September 2018

Prioritization approaches for hazardous chemicals associated with plastic packaging

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DOI: 10.5281/zenodo.1436442

For more information

"Hazardous chemicals in plastic packaging: State of the art, prioritization, and assessment"
https://www.foodpackagingforum.org/about-us/research-project

Acknowledgments

This project was funded by a grant from MAVA Foundation.

Executive summary

Plastic packaging consists of various polymers that usually contain additives and non-intentionally added substances. In the recently published database of *Chemicals associated with Plastic Packaging* (CPPdb) more than 4000 substances are listed as likely/possibly used during manufacturing of plastic packaging or present in the final packaging articles [1].

In this report, we present two approaches to chemical prioritization using the CPPdb as starting point. The goal was to identify substances likely used in plastic packaging that should be further assessed with regard to their potential impact on human health or the environment. Prioritization as defined in the context of this work is a decision tool and strongly depends on a set of criteria identified a priori, the application of these criteria, and expert judgement. Therefore, the priority criteria influence the outcome of the process, which can lead to different priority chemicals. In general, prioritization is not risk assessment, i.e., substances that receive high-priority designations do not necessarily cause an immediate risk and vice versa.

In the first prioritization step, only those CPPdb substances that are likely used in plastic packaging were prioritized. Subsequently, harmonized hazard classifications assigned under the Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008 were considered by excluding all substances with low or non-existing CLP-based sum hazard scores for environmental and human health hazards [2]. For the remaining 68 substances with high CLP sum hazard scores for environmental hazards, further prioritization steps referred to information from ecotoxicological databases and the primary scientific literature. In the last step, benzyl butyl phthalate (BBP, CAS 85-68-7) was selected as first substance for further risk assessment. Prioritization of the 63 substances with high CLP-based sum hazard scores for human health hazards focused on biomonitoring data, endocrine disrupting properties, and regulatory requirements in Europe. The result of this approach was a list of five phthalates (BBP; dibutyl phthalate (DBP), CAS 84-74-2; diisobutyl phthalate (DiBP), CAS 84-69-5; bis(2-ethylhexyl) phthalate (DEHP), CAS 117-81-7; dicyclohexyl phthalate (DCHP), CAS 84-61-7), for which both the risk to human health resulting from their use in plastic packaging as well as their potential for substitution should be assessed. National and transnational laws already regulate the use of phthalates in some countries and/or for selected applications. Besides these restrictions, phthalates are still widely found in plastic packaging, justifying their designation as high-priority substances.

1 The project

Plastic packaging of food and non-food products accumulates in the environment after littering, generates micro- and nanoplastic particles, and is a source of hazardous chemicals that can be released during manufacturing, use, and end of life. Hazardous chemicals also hamper the use of plastic packaging in a circular economy [3]. Many thousands of chemicals are associated with the production of plastic packaging, but data on toxicity, as well as uses and exposure, are often not available in the public domain. The research project entitled "Hazardous chemicals in plastic packaging: State of the art, prioritization, and assessment" (HCPP) is a multi-partner collaboration funded by the MAVA Foundation and running from mid-2017 until mid-2019. The project aims at collecting data on chemicals in plastic packaging (both food and non-food) and identifying hazardous substances that may impact human health and the environment.

During the first part of the project, a database of *Chemicals associated with Plastic Packaging* (CPPdb) has been compiled, listing 4283 chemicals that are likely or possibly used during manufacture of plastic packaging and/or present in the final packaging article [1, 2]. The CPPdb includes information about the use of these chemicals in plastic packaging as well as their hazard properties. Thereby the database serves several purposes: It (i) provides an overview of the numerous monomers and additives used in plastic packaging, further complemented by chemicals used in adhesives and coatings, (ii) summarizes CLP-based hazard data available for substances likely or possibly associated with plastic packaging, (iii) identifies knowledge gaps regarding use and toxicity, and (iv) serves as a basis to collect further information and fill knowledge gaps to facilitate risk assessments. The CPPdb can also be used as a starting point to prioritize substances for further assessments focusing on their environmental, human health, or socio-economic impact.

