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Fillable articles made from melamine formaldehyde resin, such as *coffee-to-go* cups sold as 'bambooware', may leak harmful substances into hot foods

BfR opinion No 046/2019 issued 25 November 2020

The plastic known as melamine formaldehyde resin (MFR) is especially resistant to breakage and is therefore often used to manufacture tableware products. In recent years, alternative materials such as bamboo fibre have been increasingly used as fillers for this plastic. Articles manufactured in this way are frequently described and marketed as 'bambooware'.

The German Federal Institute for Risk Assessment (BfR) has assessed whether the routine use of refillable MFR tableware—such as reusable *coffee-to-go* cups, children's cups or trays—with hot liquid foods such as coffee, tea or baby food involves any risks to health. The regular consumption of high quantities of melamine over a prolonged period of time can result in the formation of urinary tract stones and damage to the kidneys. In animal experiments, inflammation in the area of the stomach has been observed following the prolonged intake of high formaldehyde doses.

The BfR has based its health risk assessment on data provided by the German food monitoring authorities as well as on its own research data. Overall, data were available on formaldehyde release from 366 mugs, cups and bowls (138 made from 'conventional' MFR and 228 made from 'bambooware'), and melamine release from 291 objects (111 from 'conventional' MFR and 180 from 'bambooware'). The assessment distinguishes between 'conventional' MFR tableware and 'bambooware'. BfR has no information as to whether the samples considered here accurately reflect MFR tableware that is typically available on the German market.

The BfR risk assessment was based on the assumption that adults consume coffee beverages from a reusable *coffee-to-go* cup on five days a week. Infants were assumed to daily consume tea, milk-based drinks or baby food from cups, mugs or bowls made from MFR. These assumptions are based on the results of consumption studies.

In order to assess potential risks to health, the BfR compared the estimated daily exposure to melamine and formaldehyde, respectively, with health-based guidance values, the so called tolerable daily intake values (TDI). A TDI defines the amount of a substance that consumers could take up on a daily basis over their whole lifetime without any risk to their health.

For melamine, the BfR used the TDI of 0.2 milligrams per kilogram of body weight per day, derived by the European Food Safety Authority (EFSA) in 2010. For formaldehyde, the BfR derived a TDI of 0.6 mg per kg of body weight per day. However, it is important to note that the proportion of formaldehyde taken up from food contact materials should in adults not exceed 20% of this TDI value. This is because formaldehyde also occurs naturally in several types of food. In addition, the BfR considers the potential health risk posed by the uptake of formaldehyde to depend not merely on the total daily intake but also on the concentration of formaldehyde in food. Accordingly, the BfR has, in addition to the TDI, also derived a maximum tolerable formaldehyde concentration in a foodstuff resulting from the release of formaldehyde from a food contact material.

The result: For roughly one in four 'bambooware' articles, the amount of formaldehyde released led to an exposure that was up to 30 times higher than the TDI for adults and up to

120 times higher for children. Also the maximum tolerable concentration in food(simulant) was significantly exceeded by the release of formaldehyde from tableware samples in this group (up to roughly 90 times higher). Formaldehyde release was substantially lower for the rest of the ‘bambooware’ investigated. Nevertheless, it was still around 30% higher on average compared to release from ‘conventional’ MFR tableware. If consumers use fillable tableware made from either of these materials very frequently, daily formaldehyde exposure can be almost three times higher than the TDI. The maximum tolerable formaldehyde concentration in food(simulant) is exceeded by the formaldehyde release from 12% of ‘conventional’ MFR tableware and 27% of ‘bambooware’ articles.

With regard to melamine, average release from ‘bambooware’ is more than twice as high as average release from ‘conventional’ MFR tableware. For adults, the measured melamine release does not represent a health risk. However, if infants consume hot food products from MFR tableware very often—and from ‘bambooware’ in particular—their daily exposure can be up to three times the TDI.

