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Polyamide Kitchen Utensils: Keep contact with hot food as brief as possible

BfR Opinion No. 036/2019 of 17 September 2019

Cooking spoons, spatulas or whisks: polyamide (PA) kitchen utensils provide valuable baking, roasting and cooking assistance. However, components of this plastic can migrate from the utensils into the food and consequently be ingested by consumers.

These components are oligomers. They are composed of a few similar molecules of simple plastic building blocks made of specific starting chemicals. They are formed unintentionally during the production of plastics. Due to their small size, some oligomers can migrate from plastic into food. This opinion considers oligomers from two different polyamides, which are mainly used in the production of kitchen utensils. These are PA 6 (starting chemical: caprolactam) and PA 6,6 (starting chemicals: adipic acid and hexamethylenediamine).

In its opinion No. 014/2018, the BfR assessed the health risk of cyclic oligomers that migrate from the PA-varieties PA 6 and PA 6,6 into food. In the absence of experimental toxicological data, the first assessment of the health hazard potential was based on the concept of “threshold of toxicological concern”. This approach classifies substances of unknown toxicity on the basis of their chemical structure into so-called Cramer classes. Each of these classes is assigned to a maximum daily intake that is unlikely to possess a risk to human health. The PA oligomers considered here were assigned to Cramer class III and accordingly to a daily intake of 90 µg relative to a person weighing 60 kg.

However, data from the years 2016/2017 showed that the amounts of cyclic PA oligomers migrating from kitchen utensils into food can be much higher. In order to perform a conclusive risk assessment, the BfR recommended within its opinion that manufacturers of food contact materials compile toxicological data in accordance with the specifications of the European Food Safety Authority (EFSA) and make them available to BfR.

In the meantime, manufacturers have submitted studies on the toxicity of various cyclic PA compounds to the BfR. Based on this new data, PA 6 (dimer to octamer) and PA 6,6 (monomer to tetramer) oligomers were assessed using a group approach. The compounds have been assessed as non-genotoxic. However, high doses cause adverse effects in the liver and thyroid which are due to metabolism. Based on the available data, the amount of 5 mg/kg of food was assessed as being toxicologically acceptable as group migration value for the compounds mentioned. For orientation: According to European Plastics Regulation (EU) No. 10/2011, an adult is assumed to consume one kilogram of food every day that has come into contact with food contact material.

In 23 out of 33 items the group migration of cyclic PA oligomers originating from kitchen utensils, investigated in 2016/2017, was less than 5 mg/kg of food. However, in 10 of the 33 items the release exceeded 5 mg/kg of food. For this reason, manufacturing processes of kitchen utensils made of PA should be optimised in order to minimise the migration of PA oligomers. The BfR recommends that consumers keep contact with food as brief as possible when using PA kitchen gadgets, especially at high temperatures (above 70 °C).

		BfR Risk Profile: Polyamide Oligomers from Kitchen Utensils (Opinion No. 036/2019)			
A Affected persons	General population 				
B Probability of health impairment due to regular oligomer intake from kitchen utensils	Practically impossible	Unlikely	Possible	Probable	Certain
C Severity of the health impairment with regular intake	No impairment	Slight impairment conceivable	Moderate impairment	Severe impairment	
D Validity of available data	High: The most important data is available and there are no contradictions		Medium: Some important data is missing or contradictory	Low: Important data is missing	
E Controllability by the consumer	Control not necessary	Controllable through precautionary measures	Controllable through avoidance	Not controllable	

Fields marked in dark blue indicate the properties of the risk assessed in this opinion (for more details, see the text of Opinion No. 036/2019 of the BfR dated 17 September 2019).

Explanations

The risk profile is intended to visualise the risk outlined in the BfR opinion. It is not intended for the purpose of comparing risks. The risk profile should only be read in conjunction with the corresponding opinion.

1 Object of the assessment

In the production process of polyamide (PA), cyclic oligomers unintentionally form during the polymerisation reaction (see Figure 1 and Table 1). The compounds are named as shown in the example in Figure 1. The smallest cyclic PA 6,6 oligomer (1,8-diazacyclotetradecane-2,7-dione) is referred to as PA 6,6 “monomer”, even if it is already composed of two monomers (see Table 1).