In this report, we describe and discuss two approaches to identify CPPdb chemicals for in-depth evaluation in order to better understand the environmental and human-health risks of chemicals associated with plastic packaging.

2 Prioritization strategies: Background information and examples

The number and volume of chemicals produced and sold worldwide are constantly increasing [4]. Various U.S. estimates assumed that between 25'000 and 84'000 chemicals were on the market in 2014 [4], whereas the European Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) currently lists more than 21'000 registered substances (accessed: 3 July 2018). At the same time, the global plastics production is also on the rise, with around 40% of plastics being used for packaging [5]. More than 4000 chemicals are associated with the manufacture and use of plastic packaging, as the CPPdb illustrates [2].

Evaluating the risks of all commercially used chemicals is an enormous task. Even if only those chemicals that are available for specific application, such as the manufacture of plastic packaging, are considered, comprehensive risk assessments of all chemicals could be a daunting endeavor. Assessing chemical risk requires information on both the exposure to and the hazard of a specific substance. The exposure assessment considers the levels of a chemical used in plastic packaging, levels migrating into food or environmental media, or levels found with human biomonitoring. The hazard assessment comprises hazard identification which provides information on a substance's toxicological properties (e.g., mutagenic or toxic to reproduction) and hazard characterization which defines the doses at which harmful effects are observed.

Table 1. Prioritization approaches for chemicals under various international regulatory frameworks.

Authority	Task	Criteria	Data sources	Scoring / selection
European Chemicals Agency (ECHA)	Recommendations of priority substances from the SVHC Candidate List for inclusion in Annex XIV of REACH	PBT or vPvB properties, wide dispersive use, or high volumes (Art. 58 of REACH)	Registration data, additional data (e.g., CLP, Annex XV dossiers); realistic worst-case assumptions in the case of data gaps [6]	Categorization and application of scoring criteria, including verbal descriptions, and use of data in an integrated manner [6]
U.S. Environmental Protection Agency (U.S. EPA)	Prioritization of chemicals for risk evaluation under the Toxic Substances Control Act (TSCA): Designation of 20 high-priority substances for risk evaluation and 20 low-priority substances for which risk evaluations are not warranted at the time; preference given to substances listed on the 2014 Update of the TSCA Work Plan for chemical assessments	Persistence and bioaccumulation scores, known human carcinogens, or high acute or chronic toxicity [7]; exposure related information (use in children's and consumer products, biomonitoring data)	Reasonably available information on hazard, exposure, and potential for persistence and/or bioaccumulation; if not available, voluntary means of information gathering and, as necessary, exercising U.S. EPA's authorities under TSCA to require submission or generation of new data [7]	Selection of substances with the greatest hazard and exposure potential; no additional preferences for selection included in the regulatory text [7]
U.S. EPA	Endocrine Disruptor Screening Program: Prioritization of more than 87'000 chemicals, initially focused on pesticides and later extended; prioritized chemicals to be screened (Tier 1) and tested (Tier 2) [8-10]	Potential to interact with the estrogen, androgen, or thyroid hormonal system	Data on exposure, effects-related information, statutory criteria, results of *in silico* models and *in vitro* high-throughput assays [11]	First and second lists of chemicals for Tier 1 screening based on the pesticide registration status of the substances and/or their occurrence in drinking water [10, 12]
Health Canada & Environment Canada	Categorization of substances from the Domestic Substances List (DSL) as required by the Canadian Environmental Protection Act (CEPA 1999): > 23´0000 substances from the DSL, > 4300 substances identified for further assessment work (Chemicals Management Plan)	Inherently toxic to humans or the environment, and persistent and/or bioaccumulative; substances with greatest potential for human exposure (CEPA 1999)	Prioritization based on "categorization decisions, industry information, decisions from other jurisdictions in Canada, international assessments or data collection, public nominations, trends in new substance notifications, and emerging science or monitoring data" [4]	

CLP: classification, labelling and packaging; PBT: persistent, bioaccumulative, and toxic; vPvB: very persistent & very bioaccumulative; SVHC: substance of very high concern

Further complicating risk assessment, many chemicals lack important information that is needed for their evaluation. Acknowledging the missing data, many ongoing initiatives by governments, academia, and industry aim at reducing information gaps in chemicals' safety. As it is impossible to assess all commercially used chemicals at once, prioritization schemes can be applied to identify those substances that are of high concern due to their potential impact on human health or the environment. Prioritized substances should then undergo further evaluation, followed by risk management measures deemed appropriate. Ideally, prioritization approaches should be based on comprehensive toxicity and exposure data. In the absence of such information, high throughput screening assays, *in silico* models and biomonitoring data may provide supporting information.

