Insufficient information on chemicals' use patterns prevents any scientific, exposure-based assessments, since

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filling these data gaps using a systematic, scientific approach is nearly impossible for anyone outside industry. However, chemical risk assessments are essential for assessing impacts on human health and the environment. Reliable risk assessments should be based on actual data and not on estimates or assumptions. Therefore, there is an urgent need for publicly available information on the use of chemicals in plastics, and the exact chemical composition of finished plastics articles. Second, harmonized toxicological information, such as CLP hazard classifications, is currently not available for many chemicals that are associated with plastic packaging, even for substances for which hazards have been identified and characterized in academic studies. The incompleteness of harmonized CLP classifications for many chemicals affects the hazard ranking performed in this study, as such substances are excluded. The peer-reviewed literature and *in silico* predictions can provide hazard information for additional substances and should therefore be integrated into comprehensive hazard assessments. Third, many of the substances that are likely or possibly associated with plastic packaging lack any publicly available hazard data at all. Fourth, the chemical inventory-based approach taken in this study does not comprehensively address the issue of NIAS, since many of them remain unidentified and therefore cannot be risk-assessed as individual substances. Novel approaches, such as toxicity testing for the overall migrate from finished plastic packaging, address the issue of unidentified NIAS, and in addition deal with the challenge of mixture toxicity. In the future, *in vitro* toxicity assays could be used to test the safety of finished packaging articles. Therefore, broader application and further development of such effect-based testing approaches is desirable to guide the substitution efforts and ensure the toxicological safety of plastic packaging in the circular economy.

Acknowledgements

Work on this project was financed by a grant from MAVA foundation. K.G., B.G., and J.M. are employees of Food Packaging Forum Foundation (FPF). They were not restricted in any way in their work on this article. FPF is funded by unconditional donations and project-based grants. Donors and funders have no influence on the conception and execution of FPF's work. B.C.A. is financed by the Swedish research council, FORMAS grant 216-2012-625.

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