The BfR therefore considers an increased risk to health to be possible, if consumers fill hot liquid foodstuffs into MFR tableware and consume these foods on a daily basis. In the case of a long-term daily use of ‘bambooware’ tableware with exceptionally high formaldehyde release, the BfR considers an increased risk to health to be likely.

Repeated tests on the very same piece of tableware have also shown an increase of melamine release from test to test. These results suggest that the material is degraded and damaged by contact with hot liquids. In the opinion of the BfR, MFR is therefore generally not suited for repeated usage in contact with hot liquid foodstuffs, as is the case with reusable *coffee-to-go* mugs or cups, for example. Accordingly, the BfR recommends (as previously, in opinion no. 012/2011) not to consume hot meals or beverages from MFR tableware. This recommendation applies both to tableware made from ‘conventional’ MFR and especially to ‘bambooware’.

Once again, the BfR points out that all articles made from MFR are unsuitable for use in microwave ovens. MFR tableware can be used to consume foodstuffs at room temperature safely, however, since the release of melamine and formaldehyde at levels relevant for health occurs at high temperatures only.

To ensure that consumer health is adequately protected, the BfR also recommends lowering the specific migration limit (SML) set out in the EU Plastics Regulation (Regulation (EU) No 10/2011) for formaldehyde from 15 to 6.0 mg per kg food.

	BfR risk profile: Fillable articles made from melamine formaldehyde resin, such as *coffee-to-go* cups sold as 'bambooware', may leak harmful substances into hot foods (opinion no. 046/2019)					
A	Affected persons	General population Children				
B	Probability of an impairment to health from the daily consumption of hot liquid food products from MFR tableware	Practically impossible	Unlikely	**Possible**	**Likely**	Certain
C	Severity of an impairment to health from the daily consumption of hot liquid food products from MFR tableware	No impairment	Mild impairment [reversible/irreversible]	**Moderate impairment [irreversible]**	Severe impairment [irreversible]	
D	Validity of available data	High: The most important data are available and there are no contradictions	**Medium: Some important data are missing or contradictory**	Low: Much important data are missing or contradictory		
E	Controllability by the consumer	Control not necessary	**Controllable through precautionary measures**	**Controllable through avoidance**	Not controllable	

Explanations

The risk profile is intended to visualise the risk outlined in the BfR opinion. The profile is not intended to be used to compare risks. The risk profile should only be read in conjunction with the corresponding opinion.

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT (BfR)

1. Subject of the assessment

In this assessment, the German Federal Institute for Risk Assessment (BfR) evaluates the risks to health resulting from the migration of melamine and formaldehyde from fillable articles made from 'conventional' melamine formaldehyde resin (MFR) and 'bambooware' into food(simulant). The assessment is based on data from the German food monitoring authorities from 2014 to 2019 and from the National Reference Laboratory for substances intended to come into contact with food. Migration behaviour was measured under hot filling conditions. In this context, 'hot filling' means that the article is filled with heated food. The assessment focuses in particular on reusable *coffee-to-go* cups made from 'bambooware', which have recently been increasingly offered on the market.

2. Results

Formaldehyde

To assess the available migration data in terms of human health for this opinion, the BfR derived a tolerable daily intake (TDI) of 0.6 mg/kg body weight/day from a chronic toxicity study in rats administering formaldehyde orally. In addition, a maximum tolerable concentration of 10.4 mg/l for formaldehyde in foodstuffs, resulting from formaldehyde release from a food contact material, was derived for daily exposure. As critical toxicological effects, hyperplasia and ulceration affecting the forestomach as well as proliferative changes to the forestomach and stomach were identified.

Migration experiments were conducted in accordance with the provisions of Regulation (EU) No 10/2011 (on plastic materials and articles intended to come into contact with food) for hot-fill conditions of 2 h at 70 °C with the food simulant 3% acetic acid. Data were available for 138 articles made from 'conventional' MFR and 228 'bambooware' articles. The term 'bambooware' is used to describe articles made from MFR that entail alternative materials such as bamboo fibres as fillers in the manufacturing process. The formaldehyde release from one group of 'bambooware' articles was considerably higher compared to other 'bambooware' articles and all other articles investigated made from 'conventional' MFR. The articles with these very high levels of formaldehyde release have been addressed separately in this risk assessment.