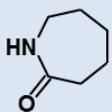
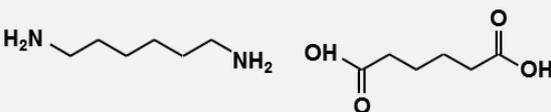
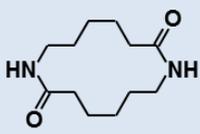
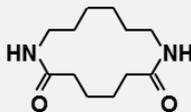
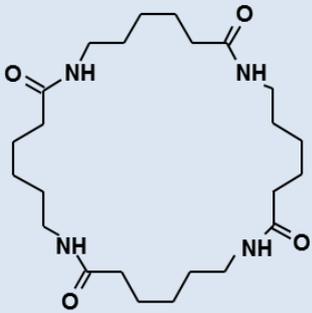
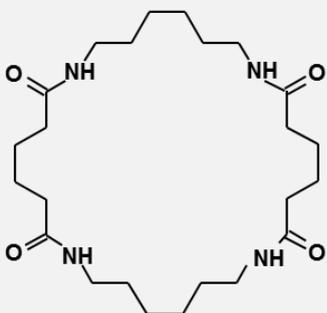
	PA 6	PA 6,6
monomers	 ε-caprolactam	 hexamethylenediamine adipic acid
smallest oligomers	 1,8-Diazacyclotetradecane-2,9-dione (polyamide 6, cyclic dimer)	 1,8-Diazacyclotetradecane-2,7-dione (polyamide 6,6, cyclic „monomer“)
higher oligomers	 polyamide 6, cyclic tetramer	 polyamide 6,6, cyclic dimer

Figure 1: Monomers and selected oligomers of polyamide 6 and polyamide 6,6. Polyamide 6 is created from ε-caprolactam and polyamide 6,6 from the monomers adipic acid and hexamethylenediamine.

According to a report of the food monitoring authorities from the years 2016/2017, PA oligomers from kitchen gadgets (e.g. cooking spoons, spatulas) migrate into food simulants. In its Opinion No. 014/2018, the BfR discussed the health hazard of cyclic PA oligomers (BfR, 2018). Since no toxicology data were available at the time, this initial assessment was based on the concept of “threshold of toxicological concern”, which classifies substances of unknown toxicity by their chemical structure into so-called Cramer classes, which are assigned a maximum daily intake. The PA oligomers under consideration were assigned to Cramer class III and accordingly to a daily intake of 90 µg relative to a person weighing 60 kg. However, the migration data from the years 2016/2017 showed that much higher amounts of cyclic PA oligomers can migrate from kitchen utensils into food. In order to perform a conclusive risk assessment, the BfR recommended in its Opinion No. 014/2018 that manufacturers of food contact materials prepare toxicological data in accordance with

the specifications of the European Food Safety Authority (EFSA) and make them available to the BfR.

In the meantime, manufacturers have provided the BfR with data on genotoxicity as well as sub-acute and (sub)-chronic toxicity of various cyclic PA oligomers. This formed the basis for the present assessment of the health risks from PA oligomers released from food contact materials (BfR, 2019).

2 Result

In 2016/2017, 33 kitchen utensils were tested for the release of cyclic oligomers from PA 6 (dimer to heptamer) and PA 6,6 (“monomer” to trimer) into food simulant. The measured migration values form the basis for assessing consumer exposure to cyclic PA oligomers and the potentially resulting health risk. The measured migration values per kitchen utensil were each related to one kilogram of food, which is the reference consumption for a person weighing 60 kg (EU, 2011). The highest transfers were determined for the cyclic PA 6,6 “monomer” (5.1 mg/kg of food) and for the cyclic PA 6,6 dimer (4.1 mg/kg of food).

The currently available data are insufficient to assess each PA oligomer (e.g. dimer, trimer, tetramer) individually. There are, however, sufficient data to assess PA 6 and PA 6,6 oligomers in a group approach and derive a toxicologically acceptable cumulative migration value for the migration into food. This BfR assessment includes PA 6 oligomers with $n = 2$ to 8 (dimer to octamer) and PA 6,6 oligomers with $n = 1$ to 4 (“monomer” to tetramer). Longer-chain oligomers are not relevant for the toxicological assessment due to their high molecular weight (> 1000 Da) and associated low absorption potential (EFSA, 2016).

There is no evidence of genotoxic effects for either PA 6 or PA 6,6 oligomers. According to the available data, hydrolysis of the compounds into the starting chemicals does not occur in any significant degree. Accumulation in humans is unlikely due to the octanol/water partition coefficients, the chemical structure of the compounds, and *in silico* predictions. Based on the available data on sub-acute and sub-chronic toxicity, the BfR considers a group migration value for the above defined PA oligomers of 5 mg/kg of food to be toxicologically acceptable.

The calculated group migration values from the kitchen utensils examined are between 0.9 and 10.9 mg/kg of food (median 2.8 mg/kg of food). For 10 of the 33 kitchen utensils group migration values higher than 5 mg/kg of food were determined. There are no studies on the toxicity of life-long intake, carcinogenicity and reproductive toxicity. The BfR recommends reducing the group migration of the mentioned oligomers from food contact materials to a maximum of 5 mg/kg of food. To assess the safety of a release higher than 5 mg/kg of food, further toxicological studies are required.

3 Justification

3.1 Risk assessment

3.1.1 Possible sources of danger

Many kitchen utensils, such as spatula, whisk or barbecue tongs, are made of polyamide (PA). PA oligomers are formed during the manufacturing process and remain in the finished polymer as NIAS (“non-intentionally added substances”). The monomer of PA 6 is ϵ -caprolactam (CAS: 105-60-2), while the structurally similar PA 6,6 consists of the monomers hexamethylenediamine (CAS: 124-09-4) and adipic acid (CAS: 124-04-9) (Figure 1).

