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Risk Assessment of Food Contact Materials II

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Abstract

Food contact materials (FCMs) are materials and articles intended to be placed in direct or indirect contact with foodstuffs, or which can reasonably be expected to come into contact with food under normal or foreseeable conditions of use. Substances intentionally used to manufacture FCMs, as well as non-intentionally added substances resulting from impurities, by-products and/or degradation products, can migrate from FMCs into food and, consequently, are taken up by humans. To protect consumers' health, EU legislation requires that FCMs must be sufficiently inert to prevent substances from being transferred into the food in quantities that could endanger human health. At the German Federal Institute for Risk Assessment (BfR), Unit 74 'Safety of Food Contact Materials' deals with the risk assessment of FCMs and provides recommendations on the use of substances for the production of FCMs for which no specific European measures exist yet (e.g. silicone, rubber, paper and board). The BfR 'Recommendations on Food Contact Materials' are not legally binding; however, they represent the current state of the scientific and technical knowledge for the conditions under which these materials meet the requirements for consumer safety. As part of the EU-FORA programme, the fellow was involved in the risk assessment tasks and projects undertaken by Unit 74, which include: (i) the scientific evaluation of analytical and toxicological data from dossiers for adding new substances to the database 'BfR Recommendations on Food Contact Materials'; (ii) the hazard assessment of cyclic volatile methylsiloxanes (cVMS) migrating from silicone FCMs into foodstuff; and (iii) *in vitro* metabolic stability study of cyclic methylsiloxanes in the presence of S9 fraction, performed in the BfR laboratories. Moreover, the EU-FORA fellowship was a great opportunity for the fellow to build a strong network of food safety experts and to be part of an international community of risk assessment professionals.

Keywords: chemical risk assessment, food contact materials, FCM, BfR recommendations, toxicology, migration

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1. Introduction

Risk analysis is a process consisting of three components: risk assessment, risk management and risk communication (CAC, 2015). The first component, risk assessment, is the scientific foundation of risk analysis, intended to estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system (IPCS, 2004). The risk assessment (RA) process begins with problem formulation and includes four additional steps: (i) hazard identification; (ii) hazard characterisation; (iii) exposure assessment; and (iv) risk characterisation (WHO, 2021). To develop the next generation of European food risk assessors and to build a common culture for RA, the European Food Safety Authority (EFSA) created the European Food Risk Assessment Fellowship (EU-FORA) Programme. Within the scope of the EU-FORA programme, the goal of this fellowship is to gain insight into the RA of Food Contact Materials (FCMs), in order to protect consumers from health risks associated with exposure to migrating chemicals from FCMs into food. An FCM is any material or article intended to be placed in direct or indirect contact with foodstuffs, or which can reasonably be expected to come into contact with food under normal or foreseeable conditions of use. To ensure food safety, FCMs must be sufficiently inert to prevent substances from being transferred into the food in quantities large enough to endanger human health or to bring about an unacceptable change in the composition of the food or a deterioration in its organoleptic properties, as laid down in Article 3 of the European Framework Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food (European Commission, 2004). Despite the enforcement of safety requirements, several food safety crises have been associated with FCMs. In 2005, Italian authorities withdrew 30 million litres of infant milk from the market due to high level of 2-isopropylthioxanthone (ITX), a photoinitiator used in UV-inks (Morlock and Schwack, 2006). In 2009, another photoinitiator, 4-methylbenzophenone, was notified by German and Belgian authorities due to its migration from food packaging into cereal products (EFSA, 2009). Over the last years, several chemicals used in FCM applications have been demonstrated to pose a health risk if consumers are exposed to those substances above safety levels. For instance, certain primary aromatic amines (PAAs) were shown to possess genotoxic and carcinogenic properties. Food contamination with PAAs can originate from printing azo-dyes, azo-pigments, isocyanate-based adhesives, monomers present in plastics and printed or recycled paper used for food packaging (Trier et al., 2010; Campanella et al., 2015; Yavuz et al., 2016). Some substances in the group of phthalates and perfluoroalkyl and polyfluoroalkyl substances (PFAS), as well as bisphenol A (BPA), have been classified as endocrine-disrupting chemicals (EDCs), exogenous substances or mixtures that alter functions of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny, or (sub) populations (Zoeller et al., 2012). With more than 12,000 intentionally added substances (IAS) that could be possibly used to make FCMs worldwide (Groh et al., 2021) and the potential formation of non-intentionally added substances (NIAS), such as impurities, by-products, side reaction products and degradation products, FCMs can be a significant source of chemical food contamination (Grob et al., 2006). It does not necessarily imply that food contamination with substances migrating from FCMs leads to adverse health effects in humans. Nevertheless, the potential health risks resulting from the exposure to migrating non-evaluated chemicals, or due to improper conditions of use of an evaluated/authorised substance (e.g. level used, time, temperature, food types) or manufacturing process (e.g. curing), need to be assessed. At the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung – BfR), Unit 74 'Safety of Food Contact Materials' has the task to assess the nature and likelihood of harms resulting from human exposure to chemicals used in FCMs. The chemical/analytical and toxicological data provided by applicants in course of the inclusion of new substances into the BfR recommendations on food contact materials or data gathered from the literature and/or authoritative sources serve as the basis for the FCM risk assessment. Finally, the BfR publishes the results in the form of statements and publications.