Different prioritization strategies are currently applied by government agencies such as the European Chemicals Agency (ECHA) [6], the U.S. Environmental Protection Agency (U.S. EPA) [7, 10], as well as Health Canada and Environment Canada [4] (Table 1). These approaches differ in terms of the chemicals covered, data sources, and selection criteria. Prioritized substances will, e.g., be subject to further risk assessments or stricter regulation.

The amount and quality of the data strongly affect the choice of selection criteria and, ultimately, the outcomes of any prioritization process. Outdated, limited and/or non-existent data on uses, hazard or exposure make the process especially difficult [13]. Scoring and weighting of the criteria applied during prioritization is largely based on expert judgement and agreement among the stakeholders on how to use the available information in assessing a particular concern [6]. Prioritization is a decision tool that usually results in different outcomes. Therefore, the rationale underpinning the decision-making process must be transparent. This also implies that high-priority designations are not an indication of immediate risk and low-priority designations should not be interpreted as safety guarantee.

3 Prioritization of CPPdb substances: Two case studies

The information that is available in the CPPdb was used to prioritize chemicals associated with plastic packaging for further assessments. Two strategies were applied to prioritize substances with respect to their potential impact on human health or the environment (Figure 1). Both prioritization strategies were based on preselected criteria involving expert judgement.

Evaluation of use patterns and CLP-based ranking

In the first prioritization step, we included only those CPPdb substances that are likely used during the manufacture of plastic packaging or are likely present in the final packaging article. The CPPdb consists of two parts listing substances with different strength of evidence indicating their association with plastic packaging [2]. CPPdb_ListA comprises 906 substances identified to be "likely associated with plastic packaging", whereas CPPdb_ListB contains the remaining 3377 substances identified as "possibly associated with plastic packaging" [1, 2]. In our prioritization approach, we focused only on chemicals from CPPdb_ListA (Figure 1, step 1).

During the creation of the CPPdb, harmonized hazard classifications assigned under the Classification, Labelling and Packaging (CLP) Regulation [(EC) No 1272/2008] were consulted and hazard grade scores were assigned to all chemicals according to a previously developed model for hazard ranking [14]. This model allowed the separate calculation of sum hazard scores for environmental and human health hazards resulting, respectively, in 68 and 63 high-ranking substances from CPPdb_ListA. These high-ranking substances were prioritized in the second step (Figure 1) [2].