In order to assess exposure, it was assumed that an adult daily drinks coffee beverages from a reusable cup made from 'conventional' MFR or 'bambooware'. For infants, it was assumed that children daily consume milk-based drinks, dairy products or tea from fillable articles (cups, mugs, bowls) made from the abovementioned materials.

Based on these exposure scenarios and migration data for the articles with release of up to 50 mg formaldehyde/l food simulant, daily intakes were calculated. For highly exposed infants (95th percentile), these intakes significantly exceed the TDI of 0.6 mg/kg body weight/day (by up to 170%). For highly exposed adults, these intakes were as much as 37% of the TDI. However, for adults formaldehyde exposure through food can already exhaust or even exceed the TDI. Accordingly, the BfR considers the maximum formaldehyde intake resulting from the release from food contact materials of 20% of the TDI to be acceptable.

With regard to possible concentration-dependent local formaldehyde effects, the BfR utilised toxicological studies to derive a maximum tolerable formaldehyde concentration for chronic exposure through food. This maximum tolerable formaldehyde concentration of 10.4 mg/l was exceeded as a result of the formaldehyde release from 12% of the articles made from 'conventional' MFR and from 44% made from 'bambooware', respectively. As a result, the BfR concludes that an increased health risk is possible for both adults and infants as a result of the usage of particularly 'bambooware' articles in contact with hot liquid food products—especially if these articles are used exclusively and on a daily basis.

The formaldehyde release from about 24% of the 'bambooware' articles was exceptionally high. Their usage according to the above described exposure scenarios would result in exceedance of the TDI by a factor 30 (for adults) or 120 (for infants). The maximum tolerable formaldehyde concentration was exceeded up to 86 times. If these articles are used in contact with hot liquid foods—such as hot beverages or hot dairy products—over a prolonged period of time, the BfR considers a health risk for consumers to be likely. In the BfR's opinion, these articles should not be used when in contact with these kinds of food.

Moreover, the TDI of 0.6 mg/kg body weight/day could even be significantly exceeded, if articles released formaldehyde into food at the level set out in Regulation (EU) No 10/2011 as the total specific migration limit (SMLT) of 15 mg/kg. A migration of 15 mg/kg would result in an exposure of 50% of the TDI for adult high consumers and 200% of the TDI for infants, according to the above described exposure scenarios. The maximum tolerable formaldehyde concentration of 10.4 mg/l would also be exceeded. Accordingly, the BfR considers the current SMLT in Regulation (EU) No 10/2011 to be too high. Based on a TDI of 0.6 mg/kg body weight/day, the BfR considers an SMLT of 6.0 mg formaldehyde/kg food to be an appropriate value to protect the health of consumers in all age groups.

Melamine

To assess the available migration data in terms of human health, the BfR used a TDI of 0.2 mg/kg body weight/day, which was derived from a chronic toxicity study in rats using an oral exposure route. The formation of stones in the efferent urinary system was identified as the critical toxicological effect, as was an associated increased incidence of bladder cancer. Damage to the kidneys was also observed.

The migration experiments were conducted as described above in accordance with the provisions of Regulation (EU) No 10/2011. Data were available for 111 articles made from 'conventional' MFR and 180 'bambooware' articles. Both the median and the 95th percentile of migration from 'bambooware' were approximately twice as high as the respective values for articles made from 'conventional' MFR. The specific migration limit (SML) of 2.5 mg melamine/kg food set out in Regulation (EU) No 10/2011 was exceeded by 15% of the articles made from 'conventional' MFR and by 35% of 'bambooware' articles.

