Food and Chemical Toxicology 106 (2017) 496–505

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Coatings in food contact materials: Potential source of genotoxic contaminants?

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ARTICLE INFO

Article history:
Received 30 March 2017
Received in revised form
4 May 2017
Accepted 30 May 2017
Available online 3 June 2017

Keywords:
DNA damage
ECHA database
Food contact materials
In silico
Prioritization strategy
Structure-activity relationship

ABSTRACT

Up till now, no harmonized EU regulation exists on chemicals used in coatings for food contact materials (FCM). Therefore, these substances need to comply with the general provisions of EU Regulation 1935/2004 and, if present, with national legislation. Different 'inventory lists' of compounds that might be present in coatings are available, but for hundreds of these substances, the potential human health impact of their use in FCM coatings has not (recently) been evaluated. Since detailed evaluation of all compounds is not feasible, a pragmatic approach was developed to identify substances with a potential concern for human health. First, an inventory was assembled containing all substances potentially used in coatings. Afterwards, the genotoxic potential of the non-evaluated substances was predicted *in silico* using two structure-activity relationship (SAR) software programs. For substances yielding structural alerts in both models, genotoxicity data were collected from previous European evaluations in a non-FCM context and from the European CHemicals Agency (ECHA) website. In total, 53 substances were identified as genotoxic in both *in silico* models, of which ten were considered to be of high concern. For most of the substances, additional toxicological information is needed.

1. Introduction

Over the last decade, several incidents with contaminants migrating from food packaging materials (FCM) into food and drinks have raised concerns regarding the potential adverse health effects following exposure to these chemicals. Furthermore, it has been reported that chemicals of concern can be used in FCMs (Geueke et al., 2014; Geueke and Muncke, 2017; Van Bossuyt et al., 2016; Mertens et al., 2016). In 2011, the European Commission adopted a new regulation (EU) No 10/2011 on the use of chemicals in plastic materials and articles intended to come into contact with food. Consequently, only substances included in Annex I of Regulation (EU) No. 10/2011 can be used as starting product for the manufacture of plastic FCMs and migration should be below the specific migration limit (SML), if established (EU, 2011). However, up till now, no harmonized EU regulation exists on chemicals used in most other types of FCMs and these substances thus need to comply with the general provisions of EU Regulation 1935/2004 (EU, 2004a) and with national legislation, if present.

Coatings are one example of an FCM type for which a specific European regulation is currently lacking. Nevertheless, several non-legally binding European documents exist which list substances that can be used in coatings. First, there is the Framework Resolution AP(2004)1 issued by the Council of Europe (CoE) (CoE, 2004a). This document includes general recommendations formulated by the CoE, containing 'inventory lists' of compounds that might be present in coatings. Importantly, for hundreds of substances included in these inventory lists, their safe use in FCM has not been

List of abbreviations: BADGE, bisphenol A diglycidyl ether; BFDGE, bisphenol F diglycidyl ether; CHL, Chinese hamster lung; CLP, Classification, Labelling and Packaging; CoE, Council of Europe; CoRAP, Community rolling action plan; ECHA, European CHemicals Agency; EFSA, European Food Safety Authority; EU, European Union; FCM, food contact materials; IARC, International Agency for Research on Cancer; NOGE, novolac glycidyl ether; NTP, National Toxicology Program; RAC, Risk Assessment Committee; REACH, Registration, Evaluation, Authorisation and Restriction of Chemicals; SA, structural alert; SCCP, Scientific Committee on Consumer Products; SCCS, Scientific Committee on Consumer Safety; SCHER, Scientific Committee on Health and Environmental Risks; SCF, Scientific Committee on Food; SMILES, Simplified Molecular Input Line Entry System; SML, specific migration limit; WHO, World Health Organisation.

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http://dx.doi.org/10.1016/j.fct.2017.05.071
0278-6915/

evaluated. Second, there is the inventory list of the ESCO working group. This Working Group was set up in February 2010 in order to collect the information present at member state level on substances used in non-plastic FCMs, including coatings. The ESCO inventory list contains only substances for which the use in FCM coatings has already been evaluated. However, these evaluations may be very old and do not necessarily comply with the principles of the European Food Safety Authority (EFSA). Therefore, substances on the ESCO inventory list are divided into two groups, according to their date of evaluation. Importantly, most of the substances are included in list B, indicating that they have been evaluated before 1991 (EFSA, 2012). Both the CoE and the ESCO document highlight that a large number of substances can be present in coatings, many of which have not or not recently (i.e. after 1991) been evaluated for their safe use in FCM at European level. The presence of these substances in coatings cannot be excluded and consequently, more toxicological data, and especially genotoxicity data, on the substances are urgently needed. Genotoxicity is indeed an important toxicological endpoint, as genetic alterations in somatic and germ cells have been associated with serious health effects including cancer, degenerative diseases, reduced fertility and inherited diseases (Erickson, 2010; Hoeijmakers, 2009; Kong et al., 2012). Results of genotoxicity tests are key elements in risk assessment of chemicals in general, including those present in food and feed (EFSA, 2011). For substances intended to be included in Annex I of Regulation (EU) No. 10/2011, genotoxicity tests also have to be performed, independent of the level of migration of the compound. An exception to this rule are substances with a molecular weight above 1000 Da as it has generally been recognized that such compounds will not be absorbed (EFSA, 2008a). Although there is no specific regulation for substances used in non-plastic FCMs such as coatings, their genotoxicity should be investigated as they can migrate into the food. Detailed safety evaluation of all these compounds would be preferred but unfortunately, this is not feasible in the short term. Consequently, a pragmatic approach needs to be developed in order to identify substances that might be of high concern for human health.