The available data from the food monitoring authorities show that, at least at high temperatures (above 70 °C), a substantial transfer of PA oligomers from kitchen gadgets into food may occur (Table 2).

3.1.2 Hazard

According to Article 19 of Regulation (EU) No 10/2011 “On plastic materials and articles intended to come into contact with food” (Plastics Regulation), all substances migrating from food contact materials, including NIAS, which include PAs oligomers, must undergo an individual toxicological assessment. This is also required by the European Food Safety Authority (EFSA) (EFSA, 2016). In particular, oligomers with a molecular weight <1000 Da require assessment, since the probability of gastrointestinal absorption is high. The present opinion refers to cyclic oligomers of PA 6 and PA 6,6. The term oligomers encompasses a variety of structurally very similar molecules which differ only in the number of monomers of which they are composed (e.g. dimer, trimer, tetramer). For the release of the monomers of PA 6 or PA 6,6 from plastic, specific migration limits (SML) are specified in the Plastics Regulation. An SML of 15 mg/kg of food is specified for the PA 6 monomer ϵ -caprolactam, the SMLs for the PA 6,6 monomers hexamethylenediamine and adipic acid are 2.4 mg/kg of food and 60 mg/kg of food, respectively. The BfR risk assessment of PA oligomers is based on existing data on genotoxicity, and the sub-acute and sub-chronic toxicity of individual PA oligomers, as well as on existing assessments of the respective starting compounds. Furthermore, *in silico* predictions of genotoxicity based on chemical structures are taken into account.

3.1.2.1 Genotoxicity

According to the opinion of EFSA (2016), the assessment of genotoxicity of oligomers can use results from studies on the respective monomers, provided that their functional groups are consistent. If reliable data demonstrating the absence of genotoxic effects of the monomers are available, genotoxicity tests for functionally related oligomers are not required (EFSA, 2016).

The formation of dimers or higher homologues from ϵ -caprolactam (PA 6) does not introduce any new functional groups. The oligomers are cyclic and possess exclusively amide groups. The number of amide groups depends on the size of the respective oligomer (Figure 1). This also applies to PA 6,6 cyclic oligomers. The BfR has data on the genotoxicity of the respective monomers as well as individual oligomers. In addition, available information from *in silico* predictions was included in the assessment of genotoxic potential.

PA 6

The monomer of PA 6 oligomers, ϵ -caprolactam, is not mutagenic in the AMES test (Zeiger et al., 1990). In addition, mice given oral ϵ -caprolactam showed neither chromosomal aberrations in the bone marrow nor DNA damage in the comet assay (EFSA, 2015). Overall, there is no indication of genotoxicity of ϵ -caprolactam. Based on an NTP study (NTP, 1982) in mice (dose of up to 2140 mg/kg bodyweight (bw) per day) and rats (dose of up to 750 mg/kg bw/day), the International Agency for the Research on Cancer (IARC) of the World Health Organization assessed ϵ -Caprolactam as “probably not carcinogenic to humans (Group 4)” (IARC, 1999). *In silico* analyses of PA 6 dimer (1,8-diazacyclotetradecane-2,9-dione) using the OECD QSAR Toolbox (OECD, 2016) and the prediction algorithm DEREK (version 5.0.2) of the “Nexus” software (Lhasa Limited; 2.1.1) did also provide no evidence of genotoxic effects. No structural characteristics of genotoxicity nor structural similarities with known genotoxic substances were identified. The PA 6 oligomers were assessed as non-genotoxic.

PA 6,6

For the two PA 6,6 homologues cyclic “monomer” and cyclic dimer (see Figure 1), the BfR has access to genotoxicity studies (AMES test) which showed no evidence of mutagenic effects (BASF SE, 2013; CiToxLab France, 2014). Examination of a mixture of PA 6,6 oligomers consisting of cyclic “monomer”, dimer and trimer also revealed no evidence of genotoxic effects in two *in vitro* mutagenicity tests (mouse lymphoma assay and micronucleus assay) (CiToxLab France, 2016; 2017). An *in vivo* micronucleus test with the cyclic “monomer” of PA 6,6 (1,8-diazacyclotetradecane-2,7-dione) was also negative (Harlan CCR, 2013). For the starting compounds of the PA 6,6 oligomers, hexamethylenediamine and adipic acid, no evidence of a genotoxic effect exists according to current data. Data from *in silico* analyses of the PA 6,6 cyclic “monomer” with the above-mentioned software tools confirm these findings. The PA 6,6 oligomers were assessed as non-genotoxic.

3.1.2.2 Studies on sub-chronic and chronic toxicity

PA 6

The sub-chronic and chronic toxicity of ϵ -caprolactam has been tested in dogs and rats in various feeding studies. An exposure-related decrease in body weight as well as sex-specific renal toxic effects were observed, but these are considered to be of little or no relevance to humans (OECD, 2001).