Based on the exposure scenarios for adults and infants described above and the available migration data, daily intakes were calculated. For highly exposed infants (95th percentile), daily intake significantly exceeds the TDI of 0.2 mg/kg body weight/day (by up to 180% for 'bambooware' and up to 40% for 'conventional' MFR). For highly exposed adults, these intakes were as much as 35% of the TDI. As a result, the BfR concludes that an increased health risk is possible for infants as a result of the usage of particularly 'bambooware' articles in contact with hot liquid food products—especially if these articles are used exclusively and on a daily basis.

A release of melamine from fillable articles into food at the level of 2.5 mg/kg, the SML as set by Regulation (EU) No 10/2011, would result in a 100% exhaustion of the TDI for infants (high consumers). In consideration of the conservative assumptions used for this exposure estimation as well as the negligible melamine exposure from other sources (e.g. from food), the BfR considers the SML to be appropriate to protect the health of consumers in all age groups. Nevertheless, according to the exposure scenario used here, the release of melamine from fillable articles intended for use by children should not exceed the SML of 2.5 mg/kg food. For adults (body weight = 60 kg), according to the exposure scenario used here, the BfR considers a release of melamine of up to 10 mg/kg food as acceptable from a health point of view.

In 2011, the BfR has already advised consumers that all articles made from MFR are unsuitable for use in microwave ovens (BfR, 2011).

3. Rationale

3.1 Risk assessment

3.1.1 Hazard identification

Melamine and formaldehyde are used to create polymers (melamine formaldehyde resin, MFR) that are then used in the manufacture of everyday tableware such as plates, mugs or bowls, as well as kitchen utensils like cooking spoons and spatulas. A filler is always added to the MFR to achieve the desired properties for the final material. If the filler additive is listed in the table included in annex I of Regulation (EU) No 10/2011, then the BfR refers to the

MFR in this opinion as a 'conventional' MFR. For some time now, objects made from MFR have also been marketed that use alternative filling materials such as wood shavings or waste residues sourced from rice, coffee or bamboo production processes. The last in this list is often referred to as 'bambooware'. Reusable *coffee-to-go* cups are a typical 'bambooware' product. At high temperatures in particular, the two monomer starting materials melamine and formaldehyde are released on contact with food products, and migrate into these products. Back in 2011, the BfR published an opinion on the release of melamine and formaldehyde from tableware and kitchen utensils (BfR, 2011).

Regulation (EU) No 10/2011 defines a total specific migration limit (SMLT) of 15 mg/kg of the food (simulant) for the total calculated from formaldehyde, 1,4-butanediol formal and urotropin (each calculated separately as formaldehyde). For melamine, a specific migration limit (SML) is defined of 2.5 mg/kg food (simulant). The BfR considers the current SMLT for formaldehyde to be set too high. A health risk may be present even if this value is not exceeded. (See section 3.2.1.)

3.1.2 Risk potential

3.1.2.1 Toxicological characterisation of formaldehyde

Formaldehyde is reabsorbed readily via the lungs and gastrointestinal tract, although absorbed only minimally via the skin (NTP, 2010). The chemical is metabolised rapidly into formic acid; its biological half-life is around 1 to 2 minutes in vertebrates (BfR, 2006; EFSA, 2007; JECFA, 1974). A key enzyme in this process is alcohol dehydrogenase 5 (ADH5) (Gutheil et al., 1992; Reingruber et al., 2018). ADH5 is present in many organs and types of tissue, including the oral mucosa, and the epithelial cells lining the oesophagus and the stomach (THPA, 2019). Other enzymes such as aldehyde dehydrogenases are also involved in the metabolisation of formaldehyde (Schulte et al., 2006). The formic acid thereby formed is further metabolised in the body or excreted via the kidneys or the lungs (as CO_2); its persistence in the body depends on the presence of folic acid and is very short, with a half-life of 10 to 100 minutes (JECFA, 1974).