In the present study, substances of concern potentially used in coatings were identified based on hazard information related to genotoxicity obtained with *in silico* methods combined with literature data. Firstly, an inventory was compiled containing all substances related to coatings. Next, for all substances that have not been evaluated within a European FCM context and for which the CAS number was available, an analysis of their genotoxic potential was performed using the *in silico* model ToxTree. Substances with a structural alert (SA) for genotoxicity were further investigated with Derek Nexus™, another *in silico* tool. For substances with SAs for genotoxicity in both models, a literature search was performed to check whether the substance has been evaluated in another European regulatory framework. Furthermore, information on the genotoxic potential of compounds that has been submitted in the context of the REACH regulation (Registration, Evaluation, Authorisation and Restriction of Chemicals) (EU, 2006) and the Classification, Labelling and Packaging (CLP) Regulation of substances and mixtures (EU, 2008) was also collected by consulting the database of the European Chemicals Agency (ECHA). Finally, all information was combined in order to prioritize the substances into high/medium/low concern for human health.

2. Materials and methods

2.1. Compilation of an inventory of substances potentially used in coatings

An inventory containing substances potentially used in coatings was compiled. To this extent, all substances present in the following lists were included in the inventory:

- Inventory list of the Framework document on coatings Resolution AP(2004)1

The Council of Europe has issued a series of recommendations for non-plastic FCMs including paper and board (CoE, 2002), printing inks (CoE, 2005), rubber (CoE, 2004b) and also coatings (CoE, 2004a). Each recommendation contains an inventory list with substances known to be used in the respective FCM. The inventory list for coatings is subdivided into lists containing the evaluated substances (list A and C) and temporary annexes with substances for which the restriction still has to be fixed (list B and D). Since there is currently no consensus on whether substances included in the temporary annexes have been sufficiently evaluated, they were considered 'non-evaluated' in the present study. The inventory list of coatings comprises 1147 substances, and toxicity has been clearly evaluated for more than half of them (List A and C = 648; List B and D = 499).

- ESCO working group list on coatings

In 2011, the ESCO working group composed an inventory of substances used in non-plastic FCMs which have been evaluated or regulated under member state law (EFSA, 2012). For coatings, the substances of the ESCO list are limited to those included in the "Warenwet" of the Netherlands (The Netherlands, 2005). The 456 substances present in the list are further subdivided according to their date of evaluation. Substances evaluated after 1991 are included in List A as these substances have probably been evaluated according to the standards of the EFSA, or to those of its predecessor, the Scientific Committee on Food (SCF). List A only contains eight substances. The majority of the substances has been evaluated before 1991 and is therefore taken up in list B (444 substances). Furthermore, there are four substances for which it is not indicated whether they are part of List A or List B. In the current study, substances of list B as well as substances not included in List A or B were considered non-evaluated.

- Substances included in Annex I of European Regulation No. 10/2011

The Annex I of Regulation (EU) No. 10/2011 contains all substances, 869[1] in total, that are allowed to be used in plastic FCMs (EU, 2011). Specific migration limits or (quantitative) restrictions for use are established in order to guarantee the safety of the FCM. Substances included in Annex I of Regulation (EU) No. 10/2011 may also be used in coatings. All substances included in Annex I of Regulation (EU) No. 10/2011 have been evaluated for use in the manufacture of plastic FCM. Some of these evaluations also data back from before 1991, but since these substances are legally considered as evaluated, they were also regarded as evaluated in the present study.

- Substances covered by European Regulation 1895/2005

European Regulation 1895/2005 restricts the use of certain epoxy derivatives in FCM. According to this regulation, migration of

[1] This number refers to the total number of substances that was included in Annex I of Regulation (EU) No. 10/2011 the moment the inventory of substances potentially used in coatings was compiled. In the meantime, further amendments to Regulation (EU) No. 10/2011 have been made.