For the PA 6 oligomers, the BfR has access to two feeding studies in rats from the 1970s, which examined the sub-acute (after 28-day exposure) or sub-chronic (after 90-day exposure) toxicity of a mixture of PA 6 oligomers (dimer – octamer) (Central Institute for Nutrition and Food Research, 1971; 1972). The scope of the parameters investigated in these studies does not comply with current OECD guidelines. A comprehensive risk assessment cannot be performed on the basis of these studies. Nevertheless, they provide important data for the assessment of the risk potential of PA 6 oligomers, in particular because of the special attention given by the studies to potential renal toxic effects, as described for ϵ -caprolactam. Neither the sub-acute nor the sub-chronic study found toxic effects for the feed mixture of PA 6 oligomers.

PA 6,6

The BfR has access to two studies on the toxicity of PA 6,6 cyclic “monomer” (1,8-diazacyclotetradecane-2,7-dione, Figure 1) after 28 days of exposure (sub-acute) and 13 weeks of exposure (sub-chronic) in rats (BASF SE, 2015a; 2015b). In both studies, feeding the highest test concentrations (1000 and 1100 mg/kg bw/day, respectively) resulted in an increase in liver weight associated with centrilobular hepatocyte hypertrophy. The

concentration of classical marker enzymes for liver damage (e.g. aspartate/alanine aminotransferase) in the blood remained unchanged. Bilirubin and urea levels in the blood were significantly increased indicating enhanced metabolism. In addition, mild effects on the thyroid gland (hyperplasia/hypertrophy) were noted in both studies. The highest dose causing no adverse effect (NOAEL, no observed adverse effect level) was 320 mg/kg bw/day in the sub-acute study and 350 mg/kg bw/day in the sub-chronic study.

The BfR also has access to a 2-year study in rats and a 1-year study in dogs, in which finely ground PA 6,6 was administered via the feed (Haskell Laboratory for Toxicology and Industrial Medicine, 1959). The extractable oligomers were determined qualitatively and quantitatively using chemical extraction. The extract contained the cyclic “monomer” and the cyclic dimer. In both studies only one PA 6,6 dose was tested. The actual treatment dose, which is the amount of oligomers released from PA 6,6 in the gastrointestinal tract of the animals, is unknown. Also, the scope of examination parameters does not comply with the current OECD guidelines. Therefore, both studies have only a low validity for risk assessment. Both studies showed no evidence of toxic effects.

3.1.2.3 Gastrointestinal absorption

The results of the above-mentioned sub-acute toxicity study of the cyclic PA 6,6 “monomer” show not only dose-dependent increase in liver weight but also systemic availability of the test substance (BASF SE, 2015a).

In silico predictions using SwissADME software (Daina et al., 2017) postulate a high gastrointestinal absorption of ϵ -caprolactam, the PA 6 oligomers up to the PA 6 tetramer, and the PA 6,6 oligomers up to the PA 6,6 dimer (Table 1). This theoretical assumption is based on the “rule of five”, which takes into account the molecular weight, the octanol-water partition coefficient ($\log K_{OW}$) and the number of hydrogen-bond donors and acceptors (Lipinski et al., 2001). It is assumed that PA oligomers with a molecular weight (MW) < 500 Da are well absorbed and are therefore available systemically. An accumulation of these lower homologues in the human body is, however, very unlikely, since the bioaccumulation potential estimated using the respective $\log K_{OW}$ is very low ($\log K_{OW} < 3$). Higher PA homologues have a decreasing potential for gastrointestinal absorption due to their increasing MW, however, the probability of bioaccumulation increases slightly (Table 1). For substances with MW > 1000 Da, systemic uptake via the digestive system is unlikely (EFSA, 2016). The predictions described have not been fully validated experimentally.

Table 1: *In silico* predictions (not fully experimentally validated) of monomers and PA oligomers for log K_{ow} and gastrointestinal absorption with SwissADME (Daina et al., 2017).