Genotoxicity
Formaldehyde is genotoxic *in vitro* in bacterial strains and eukaryotic cells. Chromosomal aberrations, chromatid exchanges and mutations have all been detected (Merk et al., 1998; Speit et al., 2002). DNA strand breaks occurred in human fibroblasts and rat tracheal epithelial cells. Formaldehyde induces DNA-protein cross-links, leads to increased cell proliferation and inhibits DNA repair mechanisms (ECHA, 2012b; NTP, 2010). In an *in vivo* study (Migliore et al., 1989) on the genotoxicity of formaldehyde following oral ingestion, the induction of the formation of micronuclei in the epithelial cells of the rat gastrointestinal tract was observed. These effects occurred only in conjunction with damage to the tissue investigated, however, and only locally at the first site of contact. Systemic genotoxicity was not observed. Other *in vivo* results relate to the inhalation route of exposure and are inconsistent. While the induction of micronuclei in human cheek cells (Suruda et al., 1993) and human cells from the respiratory tract (Costa et al., 2008) has been observed, other studies report no observation of local genotoxic effects (such as micronuclei) following the inhalation of formaldehyde (Speit et al., 2007; Zeller et al., 2011). Nor has systemic genotoxicity been observed following inhalation exposure (ECHA, 2012b; Speit et al., 2009).

Based on its mutagenic and genotoxic effects at the tissue site of contact, formaldehyde has been classified as a Category 2 mutagen ("suspected of causing genetic defects") in accordance with Regulation (EC) No 1272/2008 (CLP Regulation).

Carcinogenicity
Furthermore, formaldehyde is also classified as a Class 1B carcinogen ("may cause cancer") according to this regulation (for a toxicological evaluation, see ECHA (2012b)). This classification is primarily justified by experiments showing the formation of tumours in rat nasopharyngeal tissue following inhalation of formaldehyde. Human data have also been consulted, although these are inconsistent (ECHA, 2012b). The carcinogenicity of formaldehyde is based on multiple properties. Due to its high cytotoxicity, it causes irritation and ulceration to exposed tissues and mucous membranes. Formaldehyde also forms protein adducts and cross-links, and increases cell proliferation while simultaneously inhibiting DNA repair mechanisms (see above).

Opinions differ as to whether formaldehyde can also cause cancer following oral exposure. Corresponding human studies are not available. In a 30-week study in Wistar rats (Takahashi et al., 1986), papillomata in forestomach epithelial cells were observed at a dose of 5,000 mg/l of drinking water. Since the animals' body weight was not specified, a calculation using the standard factors from EFSA (2012) produces an exposure level of 260–285 mg/kg body weight/day. Since only 10 male animals were used for each dose, the findings are not especially reliable. A test conducted in parallel on tumour-promoting properties of formaldehyde following exposure with methylnitronitrosoguanidine (MNNG) also produced positive results (Takahashi et al., 1986). In a lifetime study in rats (Soffritti et al., 1989), a statistically higher incidence of adenocarcinomas and leukaemia was observed in concentrations above 1,000 mg/l of drinking water. Since the formaldehyde administered contained 0.3% methanol by weight, a methanol control group (15 mg methanol/l of drinking water) was also monitored. It should be noted that the incidence of tumours in the methanol control group was also higher. In addition, for rats who had been administered formaldehyde since birth, even 2,500 mg/l of drinking water increased tumour rates only in female animals, while not a single incidence of neoplasms was recorded in male animals. During a re-evaluation (Soffritti et al., 2002) by the same team (described in ECHA (2012b)), a significantly higher rate of tumour incidence was established. Even at a dose of 100 mg/l of drinking water, the researchers reported a wide range of diverse tumour types, with cases of adenocarcinoma, leiomyosarcoma and leukaemia occurring most often. The study authors did not provide an explanation of the major discrepancies between tumour incidence in the two evaluations of the same study (Soffritti et al., 2002; 1989). Furthermore, the 'pooling' of lymphomas and leukaemias (designated as haemo-lymphoreticular neoplasias) and the lack of reporting of non-neoplastic lesions was also criticised by the IARC (IARC, 2006). A statistical significance for the tumours observed compared with the methanol control group was observable only for the increased incidence of the haemo-lymphoreticular neoplasias (lymphomas and leukaemias) at the highest dose and also for male animals only (IARC, 2006). As a result of the widespread incidence of tumours in the low-dose groups and the control group, as well as the abovementioned deficiencies in terms of evaluation, the study is not considered reliable (ECHA, 2012b; EFSA, 2007; Gelbke et al., 2019; Schulte et al., 2006).