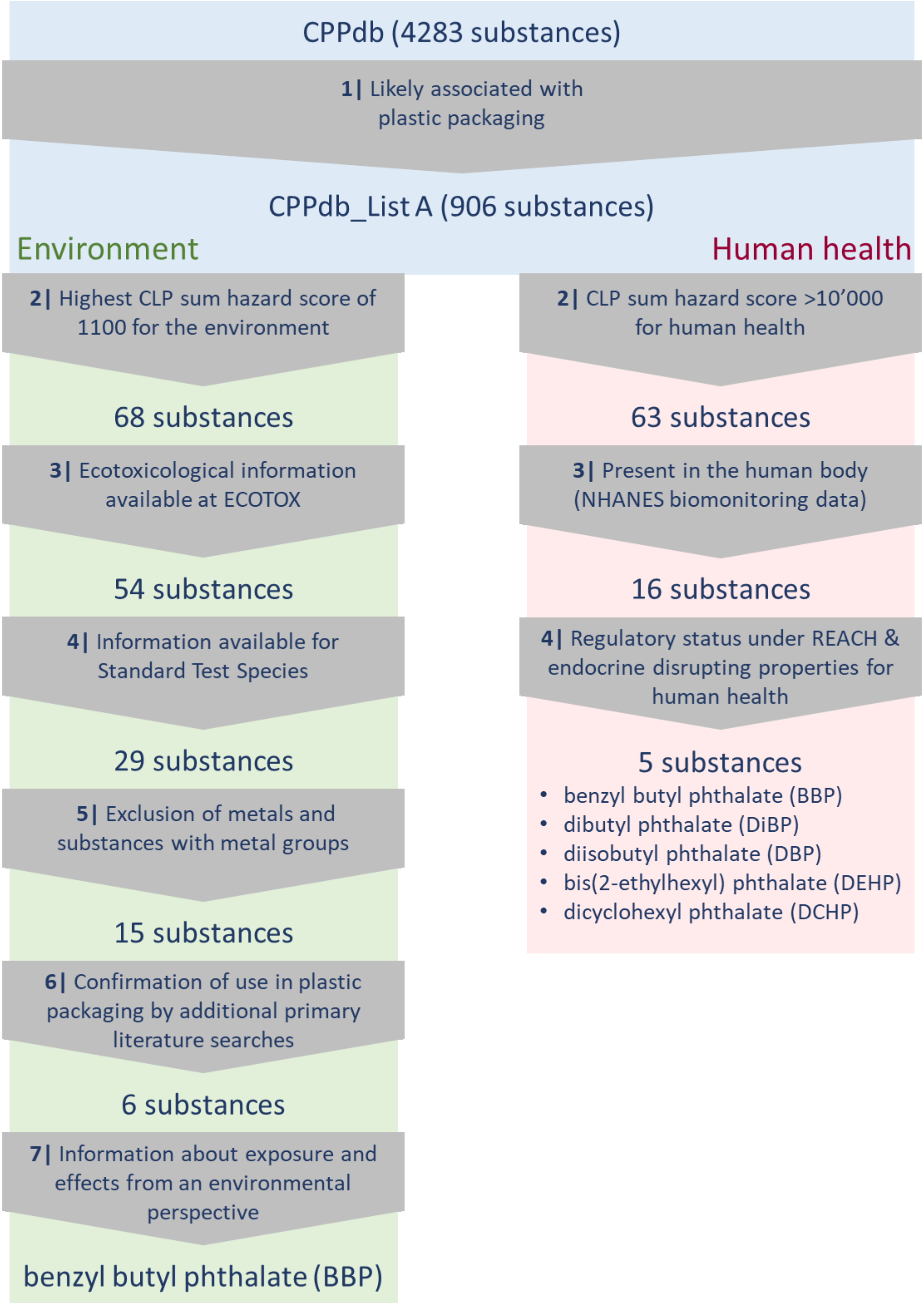

Figure 1. Prioritization strategies applied to identify chemicals that pose potential risks for the environment and human health. The database of *Chemicals associated with Plastic Packaging* (CPPdb) was used as a starting point. In the first step, chemicals likely associated with plastic packaging (listed on CPPdb_ListA) were prioritized. Chemicals that may be of concern for the environment and human health were prioritized in six and three further steps, respectively. ECOTOX is the U.S. EPA’s ecotoxicological knowledgebase.

Substances of potential concern for the environment

68 substances considered likely associated with plastic packaging had the highest CLP-based sum hazard score of 1100 for environmental hazards (Figure 1, environment, step 2). In step 3, we excluded all substances with insufficient ecotoxicological information in the ECOTOXicological knowledgebase (ECOTOX) from the U.S. EPA. For 29 of the remaining 54 substances, information was available for Standard Test Species (STS; algae, crustaceans, and fish). STS are commonly selected for regulatory risk assessment in ecotoxicology, as they are thought to represent the major trophic levels in an ecosystem. Hence, the 25 substances with unavailable or incomplete information for STS were excluded. In step 5, all metals and metal-containing substances were omitted, because we decided to focus on environmental organic contaminants only. This eliminated 14 substances from the list. The use of the remaining 15 substances for plastic packaging was then scrutinized in detail by searching the databases SCOPUS, Web of Science, and Google Scholar using the keywords "(substance name)" AND "plastic" AND/OR "plastic packaging." For six substances we could confirm their use in plastic packaging (Table 2). In the final prioritization step, the occurrence of ecotoxicological effects as well as availability of exposure data, i.e., whether a substance has been measured in environmental compartments, were considered. This information is needed in order to support subsequent risk assessments and evaluation of substitution options. We finally selected benzyl butyl phthalate (BBP, CAS 85-68-7) as the first substance for further in-depth assessment with regard to environmental risk posed by its use in plastic packaging.

