Oligomers in polyester food contact materials

Identification and migration studies

Hoppe, M.

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Chapter 6  Synthesis

The work presented in this thesis deals with the presence of oligomers in polyester-type food contact polymers, their ability to migrate into food and how migration values and the resulting exposure can be assessed by modelling. While the preceding chapters provide answers to the three key questions introduced in chapter 1, this chapter offers a more extended discussion of the findings.

6.1 Answers to research questions

Research question 1: Which species of polyester-related oligomers can be expected in food contact plastics?

The literature review in chapter 2 together with the subsequent chapters identify and summarise a variety of oligomers which are present in food contact polymers especially in polyesters. These oligomers, which are structurally linked to the used (co)monomers, are inevitably formed during the synthesis of polymer materials. They can also be generated during storage periods due to external physical factors like UV-light, mechanical and thermodynamic stress for instance during microwave applications or chemical influences e.g. when the polymer is in contact with food (possible hydrolysis reactions). Hence, oligomers might be classified as polymer related and accompanying substances rather than non-intentionally added substances. The structures of these oligomers are related to the (co)monomers used for the polymerisation reaction and may be also triggered by the polymer production process conditions. This makes oligomers and oligomer patterns polymer-specific by-products. Regarding the four polyesters investigated in this work (PET, PEF, PBT and PEN), the predominant structure characteristic is the ring configuration of the oligomers. Linear oligomers have also been detected in extracts of PEF, PBT and PEN, but were found to represent a minor fraction only since their concentration was invariably below 5% of the total oligomer content. Linear PET oligomers have been detected in other studies (Freire et al., 1999; Kim & Lee, 2012b), but not in the studies presented in this work. However, the concentrations of linear oligomers depend on the production process conditions employed. Linear oligomers, in contrast to cyclic ones, are able to react further to longer polymer chains. Cyclic oligomers do not contain the reactive acid and alcohol group. Especially reactions to oligomers of small ring sizes (n = 2–4) are thermodynamic favourable and, once they are built, these oligomers will stay in the polymer matrix which explains their high abundance.

The monomer number $n$ of the most abundant oligomer depends on the monomeric units. In PET and PEN materials the cyclic trimer was found to be the major oligomer. In contrast, the cyclic dimer was the most abundant oligomer present in PEF and PBT polymers. The reactions to these oligomers are thermodynamically most favourable which was already shown in the case of the PET cyclic trimer (Vermylen et al., 2000). Two factors are supposed to have a major influence on the size of the oligomeric ring. One is the bond angles that result from the substitution pattern and size of the monomeric aromatic ring. The second is the size of the dialcohol unit which can be observed in PBT and PET. The difference between these polymers lies in the type of the dialcohol
monomer – butylene glycol and ethylene glycol – which determines the size of the most abundant oligomer.

The total oligomer concentration in the polyesters investigated in this study ranges between 0.3% and 0.9% (w/w). This depends on the type of polyester, the way of production and on previous storage conditions. However, in general, the oligomer concentration in polyester-type polymers can be expected to be always around 1% (w/w). This is useful information when migration of these oligomers is considered. For a quick risk assessment 1% oligomer concentration in the polymer can be assumed as the maximum concentration that triggers the migration into food.