2. Description of the work programme

2.1. Aims

The aim of the work programme was to gain insight into the RA of FCMs performed at the BfR, in accordance with the EFSA guidelines. In particular, the fellow acquired hands-on experience in the evaluation of analytical and toxicological (*in vitro* and *in vivo*) data for the inclusion of new substances

into the database 'BfR Recommendations on Food Contact Materials' (https://bfr.ble.de/kse/faces/DBEmpfehlung_en.jsp). He gained relevant knowledge of risk assessment tools, such as the PROAST software for Benchmark Dose Modelling (BMD), the FoodEx2 database and *in silico* toxicology tools (OECD Toolbox, Toxtree). In addition, part of the work programme included practical experience in the German national reference laboratory for materials in contact with food (NRL-FCM).

2.2. Activities/Methods

In order to achieve the training objectives, the fellow was involved in the ongoing risk assessment tasks undertaken by the BfR Unit 74, providing his contribution to the risk assessment issues. The following activities and projects were carried out:

i) Scientific evaluation of two dossiers for the inclusion of new substances in the 'BfR Recommendations on Food Contact Materials'. Due to the confidentiality concerning the dossiers, the data will not be disclosed.
ii) Hazard assessment of cyclic volatile methylsiloxanes (cVMS) that migrate from silicone FCMs into foodstuff.
iii) *In vitro* metabolic stability study of cyclic methylsiloxanes using S9 fraction.

2.2.1. Data evaluation in the context of an application of new substances into the 'BfR Recommendations on Food Contact Materials'