Molecule	Description	CAS	Formula	Molecular mass in Da	log K _{ow}	Absorption ("rule of five")	Substrate for P-glycoprotein
Caprolactam	Caprolactam	105-60-2	C ₆ H ₁₁ NO	113.2	0.74	High	No
PA 6 dimer (1,8-diazacyclotetradecane-2,9-dione)	PA 6 n = 2	56403-09-9	C ₁₂ H ₂₂ N ₂ O ₂	226.3	1.17	High	No
PA 6-trimer	PA 6 n = 3	56403-08-8	C ₁₈ H ₃₃ N ₃ O ₃	339.5	1.59	High	Yes
PA 6-tetramer	PA 6 n = 4	5834-63-9	C ₂₄ H ₄₄ N ₄ O ₄	452.6	1.77	High	Yes
PA 6-pentramer	PA 6 n = 5	---	C ₃₀ H ₅₅ N ₅ O ₅	565.8	2.08	Low [#]	Yes
PA 6-hexamer	PA 6 n = 6	---	C ₃₆ H ₆₆ N ₆ O ₆	679.0	2.32	Low ^{#*}	Yes
PA 6-heptamer	PA 6 n = 7	---	C ₄₂ H ₇₇ N ₇ O ₇	792.1	2.83	Low ^{#*}	Yes
PA 6-octamer	PA 6 n = 8	---	C ₄₈ H ₈₈ N ₈ O ₈	905.3	3.13	Low ^{#*}	Yes
PA 6-nonamer	PA 6 n = 9	---	C ₅₄ H ₉₉ N ₉ O ₉	1018.4	3.39	Low ^{#*}	Yes
PA 6,6- "monomer" (1,8-diazacyclotetradecane-2,7-dione)	PA 6,6 n = 1	4266-66-4	C ₁₂ H ₂₂ N ₂ O ₂	226.3	1.16	High	No
PA 6,6-dimer	PA 6,6 n = 2	4238-35-1	C ₂₄ H ₄₄ N ₄ O ₄	452.6	1.79	High	Yes
PA 6,6-trimer	PA 6,6 n = 3	4174-07-6	C ₃₆ H ₆₆ N ₆ O ₆	679.0	2.33	Low ^{#*}	Yes
PA 6,6-tetramer	PA 6,6 n = 4	---	C ₄₈ H ₈₈ N ₈ O ₈	905.3	3.02	Low ^{#*}	Yes

Exceeding a molecular weight of 500 Da

* Exceeding the number of possible hydrogen-bond donors (> 5) and acceptors (> 10)

3.1.2.4 Metabolism

Whether and how ingested substances are altered metabolically during resorption is of crucial significance for their toxicological assessment. The BfR currently has no data on the (bio-)chemical stability of PA 6 and PA 6,6 oligomers in the human digestive system. By contrast, data from an *in vivo* rat study and a human intoxication case are available for ϵ -caprolactam. In the rat, after a single oral dose of 0.18 mg/kg bw, ϵ -caprolactam and its metabolites were excreted within 24 hours as follows: 77.7% via urine, 3.5% via faeces and 1.5% via breath. The urine contained 79.3% and 17.7% of two unidentified metabolites. Only 2.3% of the administered dose was excreted as unmetabolised ϵ -caprolactam (Unger et al., 1981). After oral administration of a significantly higher dose of ϵ -caprolactam (1500 mg/kg bw), 55% was excreted as unchanged ϵ -caprolactam via the urine after 6 h and 15% after 24 h (Unger et al., 1981). After oral administration of 3500 mg/kg bw/day, 16% of the ϵ -caprolactam was predominantly excreted as 4-hydroxycaprolactam, which is in equilibrium with 6-aminocaprolactone in the acidic, aqueous medium, and to a minor extent as 6-aminohexanoic acid (Kirk et al., 1987). These data demonstrate that, in the rat, ϵ -caprolactam is absorbed after oral administration, metabolised and excreted depending on the dose. At higher doses, ϵ -caprolactam is excreted unchanged via urine. Similarly, in a human poisoning case with an unknown dose, the monomer ϵ -caprolactam and the metabolite 6-aminohexanoic acid were detected in the urine (Wu et al., 2012).

There are no studies on whether the metabolism of ϵ -caprolactam applies also to the PA oligomers. In an *in vitro* simulated gastrointestinal digestion, PA oligomers ($n = 7$ for PA 6 and $n = 3$ for PA 6,6) were neither chemically degraded nor biochemically cleaved by the digestive enzymes pepsin, pancreatin and trypsin (Säger et al., 2015). In another *in vitro* study available to the BfR with PA 6,6-“monomer”, no evidence of degradation by digestive enzymes was found.

An *in silico* prediction of possible metabolites using the OECD Toolbox (version 4.0) revealed that the PA 6,6 “monomer” may be converted into 1,8-diazacyclotetradecane-2,7,9-trione or 1,8-diazacyclotetradecane-2,7,9,14-tetrazone. In the case of the PA oligomers, there is at least no particular chemical structure preventing potential hydroxylation of an alkylic CH_2 group analogously to the ϵ -caprolactam (Kirk et al., 1987).

The molecular structures of the PA 6 dimer and of the PA 6,6 “monomer” in the solid state were determined by X-ray diffraction on single crystals (Northolt und Alexander, 1968; 1971). They demonstrate no particular steric hindrance or distortion that could impair with cytochrome P450-dependent monooxygenase reactions that play an important role in the metabolism of xenobiotics. In the above-mentioned *in vitro* studies, however, no metabolites were found after incubation with an S9 enzyme mix from the rat liver. The studies of monocrystals show analogous to ϵ -caprolactam (Oya und Myasnikova, 1974) a strong tendency to form intermolecular hydrogen bonds and a good hydratability. Therefore, an unchanged excretion, as predicted by the “rule of five”, is plausible.