Table 2. Priority list of 6 substances of potential concern for the environment identified after prioritization step 6 (Figure 1). References supporting the expert judgements in steps 6 and 7 are listed. BBP was prioritized in the final step (green background).

Substance	CAS number	Step 6: Confirmation of a substance`s use in plastic packaging	Step 7: Information about environmental exposure and ecotoxicological effects
Benzyl butyl phthalate (BBP)	85-68-7	[15-21]	[15, 21-34]
Diphenylamine	122-39-4	[35]	-
Nonylphenol	25154-52-3	[21, 36-38]	[21, 39-54]
4-*tert*-Octylphenol	140-66-9	[21, 52, 53]	[21, 44-54]
2,2',6,6'-Tetrabromobisphenol A	79-94-7	[55-57]	[58-81]
Triclosan	3380-34-5	[82, 83]	[84-87]

Substances of potential concern for human health

Starting with 63 substances from the CPPdb being likely associated with plastic packaging and ranking high for human health hazards, we prioritized 16 chemicals that have been measured in humans under the National Health and Nutrition Examination Survey (NHANES) (Figure 1, human health, step 2; Table 3) [88]. This step provides assurance that humans are exposed to these substances. However, whether exposure comes from plastic packaging or other sources cannot be differentiated based on biomonitoring data. In the next step, we focused on the chemicals' regulatory status under REACH and their listing as endocrine disruptors by the European Union and the United Nations Environment Programme (UNEP) (Table 3) [89]. Eleven of the 16 substances are on REACH's Candidate List of substances of very high concern (SVHC), and 6 of these 11 SVHC substances were classified as such based on their toxicity for reproduction and endocrine disrupting properties (benzyl butyl phthalate (BBP), CAS 85-68-7; dibutyl phthalate (DBP), CAS 84-74-2; diisobutyl phthalate (DiBP), CAS 84-69-5;

bis(2-ethylhexyl) phthalate (DEHP), CAS 117-81-7; dicyclohexyl phthalate (DCHP), CAS 84-61-7; bisphenol A (BPA), CAS 80-07-5). BBP, DBP, DiBP, and DEHP are additionally subject to authorization under REACH which is indicated by their listing on Annex XIV. We finally focused on the five phthalates BBP, DBP, DiBP, DCHP, and DEHP to be evaluated as a group because of their presence on the SVHC Candidate List and/or Annex XIV and their endocrine disrupting properties.

Table 3. Priority list of 16 substances of potential concern for human health after prioritization step 3 (Figure 1, human health). All substances have CLP-based sum hazard scores for human health ≥10000 (step 2) and human exposure has been indicated by biomonitoring studies (step 3). The regulatory status under REACH and EDC identifications of the substances are shown. Five phthalates were prioritized in the final step (red background).