**Research question 2: How can these polymer-related oligomers be identified and quantified?**

Mass spectrometry is the preferred and most frequently used technique to identify oligomers. As the monomeric units of the polymers are known, the masses of possible oligomers can be calculated and confirmed with the mass analysis of polymer extracts and fragmentation spectra. The results presented in this thesis showed that besides the intentionally used monomers also unintentionally added monomers can be generated and incorporated into the polymer chain during the polyester production. Therefore, oligomers containing these monomers can be found when analysing the oligomer content of polyesters. The dialcohol components ethylene glycol and butylene glycol can react during the polymerisation to the respective diglycol units: diethylene glycol and dibutylene glycol. Such diglycols are also known to be by-products of the monomer production (Rebsdat & Mayer, 2000). In addition to the 'by-product-monomers' which can be identified according to their different mass, there might be isomeric 'by-product-monomers', such as, for example, ortho-phthalic acid and isophthalic acid. These are inevitably present as normal impurities in the used main-monomer, the terephthalic acid (Huang et al., 2009). Isomeric oligomers of the same molecular mass can be separated by liquid chromatography and in this way be observed to be part of the total oligomer content. These two types of 'by-product' monomers are kind of unexpected since they are not intentionally added to the polymerization process. However, unintentionally added monomers have to be considered as well when the oligomer content of polyesters is studied.

The unambiguous identification of oligomers with LC-MS with the help of a reference standard of the respective oligomer is rarely possible due to the general non-availability of single oligomer standards. The cyclic PET trimer is the only commercially available standard for a polyester type oligomer. The synthesis of each oligomer as single standard substance to confirm their identity would be very time and resources consuming. Therefore, identification on a level of high probability (identification level 2 according to Schymanski et al. (2014)), using the accurate mass and fragmentation spectra in combination with information about the monomer composition of the polyester, appears to be sufficient and justifiable for oligomers. In chapter 3, 4 and 5 it was demonstrated that in extracts of polyesters the masses of several possible combinations of the respective monomers can be detected with HRMS analysis. Additionally the molecules showed characteristic fragments which display consecutive loss of monomeric units.

For quantification purposes it would also be beneficial to have single oligomers as pure standards. During LC-MS analysis atmospheric pressure ionisation techniques are commonly used. These
ionisation processes are substance-specific due to different chemical groups or structural constitutions of the molecules. This leads to varying responses of different molecules in the mass detector. Therefore, in order to quantify polymer-related oligomers in both the polymer and in food simulants without the substance itself as an available standard, alternative quantification approaches were used in the scientific literature and during the work described in this thesis. In chapter 4 oligomers present in PET were quantified using LC-MS with the cyclic PET trimer as external standard for each oligomer. It was assumed that the different PET oligomers more or less have the same ionisation behaviour due to their structural similarity. On the other hand, in chapter 5, PBT and PEN-derived oligomers were quantified with the cyclic PET trimer as external standard, using UV detection of the aromatic ring chromophore. All of the oligomers have an absorption maximum between 239–241 nm and it was assumed that the UV response for all of these substances is the same. However, these are still semi-quantitative approaches – standards of the single oligomers would be essential for complete verification. Another critical point regarding UV detection is sensitivity. The UV detector is able to detect analytes down to concentrations of approximately 100 ng mL⁻¹. Since the a total oligomer migration limit of 50 µg kg⁻¹ was recently demanded for PEF, which would correspond to a oligomer concentration of 50 ng mL⁻¹ in the testing solution, lower limits of quantification than possible with UV detection have to be reached for PEF oligomers. If this low migration limit for the total of all oligomers (for PEF) would be applied for every polyester, probably all kinds of oligomers would have to be analysed by LC-MS unless sample preparation would allow appropriate analyte enrichment. Therefore, for PEF a third quantification approach was developed in chapter 3. The methylester of furandicarboxylic acid – the monomeric unit – was chosen as a standard substance to quantify the identified oligomers with UV detection. The selected standard and the oligomers both had their absorption maximum at the same wavelength. A parallel LC-MS measurement of the same sample was conducted and dimethyl furandicarboxylate was used as an external standard as well. From here, the UV and LC response of the oligomers to dimethyl furandicarboxylate could be compared and factors for each oligomer derived to correct the different response in the MS analysis. Using such an approach it is possible to profit from the higher sensitivity of mass spectrometric detection and reach lower limits of quantification compared to UV detection. For a full verification of this alternative quantification approach, available and affordable standards of single oligomer substances would be needed. However, to determine the LC and UV response for all oligomers with regard to one external standard, as it was done in the case for PEF, is more accurate for quantification but on the other hand very time consuming. In some studies it might be more suitable to carefully choose an external standard for semi-quantification without extensive response comparison as it was done in chapter 4 and 5. The choice of the method depends on the height of the demanded migration limit and on the structural-chemical similarity of the available external standard to the oligomers.