The *in silico* prediction using “swissADME” shows differences in the pharmacokinetic properties of the individual PA oligomers. With the exception of ϵ -caprolactam, the PA 6 dimer and the PA 6,6 “monomer”, the cyclic PA oligomers are potential substrates for P-glycoprotein. This transport protein is localised in the apical membrane of the enterocytes of the intestine and can transport substances taken up by the enterocytes back into the intestinal lumen. Therefore, the absorption and, as a result, the systemic availability of foreign substances are reduced. In addition, *in silico* prediction suggests that some oligomers are potential inhibitors of the CYP3A4 enzyme system, which is critical for metabolism of xenobiotics.

The theoretical predictions have not been validated experimentally. In addition, it is not certain whether the “chemical space” of the SwissADME software includes the PA oligomers under consideration. These *in silico* predictions are therefore to be considered uncertain.

3.1.2.5 Derivation of an acceptable release amount for PA oligomers (group migration value)

The oligomers of PA 6 and PA 6,6 assessed here are structurally very similar. They are invariably cyclic and have the same functional groups. Cleavage in the gastrointestinal tract is unlikely. Toxicological studies on various oligomers and their mixtures have not revealed any evidence of varying toxicity. The existing similarities are the prerequisite for transferring the results from studies on individual oligomers to the other compounds (“read-across”). In this way, the BfR assesses oligomers using a group approach. This comprises PA 6 oligomers with $n = 2$ to 8 (dimer to octamer) and PA 6,6 oligomers with $n = 1$ to 4 (“monomer” to tetramer).

The above-mentioned oligomers of PA 6 and PA 6,6 have been assessed as non-genotoxic. Liver and thyroid effects are the most sensitive endpoints of toxicity following repeated intake. The NOAEL used to derive a tolerable daily intake (TDI) originates from a sub-chronic study and is 350 mg/kg bw/day (BASF SE, 2015b). With an uncertainty factor of 200 (10 each for intra- and interspecies differences and 2 for extrapolation of a sub-chronic to a chronic study (EFSA, 2012)), the TDI is 1.75 mg/kg bw/day. For a 60 kg person with a daily intake of 1 kg of food in contact with a respective food contact material, a group migration

value of 105 mg/kg of food is calculated. However, the maximum permissible transfer of a substance from a food contact material made of plastic into a food is 60 mg/kg of food in accordance with the Plastics Regulation. In addition, for the risk assessment of transfers higher than 5 mg/kg of food, toxicological studies on chronic toxicity, carcinogenicity and reproductive toxicity are required. As these studies are not available for the PA oligomers, a group migration value of 5 mg/kg of food is considered toxicologically acceptable according to the EFSA “Note for Guidance” (EFSA, 2008). The BfR recommends that the sum of the migration values of the above-mentioned oligomers does not exceed this value.

3.1.3 Exposure assessment

The BfR received migration data from 2016/2017 for PA oligomers from a total of 33 samples. These were kitchen utensils, of which 31 were made of PA 6,6 and two of a PA 6/PA 6,6 mixture. The tests were performed at 100 °C and, depending on the intended use of the item, for either 30 minutes or 2 hours. According to Regulation (EU) No. 10/2011, these test conditions are representative for applications at temperatures between 70 °C and 100 °C. In column (a) of Table 2 the minimum and maximum measured transfer of different PA monomers/ oligomers per item into the third migration solution are shown. These values form the basis of the exposure assessment. It is assumed that the same cooking utensil is always used in the daily preparation of a meal in a one-person household. It is further assumed that the total amount of PA oligomers released per kitchen utensil is transferred into the meal, which is completely ingested by the consumer within one day. According to the Plastics Regulation (EU, 2011), an adult's meal is estimated at 1 kg per day. Hence, the measured values shown in column (a) of Table 2, “transfer measured per kitchen utensil” correspond to the consumer exposure per day, or the PA migration per kilogram of food. The values detected for the individual PA oligomers range between 0.13 and 5.1 mg/person/day and 0.13 and 5.1 mg/kg of food, respectively. Summation of all determinable transfers per examined object results in the group migration value. The median of the group migrations is 2.81 mg/kg of food with a minimum of 0.94 mg/kg of food and a maximum of 10.87 mg/kg of food (Figure 2). In 10 out of 33 items of the kitchen utensils examined the total migration of PA oligomers exceeded the value of 5 mg/kg of food (Figure 2).