Name	CAS No	CLP hazard score for human health	REACH: SVHC Candidate List (and reason for inclusion)	REACH: Annex XIV	UNEP: EDC
Benzyl butyl phthalate (BBP)	85-68-7	10000	yes (toxic for reproduction, EDC properties human health)	yes	yes
Bis(2-ethylhexyl) phthalate (DEHP)	117-81-7	10000	yes (toxic for reproduction, EDC properties human health and environment)	yes	yes
Dibutyl phthalate (DBP)	84-74-2	10000	yes (toxic for reproduction, EDC properties human health)	yes	yes
Diisobutyl phthalate (DiBP)	84-69-5	10000	yes (toxic for reproduction, EDC properties human health)	yes	yes
Dicyclohexyl phthalate (DCHP)	84-61-7	11000	yes (toxic for reproduction, EDC properties human health)	no	yes
Acrylamide	79-06-1	22240	yes (carcinogenic, mutagenic)	no	no
Acrylonitrile	107-13-1	11420	no	no	no
Benzene	71-43-2	21120	no	no	no
Bisphenol A (BPA)	80-05-7	11110	yes (toxic for reproduction, EDC properties human health and environment)	no	no
1,3-Butadiene	106-99-0	20000	no	no	no
Cadmium	7440-43-9	13100	yes (carcinogenic, specific target organ toxicity)	no	no
Chloroethylene	75-01-4	10000	no	no	no
Dimethyl-formamide	68-12-2	10030	yes (toxic for reproduction)	no	no
Mercury	7439-97-6	12000	no	no	no
Perfluorooctanoic acid	335-67-1	11320	yes (toxic for reproduction, PBT)	no	no
Propylene oxide	75-56-9	20230	yes (carcinogenic, mutagenic)	no	no

4 Discussion

Two prioritization strategies were developed to identify chemicals from the CPPdb that shall be assessed for their impact on the environment and human health in the course of the ongoing project.

The CPPdb provides a collection of information about hazards, use, exposure, and regulatory status for 4283 chemicals associated with plastic packaging [2]. This allowed us to define several prioritization criteria based on the information already available in the database. The harmonized CLP classifications for environmental and human health hazards were used as the first criterion, reducing the number of substances to 68 and 63, respectively. However, in both approaches additional steps were needed to further shorten these two lists of chemicals (Figure 1). Substances with high CLP sum hazard scores for environmental hazards were prioritized by consulting additional sources for ecotoxicological information not included in the CPPdb, defining exclusion criteria, and extracting information from the primary literature. In contrast, the prioritization for human health hazards was based only on information already available in the CPPdb and focused on biomonitoring data, endocrine disrupting properties, and regulatory status in Europe. Despite the different approaches to prioritize chemicals posing potential risk to human health or the environment, phthalates were prominently represented among the prioritized substances in both case studies (Box 1).

Box 1:
Priority substances from the CPPdb

Phthalates are a well-investigated group of chemicals and a plethora of studies has been published describing their toxicity, use, and occurrence [41, 90-95]. The risks of phthalates have been repeatedly recognized, reviewed, and assessed by various authorities all over the world, e.g., [96-98]. As a result, national and transnational laws have been passed regulating the use of certain phthalates for specific applications. For example, in many countries the use of several phthalates in toys and other products for babies and children is banned [99-102]. In Europe, eight phthalates are subject to authorization under REACH. In July 2018, the European Commission has proposed to restrict four phthalates in consumer articles or available in indoor areas. DBP, BBP and DEHP can still be legally used in food contact plastics (Commission Regulation (EU) No 10/2011), but the European Food Safety Authority (EFSA) currently re-assesses the safety of their uses. Besides these restrictions in Europe, phthalates are still widely used in consumer products, including plastic films and sheets, in many parts of the world [103, 104].

Prioritization strategies relying on available data are likely to highlight substances that are in the spotlight already. Furthermore, only substances with sufficient data can be evaluated by such approaches. Importantly, data on hazards, use, exposure and/or regulatory status are largely missing for many chemicals in the CPPdb. For example, only 13.4% and 27% of the substances from CPPdb_ListA had harmonized CLP classifications for environmental and human health risks, respectively [2]. In order to identify potentially problematic substances in future, knowledge gaps need to be addressed by generating novel data through, e.g., *in silico* analysis or *in vitro* bioassay-based screening programs. Moreover, literature searches for individual chemicals could provide additional information. The CPPdb may serve as basis for any research aiming at filling these information gaps and covering more and more chemicals by appropriate prioritization strategies. In order to facilitate further updates and collaborations, CPPdb_ListA was uploaded into the Chemical Hazard Data Commons resource that is maintained by the Healthy Building Network (HBN) [105].

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