In the absence of specific European or national regulation for certain material groups, the BfR provides recommendations for the safe use of substances for the production of FCMs through the publicly available 'BfR Recommendations on Food Contact Materials'. The goal of these recommendations is to ensure that FCMs do not release substances into foods in quantities that could cause a health risk for consumers. Of the 17 material types of FCMs listed in Annex I of Regulation (EC) No 1935/2004, only four are currently covered by EU legislation on specific materials: (i) plastic materials and recycled plastic materials, (ii) active and intelligent materials, (iii) ceramics, (iv) regenerated cellulose film. Consequently, the BfR deals with those materials that are not subject to any harmonised EU regulation, such as silicones, natural and synthetic rubbers, papers, cartons and cardboards. It should be noted that BfR recommendations on plastic materials also exist, but are restricted only to components of catalytic systems and polymerisation auxiliaries, which are not yet accounted by the respective EU regulation. In addition, some BfR recommendations deal with a quite narrow scope of application (or intended use) of these materials (e.g. artificial sausage skins, temperature-resistant coatings for cooking, paper and paperboard for baking purposes). Even though BfR recommendations are not legally binding, they represent the current state of the scientific and technical knowledge for the conditions under which not specifically regulated materials meet the requirements for consumer safety as laid down in the framework Regulation (EC) No 1935/2004. Consequently, materials and articles that come into contact with food are often required to be manufactured in accordance with these provisions. Nevertheless, FCMs shall always be manufactured in compliance with good manufacturing practices stated in Regulation (EC) No 2023/2006 (European Commission, 2006). In order to include a new substance into the BfR 'Recommendations on Food Contact Materials', an application must be submitted to BfR. The dossier must follow the guidelines laid down in the EFSA 'Note for Guidance for the Preparation of an Application for the Safety Assessment of a Substance to be used in Plastic Food Contact Materials' (EFSA CEF Panel, 2008). The manufacturer has to supply information on the identity of the substance, data on chemistry and technology, conditions of use, migration into food (including the analytical methods used), data on substance's residual content in the FCM, antimicrobial properties (if antimicrobial substances are incorporated into FCMs) and toxicological data. In order to perform a risk assessment for migrating chemicals, both the toxicological and exposure data need to be combined. Since the generation of toxicological data is very resource and time consuming, a tiered approach is used for necessary data. Based on data from migration studies performed into food (simulants), a different amount of toxicological information must be provided as a minimum requirement. As a general principle, the greater the exposure through migration, the more toxicological information will be required. In case of:

a) High migration (i.e. > 5 mg/kg food), a full data set is needed, which comprises:
   – At least two in vitro genotoxicity tests, in line with the testing strategies of the EFSA Scientific Committee recommendations on genotoxicity testing strategies applicable to food and feed safety assessment:

i) A bacterial reverse mutation test.
ii) An *in vitro* mammalian cell micronucleus test.

- A 90-day oral toxicity study.
- Studies on absorption, distribution, metabolism and excretion.
- Studies on reproduction and developmental toxicity.
- Studies on long-term toxicity/carcinogenicity.

b) Migration between 0.05 and 5 mg/kg food, the following data are necessary (limited data set):

- At least two genotoxicity tests as indicated above.
- A 90-day oral toxicity study.
- Data to demonstrate the absence of bioaccumulation in human.

c) In case of low migration (i.e. < 0.05 mg/kg food), only two genotoxicity tests, at least, are needed.

Once the application is submitted, Unit 74 'Safety of Food Contact Materials' checks the compliance of the dossier with the requirements and assesses the scientific information with particular regard to possible consumer exposure. Studies on genotoxicity and, if necessary, on toxic effects after repeated dose (carcinogenicity, reproductive toxicity, neuro toxicity, immune toxicity and endocrine disruptor properties) are taken into account, along with findings on absorption, distribution, metabolism and excretion (ADME). In this context, the fellow worked on the evaluation of genotoxicity and subchronic toxicity studies of two substances applied for inclusion into the BfR recommendations. Afterwards, the evaluated dossiers were further discussed in the 'Toxicology' and 'Applications' subcommittee groups of the BfR Committee for Consumer Products (BeKo), staffed with external experts, which advise the BfR on the toxicological evaluation of the applied substances.