According to Article 17 of the European Plastics Regulation, a more conservative version of the exposure assessment assumes that one kilogram of food comes into contact with a surface of 6 dm² of food contact material. This specification applies to all substances listed in the Union List of Plastics Regulation under the conditions defined in Article 17. Again, this approach assumes that an adult human consumes 1 kg of food per day which has been in contact with the food contact material. The minimum and maximum transfers calculated according to these specifications are given in column (b) of table 2 “transfer calculated per kg of food”. The migration of individual PA oligomers, if they were detectable in the migrates, ranges between 0.5 and 17.6 mg/kg of food. The median of the calculated group transfer is 8.92 mg/kg of food with a minimum of 3.66 mg/kg of food and a maximum of 37.44 mg/kg of food. Assuming the conventions described above, the migration values correspond to the exposure values in mg/person/day. Compared to the exposure assessment based on the measured transfer per item, the second approach ($\text{surface area}_{\text{item}} / \text{mass}_{\text{food}} = 6 \text{ dm}^2/\text{kg}$) yields significantly higher values. For 30 of the 33 items examined (91%) the accordingly calculated migration values exceed the toxicologically acceptable value of 5 mg/kg of food. Figure 2 compares the results of both approaches.

For NIAS (e.g. oligomers) not listed in the union list of the Plastics Regulation, a risk assessment “in accordance with internationally accepted scientific principles” shall be carried out in accordance with Article 19 of this Regulation. Due to the relatively small surface area

of kitchen utensils, the ratio mentioned is generally much smaller than 6 dm²/kg. Therefore, the BfR uses the migration values per item to estimate consumer exposure to PA oligomers, as it considers this approach to be more realistic.

Table 2: Minimum and maximum values of the submitted migration data related (a) to the kitchen utensil and (b) to 1 kg of food assuming a contact area of 6 dm² per kg of food (measured surfaces of the individual utensils not indicated)

Molecule	Description	CAS	(a) transfer measured per kitchen utensil		(b) transfer calculated from (a) per kg of food*	
			mg/kitchen utensil		mg/kg of food	
			min	Max	min	max
PA 6 dimer (1,8-diazacyclotetra-decane-2,9-dione)	PA 6 n = 2	56403-09-9	0.23	0.48	0.90	1.03
PA 6-trimer	PA 6 n = 3	56403-08-8	0.17	0.29	0.56	0.75
PA 6-tetramer	PA 6 n = 4	5834-63-9	n.n.	n.n.	n.n.	n.n.
PA 6-pentamer	PA 6 n = 5	---	0.21	0.46	0.87	0.95
PA 6-hexamer	PA 6 n = 6	---	0.21	4.58	0.93	8.64
PA 6-heptamer	PA 6 n = 7	---	n.n.	0.56	n.n.	1.06
PA 6,6 "monomer" (1,8-diazacyclotetra-decane-2,7-dione)	PA 6,6 n = 1+1	4266-66-4	0.26	5.1	0.68	17.6
PA 6,6-dimer	PA 6,6 n = 2+2	4238-35-1	0.38	4.13	1.46	14.2
PA 6,6-trimer	PA 6,6 n = 3+3	4174-07-6	0.13	1.64	0.50	5.64
Sum of all PA 6 and PA 6,6 oligomers per kitchen utensil			0.94	10.87	3.66	37.44

n.n.: not detectable

*according to Regulation (EU) No. 10/2011

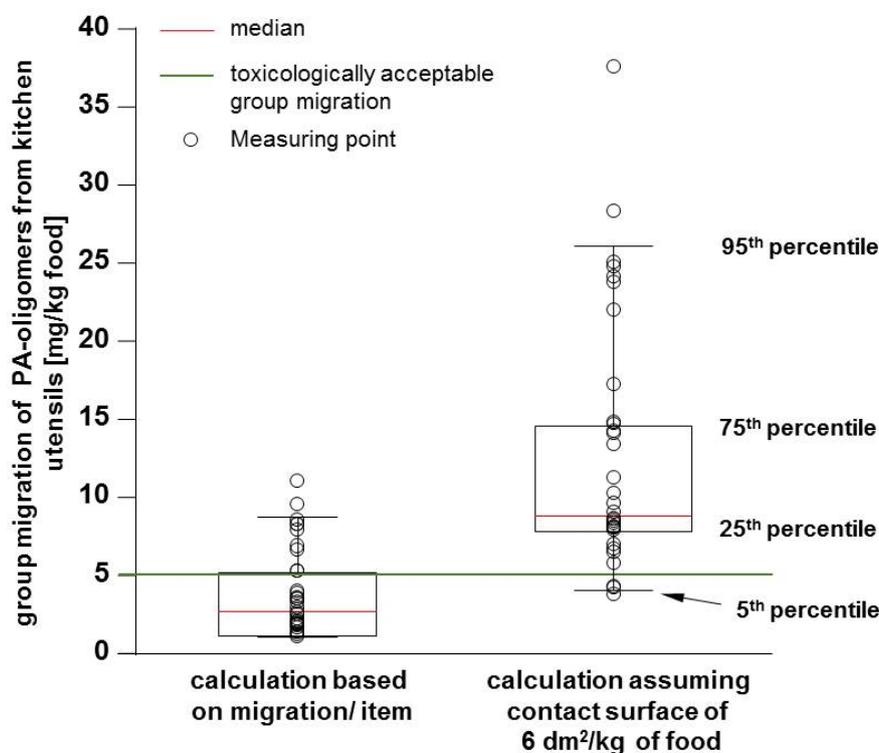


Figure 2: Migration of polyamide (PA) oligomers from 33 kitchen utensils into food simulant (contact time: 30 –120 minutes; Temperature: 100 °C). The results for total transfer with respect to 1 kg of food calculated by means of two versions of the exposure assessment are shown. The calculation based on the measured transfer per item reveals for 30% of the items a PA group transfer above the toxicologically acceptable group migration value of 5 mg/kg of food. In contrast, assuming a constant ratio of the item's contact surface to the mass of the food of 6 dm²/kg the calculation reveals for 91% of the items examined a group migration value higher than 5 mg/kg of food.