Research question 3: To what extent do oligomers migrate into food simulants or food and do migration models produce comparable data to the experiments?

Oligomers were shown to be present in the four investigated polyesters and they were shown to migrate from the materials into food simulants in chapter 4 and 5. The migration of oligomers from polyesters was only recently considered more specifically by the authorities. The two newly authorised monomers furandicarboxylic acid and 2,4,8,10-tetraoxaspiro[5.5]undecane-3,9-
diethanol, β3,β3,β9,β9-tetramethyl are allowed to be used for the production of food contact polyesters when the total oligomer migration does not exceed 50 µg kg⁻¹ which is an accepted general migration limit for non-genotoxic compounds for which no further toxicological data are available. If this migration limit would be applied to other polyesters, the oligomer migration levels reported in some of the reviewed publications would not always be in compliance with this restriction. This is especially observed when the polymers are exposed to stressful physical conditions like for example during microwave applications. Therefore, in absence of sufficient toxicological data, it should be considered to evaluate polyesters made from already authorised monomers for their possible oligomer migration under the intended application conditions and to set corresponding migration limits for those substances, in particular, for high production volume polyesters like polyethylene terephthalate. It would additionally be reasonable to investigate the behaviour of oligomers under ingestion conditions with digestive fluid simulants like proposed by the EFSA (2008) to assess whether the cyclic or linear oligomers are hydrolysed in the human body. This is a crucial question since it will show whether or not an oligomer specific migration limit should be set. In the case of complete hydrolysis of the oligomers to the respective monomers the oligomers can be considered as quasi-monomers with the consequence that the specific migration limits set for the monomers would apply. Under this circumstance, risk assessment and also determination of the oligomer content and their migration would be simplified. It would not be necessary to quantify each oligomer separately; instead hydrolysing the oligomers in the migration solution and analysing the monomer content would suffice. However, when hydrolysis of the oligomers is not feasible, it would be recommendable to investigate if and under which conditions the 50 µg kg⁻¹ migration limit can be respected, and if not, to carry out appropriate toxicological studies with pure oligomer standards or at least oligomer mixtures. This might help to assess the potential hazard of these oligomers and to what extent they might pose a risk to the consumer.

Two different approaches are available to determine the migration of a certain substance: experimental migration studies and theoretical modelling. Regulation (EU) No 10/2011 lists standardised food simulants and test conditions (time and temperature to mimic certain food packaging and storage scenarios) which should be used to assess migration. Theoretical migration modelling is also accepted by the Regulation (EU) No 10/2011 to evaluate the migration of substances conservatively. It should be noted here that results from migration modelling can legally only show compliance but never non-compliance, which means: when a conservatively modelled migration is lower than a migration limit, compliance is shown. However, when the modelled migration exceeds the limit, then another, more realistic approach may be taken to check for (non)compliance. Migration modelling is in particular beneficial in cases when substances are very difficult to be analysed or when food contact conditions include long time storage up to several months, 1 year or longer. Here, different diffusion models exist which have been validated by experimental data. The method most frequently used to calculate diffusion coefficients in a polymer is the Piringer approach. With the diffusion coefficient, migration can be calculated by commercial softwares such as the AKTS software. Another theoretical approach for determining the diffusion coefficients in PET material is the Welle equation. Experimental and theoretical methods have been used in this thesis to determine the migration of oligomers from different food contact polyesters at 40°C, 60°C or 80°C. It was shown that the Piringer approach is too conservative for oligomer migration from the polyesters PET and PBT (with the liner PBT dimer_DBG as an exception) – which, in general, is the intention of a modelling approach to
overestimate the 'real' exposure in order to be on the safe side of risk assessment. However, in some cases, if the approach is too conservative, this may lead to unnecessary exclusions of materials for some applications. The Welle model was shown to give more realistic data for the PET oligomer migration. For cyclic PBT oligomers the Welle approach was shown to underestimate their migration which might be due to the different diffusion characteristics of PBT compared to PET. To verify the applicability of model approaches for polyester oligomers during long term storage periods at room temperature future scientific studies should derive diffusion characteristics under these conditions to compare them with modelled data.