2.2.2. Hazard assessment of cyclic volatile methylsiloxanes (cVMS)

Owing to their elasticity, non-sticky surface, heat resistance and affordable price, silicone bakeware products are widely used in both industrial and consumer applications as alternative to metal or single-use paper bakeware. Silicone bakeware is often made of silicone elastomers, a rubber-like material obtained from fluid siloxanes by formation of cross-links between linear polymers during vulcanisation. However, unreacted cyclic volatile methylsiloxanes (cVMS), used in the starting materials or resulting from side reactions during the polymerisation process, can still be present in the final product and potentially migrate into foodstuff (Helling et al., 2012). cVMS (examples, see Table 1 and Figure 1) are man-made chemicals and consist of [(CH3)2SiO]n units arranged as cyclic structures. The Si–O atoms are singly bonded to form a ring and generally expressed as Dn, with n = number of Si atoms in the ring. In a recent opinion, ECHA listed three cVMS, namely octamethylcyclotetrasiloxane (D4), decamethylcyclo-pentasiloxane (D5) and dodecamethylcyclohexasiloxane (D6), in the 'Candidate List of Substances of Very High Concern' (SVHC list) for authorisation, according to the Article 57 of the Regulation (EC) No 1907/2006 (REACH Regulation), due to their properties as persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB). In addition, D4 is classified as toxic to reproduction (cat. 2) according to Regulation (EC) No 1272/2008 (CLP Regulation). Over the past decades, several scientific publications demonstrated that cVMS could migrate from silicone FCMs into food and food simulants, raising some concerns on potential adverse health effects resulting from the oral intake of cVMS (Meuwly et al., 2007; Helling et al., 2009; Fromme et al., 2019; Liu et al., 2021). In February 2021, a German official food control laboratory tested various silicone bakeware products for the potential release of D3, D4, D5, D6 and D7 (Table 1) into food simulants. For some of the tested silicone FCMs, migration into vegetable oil (food simulant D2) and poly(2,6-diphenyl-p-phenylene oxide (MPPO)) (food simulant E) exceeded 5 mg/kg food significantly. At the present, a comprehensive risk assessment on cVMS migrating from FCMs into food (simulants) does not exist yet. Due to the high uncertainties in the human exposure estimation, such as the occurrence of cVMS during repeated use, and the transferability of the migration data in food simulants to real food, a preliminary hazard assessment was performed to evaluate the nature of the potential adverse health effects associated with the oral intake of cVMS. First, a comprehensive literature review was carried out. Regulatory and authoritative reviews, together with peer-reviewed key publications, were consulted to identify potential critical endpoints relevant for human health. Once the critical endpoints were identified, the benchmark dose (BMD) approach was applied to establish a

point of departure (PoD). The BMD is a dose level, estimated from a fitted dose-response curve, associated with a specified change in response, the benchmark response (BMR) (EFSA Scientific Committee, 2017). The tool PROAST was used to calculate the BMD levels and the respective lower confidence bound (BMDL) and upper confidence bound (BMDU). The BMDL of the selected critical endpoint was used as PoD. Since the majority of the studies available were based on inhalation exposure studies, inhalation to oral extrapolation of the BMDL was conducted by applying a default physiological parameter, according to the ECHA 'Guidance on information requirements and chemical safety assessment' (ECHA, 2012). Differences between oral and inhalation uptake observed in absorption studies in animals were taken into account. The extrapolated oral BMDL was used to calculate a temporary tolerable daily intake (tTDI). Due to missing toxicological data, a read-across approach was applied to include higher molecular weight cyclic methylsiloxanes within the derived tTDI. From the tTDI, the acceptable migration into food was estimated, assuming a body weight (bw) of 60 kg and food consumption of 1 kg food/day. Based on the assessment studies performed, a tTDI was established for a group of cyclic methylsiloxanes, in order to set the basis for future risk assessment.

Table 1: Name and characteristics of five cyclic volatile methylsiloxanes

Name	Abbreviation	CASNR	Molecular formula	Molecular weight
Hexamethylcyclotrisiloxane	D3	541-05-9	C_6-H_{18}-O_3-Si_3	222.46
Octamethylcyclotetrasiloxane	D4	556-67-2	C_8-H_{24}-O_4-Si_4	296.64
Decamethylcyclopentasiloxane	D5	541-02-6	C_{10}-H_{30}-O_5-Si_5	370.80
Dodecamethylcyclohexasiloxane	D6	540-97-6	C_{12}-H_{36}-O_6-Si_6	444.93
Tetradecamethylcycloheptasiloxane	D7	107-50-6	C_{14}-H_{42}-O_7-Si_7	519.07