3.1.4 Risk Characterisation

Consistent with the requirements of the European Food Safety Authority (EFSA), and taking into account *in silico* predictions, the data currently available allow the assessment of a group of PA oligomers comprising the oligomers of PA 6 (n = 2 to 8) and PA 6,6 (n = 1 to 4). Based on the available data, the BfR considers a group migration value of 5 mg/kg of food as toxicologically acceptable for the above-mentioned PA oligomers. Health impairments are unlikely for migration values up to 5 mg/kg of food. The available data for 33 kitchen utensils show that this group migration value for PA oligomers can be met even at temperatures above 70 °C, but is exceeded by 30% of the items. For the toxicological assessment of transfers above 5 mg/kg of food, further data are required according to the EFSA Note for Guidance (EFSA, 2008), in particular on chronic toxicity, carcinogenicity, reproductive toxicity and intake, distribution, metabolism and excretion (ADME).

3.2 Other aspects

There are several microbial enzymes that can cleave PA oligomers (Braunschweig Enzyme Database, 2017). The enzyme 6-aminohexanoate oligomer endohydrolase (EC 3.5.1.117) cleaves linear and cyclic oligomers consisting of more than three 6-aminohexanoic acid

subunits into dimers or larger oligomers. The 1,8-diazacyclotetradecane-2,9-dione lactam hydrolase (EC 3.5.2.12) hydrolyses the cyclic PA 6 dimer to the linear *N*-(6-aminohexanoyl)-6-aminohexanoate. These enzymes have been detected in various micro-organisms, but not in humans (Braunschweig Enzyme Database, 2017). Whether micro-organisms associated with humans (e.g. in the digestive tract) possess these enzymes is unknown to the BfR. If this enzyme activity can be detected in the microbiome, cleavage of the PA oligomers by the microbiome in the intestine and therefore a further degradation of the cleavage products would be possible. However, whether this can lead to a complete degradation of the monomers or their metabolites is unclear.

The migration of PA 6 and PA 6,6 oligomers from 23 different kitchen gadgets has also been demonstrated by Abe and colleagues (Abe et al., 2016). Other sources of PA oligomers in foods may be artificial casings (BfR, 2012), as well as food packaging (Soto-Valdez et al., 1997). The BfR validated an analytical method for the determination of eight PA 6 and four PA 6,6 oligomers and was able to demonstrate migration of PA oligomers from teabags and kitchen utensils to food simulants (Kappenstein et al., 2018). The values determined confirm the results of the food monitoring authorities discussed in this opinion.

3.3 Recommendations and measures

When using polyamide materials (e.g. kitchen gadgets, teabags, artificial sausage casings), it is probable that PA oligomers will migrate into the food. The migration value derived by the BfR on the basis of the available toxicological data for the group of PA 6 oligomers with $n = 2$ to 8 (dimer to octamer) and PA 6,6 oligomers with $n = 1$ to 4 ("monomer" to tetramer) is 5 mg/kg of food/day (group migration value). The reported results of the food monitoring authorities show that transfer from some PA objects is above this cumulative migration value (test conditions: 30 min or 2 h at 100 °C). For the risk assessment of migrations above 5 mg/kg of food/day, there is a lack of studies on chronic toxicity, reproductive and developmental toxicity, carcinogenicity and ADME according to the EFSA Note for Guidance (EFSA, 2008).

The available data demonstrate that compliance with the group migration value of 5 mg/kg of food is feasible. Manufacturing processes should be optimised with regard to the minimisation of the migration of PA oligomers. In addition, when using PA kitchen utensils, the BfR recommends keeping the contact time with hot foods (above 70 °C) short.

Further information on oligomers is available from the BfR website

https://www.bfr.bund.de/de/a-z_index/oligomers-205184.html#fragment-2

BfR "Opinions app"



4 References

In 2019, a literature search was performed on the PA oligomers with the keywords "genotox*", "mutation*", "mutagen*", "subchron*", "liver*", "intestine*", "oral", "food", "*sorption*" in three databases.

There were 5 citations in "Pubmed", 72 citations in "Web of Science" and 97 citations in "Scopus". No genotoxicity or subchronic toxicity data for the PA oligomers were found in this search. Other studies were available internally to the BfR for further assessment (BfR, 2019).

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The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the Federal Government and Federal Laender on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

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