In chapter 4 and 5 of the present work ethanol-water mixtures with varying ethanol contents were used as food simulates to estimate the migration of the oligomers. While carrying out these experiments, oligomers, which were not present in the polyesters originally, were detected in the food simulates. This happened only when using food simulates with a high ethanol content of 50% (v/v) and was observed by other researchers as well (Paseiro-Cerrato et al., 2016). It is not known whether these additional oligomers result from the reaction of the polymer chain with ethanol or from the reaction of already into the simulant migrated oligomers. It is likely a combination of these two processes. Nevertheless, these newly formed additional oligomers are artefacts linked to the used food simulant and would most likely not appear in real food – obvious exceptions are drinks with high alcohol content. It is known that certain solvents like alcohols act as swelling agents to polyesters and will therefore change the diffusion characteristics of the respective polymers. Ethanol-water mixtures with high ethanol content were originally assigned as alternative fatty food simulates especially to test migration from polyolefins. For these types of polymers, ethanol does not significantly act as a swelling agent. Hence, the diffusion characteristics of a polyolefin will not be changed. It is questionable whether such conventional food simulates, which are known to produce artefacts or change the diffusion characteristics, should be used further to evaluate migration from food contact polyesters. However, these side reactions have only been observed for ethanolic contents of 50%. In the study using 20% ethanol as food simulant such artefacts were not detected. Hence, one can conclude that 20% ethanol represents an appropriate food simulant for polyesters as long as there is enough solubility for the migrants of interest. However, such transesterfication side-reactions are also temperature depended. It might be possible to use food simulates with a high ethanol content at low testing temperatures without producing artefacts. Finally, it may be worth to explore alternative fatty food simulates for the 50% and 95% ethanol that do not cause swelling of polyesters nor produce artefacts. Such studies that assess the migration into real foods should be part of future scientific efforts for improving the methodologies in order to validate the use of the simulants for real applications.