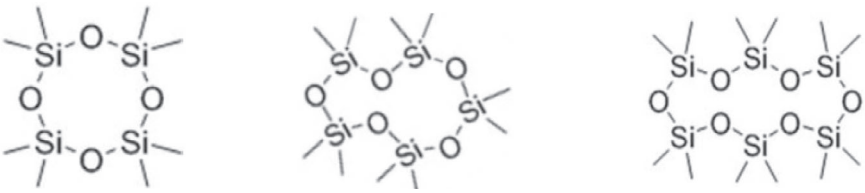

Figure 1: Chemical structures of D4, D5 and D6

2.2.3. *In vitro* metabolic stability study of cyclic methylsiloxanes using S9 fraction

In literature, *in vivo* metabolism of D4 and D5 was elucidated. According to Franzen et al. (2017) and Varaprath et al. (1999), the metabolite profiles reported in blood, tissues and excreta of rats following exposure to D4 suggest that D4 is initially oxidised to a hydroxylated derivative, presumable by cytochrome P450. The initial metabolite appears to rearrange and further hydrolysis leads to the formation of short-chain linear siloxanes, which are excreted via urine (Figure 2). The same metabolic pathway was proposed for the D5 (Dekant and Klaunig, 2016). However, beside D4 and D5, no data are available for higher molecular weight cyclic methylsiloxanes. The aim of this study was to develop a working protocol for the investigation of the metabolic stability *in vitro* of cyclic methylsiloxanes, in the presence of S9 fraction. The ability of cytochromes P450 (CYPs) enzymes to bind and metabolise higher molecular weight cyclic methylsiloxanes (e.g. Dn, $n \geq 6$) should be investigated, and possible metabolites should be identified. Due to the lipophilic properties of the cyclic methylsiloxanes (e.g. D4 logPoW = 6.98), several solubility tests were performed, taking into consideration the solvent compatibility with the S9-mix. The cyclic methylsiloxanes were incubated with S9-mix extracted from rat liver for 4 h at 37°C. The samples were extracted with a suitable organic solvent at the beginning of the experiment (t = 0 h) and after incubation at 37°C for 4 h (t = 4 h) in order to investigate if any decrease in cyclic methylsiloxane or increase in metabolites concentration occurs during the incubation period. The extracts were analysed by LC-GC coupled online to a triple quadrupole mass spectrometer for quantification of siloxanes in selected ion mode. All samples were prepared in duplicate, with and without S9-mix.

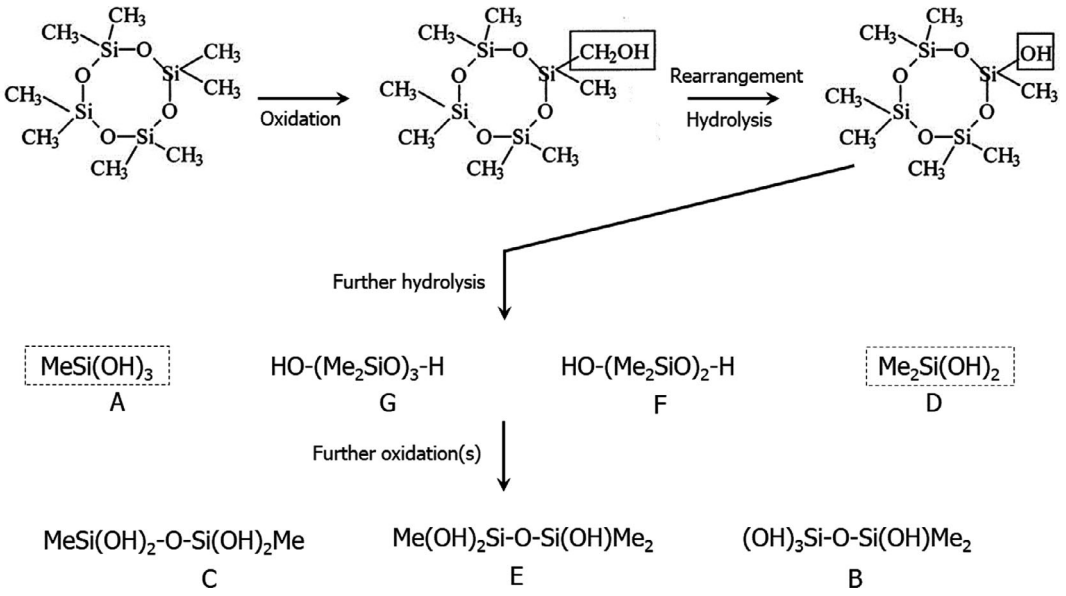

Figure 2: Adapted from Franzen et al. (2017) – Possible pathways for formation of D4 metabolites. A and D were considered major metabolites. Metabolites C, E and B can be produced by multiple pathways (Varaprath et al., 1999)

3. Conclusion

The EU-FORA programme allowed the fellow to gain deeper insight into risk assessment of food contact materials and to acquire relevant knowledge of different risk assessment tools. At the Bundesinstitut für Risikobewertung, the fellow worked side-by-side with the experts of Unit 74 'Safety of Food Contact Materials' on the scientific evaluation of two dossiers for the inclusion of new substances in the 'BfR Recommendations on Food Contact Materials', including the communication with the applicants concerning the occurring scientific questions. In a separate project, the fellow undertook the first steps to a risk assessment of cVMS migrating from silicone FCMs into food. Based on toxicological studies published in the literature or evaluated by other competent authorities, a hazard assessment for cVMS was performed, leading to a temporary tolerable daily intake value for these substances. In addition, in course of a laboratory work project in the German national reference laboratory for food contact materials, the fellow worked on the set-up of a test protocol for the *in vitro* metabolism study on cyclic methylsiloxanes. Moreover, beside the scientific knowledge, the EU-FORA fellowship was a great opportunity for the fellow to build a strong scientific network, to meet international experts and fellows and to be part of an international community of risk assessment professionals.

4. Disclaimer

The results of the hazard assessment of cVMS are intended to be published in a peer-reviewed journal. In order to avoid copyright claims, they were not included in the technical report.

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
BeKo	BfR Committee for Consumer Products
BfR	Bundesintitut Für Risikoberwertung
BMD	Benchmark Dose Modelling
cVMS	Cyclic Volatile Methylsiloxanes
EU-FOR A	European Food Risk Assessment Fellowship Programme
FCMs	Food Contact Materials
NRL-FCM	German National Reference Laboratory for Materials in Contact with Food
PoD	Point of Departure
RA	Risk Assessment

Appendix A – Training activities

Event	Title	Contribution	Location	Date
Webinar	Food Packaging Forum: Addressing endocrine disrupting chemicals (EDCs) and mixture	Attendance	Online	15.4.2021
Meeting	Toxicological subcommittee meeting BfR unit 74	Oral presentation	BfR	20.4.2021
Conference	Genetic Toxicology Association (GTA) Annual Meeting	Attendance	Online	3–6.05.2021
Webinar	Food Packaging Forum: Responding to hazardous chemicals in FCMs: substitution and simplification	Attendance	Online	13.5.2021
Conference	International Akademie Fresenius Online Conference "Residues of Food Contact Materials in Food"	Attendance	Online	24–26.6.2021
Summer School	BfR-Summer Academy 2021: Lecture Series	Attendance	BfR/Online	16–20.8.2021
Summer School	Parma Summer School 2021	Attendance	Online	28–30.9.2021
Meeting	Toxicological subcommittee meeting BfR unit 74	Oral presentation	BfR	9.11.2021
Webinar	Evidence-based Toxicology Collaboration (EBTC) 10th Anniversary Celebration	Attendance	Online	11.11.2021
Webinar	Food Packaging Forum: Is current phthalate regulation fit for purpose?	Attendance	Online	19.11.2021