6.2 Risk assessment

The work described in the present thesis demonstrates that oligomers are inevitably present in polyester-type food contact materials as a result of formation during the polymerisation and food contact material/article production process. Therefore they can be qualified as polymer-related substances. Their formation depends on both the production process and storage conditions, but not on the origin (bio-based or fuel-based) of the monomers. Due to their presence in the polyester food contact materials, oligomers are able to migrate into food and drinks that are in contact with
the polymers. Both, migration testing on polymers intended for the food contact and regulations concerning specific migration levels, are necessary to protect the consumer against possible harms which can be caused by chemical substances when released in unacceptable amounts from the food contact material. Therefore, the two important questions concerning oligomer risk assessment are: what is the level of migration and therefore exposure of the consumer and what are the toxicological hazards of polyester-related oligomers? Since toxicity testing is very elaborate and cost-intensive, a very target leading approach for the safety evaluation of the oligomers may the following: in a first step the migration of the relevant oligomers (<1000 Da) has to be determined either experimentally or theoretically which results in the possible exposure scenario. If hydrolysis of the oligomers to the starting monomers with digestive fluid simulants can be shown, the toxicological profiles and migration limits of the monomer may be applicable. If the oligomers are not hydrolysed and if toxicity data are unavailable the read across approach and structure-activity relationship analysis on a representative oligomeric structure could help to make assumptions about the toxicity of the substances. If genotoxicity can be excluded, which generally should be the case for oligomers originated from polyesters where the monomers are non-genotoxic a 50 µg kg\(^{-1}\) specific migration limit for polyester oligomers could be applied. This conclusion has been drawn by toxicologists for the evaluation of polyester oligomers as in the example of PBT where it was concluded that since the monomers are not genotoxic 'no genotoxic properties are expected' for oligomers, too (EFSA, 2009). Assuming a 60 kg weight person would consume 1 kg food packed in the respective polyester with a specific oligomer migration of 50 µg kg\(^{-1}\) would result in a human exposure of 0.833 µg (kg bw per day)\(^{\circ}\). This is even below the threshold originated from the TTC concept of 1.5 µg (kg bw per day)\(^{\circ}\) for cramer class III substances and should therefore have a low probability of adverse effects to human health (EFSA, 2016). Additionally, the specific limit applies for a whole substance group and not for a single substance. This might be reasonable since oligomers originating from one polymer all have the same structure elements and differ only in size. However, a distinction should be made between cyclic and linear oligomers from polyesters since they have different structural and chemical elements. This could result in a specific migration limit of 50 µg kg\(^{-1}\) for linear oligomers and 50 µg kg\(^{-1}\) for cyclic oligomers. However, if the possible exposure is shown to be higher than this level, appropriate toxicity data for oligomer mixtures or single oligomers are needed to exclude risks for the consumer’s health.

6.3 Concluding remarks

Polyesters have a lot of applications as food contact materials. In addition to the high consumption of PET bottles for mineral water and other kinds of drinks (alcoholic and non-alcoholic), PBT and PET are used for microwave applications. The radiation and temperatures, which are applied here, as well as the high fat content of some microwavable food, could trigger and accelerate formation of oligomer or/and increase their migration. Other polyesters based on different monomers (for example cyclohexane-1,4-dimethanol, hexahydrofuro[3,2-b] furan-3,6-diol) are used to produce reusable plastic containers to store and transport food. Metal can lacquers based on polyesters are used as replacements for traditional epoxy resin coatings because of its potential to release bisphenol A, a substance which is in controversial public discussion since some time due to its hormone-like activity and other biological effects. From these can coatings polyester-related linear and cyclic oligomers might also migrate into food. These examples show that the application of
polyesters in the food packaging industry gets broader and thus, the possible exposure of consumers to polyester related oligomers may increase concomitantly. Therefore, the migration behaviour, physical constants like diffusion coefficients in polymer, partitioning into foods and hydrolysis behaviour in the gastrointestinal tract as well as toxicity of those oligomers should be further determined.

As indicated in the introduction chapter around 40% of the plastics produced in Europe find application in the packaging sector. This means, in addition to the possible exposure to unwanted substances from food caused by polymer packaging, the influence and impact of plastic waste on the environment have to be taken into consideration. The four studied polyesters are all not readily biodegradable (Lefèvre et al., 1999; Matos et al., 2014) and will stay undegraded for a long time and increase in the environment if not efficiently recollected and burned or recycled. PET with the largest production volume of those four polymers with around 3.8 mt in Europe (Plastic Europe, 2017) has a large recycling rate of around 50% (Welle, 2011), but still, worldwide, 4.8 to 12.7 mt of different plastic waste entered the oceans in 2010 (Jambeck et al., 2015). The extensive use and the resulting waste production of plastics pollute oceans and rivers and finally affect the life of the marine ecosystem (Cole et al., 2011; Lebreton et al., 2017). Acting responsibly with regard to the use of plastics and taking into account the products we buy can already contribute to the reduction of plastic waste. This awareness is needed in every country worldwide to dam the plastic pollution of the ocean and its ecosystems. To counter this development, additionally, research activities could be conducted in the field of biodegradable plastics with the needed material properties for food packaging material (Chandra & Rustgi, 1998; Matos et al., 2014).