In addition, the tumour incidences reported in the two abovementioned studies could not be confirmed by two other chronic toxicology studies (Til et al., 1989; Tobe et al., 1989). Following the chronic oral exposure of 70 Wistar rats per dose per sex via drinking water with up to 82 mg/kg body weight/day for males and 109 mg/kg body weight/day for females, significant reductions to gains in body weight were observed, alongside an increased intake of feed and water (up to 40%) in the high-dose groups (Til et al., 1989). Cases of papillary kidney necrosis as well as thickening, hyperplasias and ulceration of the forestomach were also observed, alongside proliferative changes in the forestomach and stomach. No dose-responsive induction of tumours occurred. The highest dose at which no adverse effects were observed (NOAEL) was 15 mg/kg body weight/day for males and 21 mg/kg body weight/day for females.

The concentration of formaldehyde in drinking water was adjusted every 4 weeks to drinking water consumption and was 0.026% on average for the NOAEL group. The concentration was 0.19% in the group with the lowest dose at which adverse effects were observed (LOAEL).

Similar results were reported by another chronic toxicology oral drinking water study in 20 Wistar rats per dose per sex (Tobe et al., 1989). In the high-dose group (0.5% formaldehyde, equivalent to 300 mg/kg body weight/day), proliferative lesions and ulcerations occurred in the forestomach and stomach. Hyperkeratosis of the forestomach was also observed in the median dose group (0.1%, equivalent to 50 mg/kg body weight/day) after 18 months (1 of 6 males) and 24 months (1 of 8 females). No increase in the incidence of tumours versus the control group was observed. The authors identified an NOEC/NOAEL of 0.02% and 10 mg/kg body weight/day.

In a further subchronic toxicology study (Johannsen et al., 1986) in rats and dogs, no further effects other than a reduction in feed and water intake (reduction only in water intake in rats) was observed, alongside a reduction in body weight. The rats were administered formaldehyde via drinking water due to the greater tolerability of this route. The dogs were given formaldehyde via their feed. Since the study exhibits significant deficiencies in terms of reporting and dose identification, there is some uncertainty as to whether the specified dose values of a maximum of 150 mg/kg body weight/day in rats and 100 mg/kg body weight/day in dogs were actually reached.

In contrast to these results, hyperkeratosis of the forestomach and focal gastritis occurred after 28 days in a subacute study in rats following the oral ingestion of 125 mg/kg body weight/day via drinking water (Til et al., 1989). The NOAEL was identified at the median dose of 25 mg/kg body weight/day. Details of the concentration in drinking water are not specified here and cannot be calculated from the limited data available.

3.1.2.2 Derivation of health-based guidance values for formaldehyde

The available studies on repeated oral exposure were largely conducted in the 1980s. Neither the execution of these studies nor their reporting meets the internationally recognised guidelines now in place (e.g. OECD guidelines). This makes it harder to firmly establish the parameters responsible for triggering the local adverse effect (concentration or overall intake) or to assess potential systemic effects.

On exposure to formaldehyde, adverse effects occur primarily in the tissue or organs of first contact. This results primarily from the strong reactivity of formaldehyde with biological macromolecules and its rapid metabolism. The main effect observed in the oral studies is local lesions in the forestomach and (glandular) stomach at concentrations in drinking water of 0.10%, equivalent to 50 mg/kg body weight/day (Tobe et al., 1989) or 0.19%, equivalent to 82 mg/kg body weight/day (Til et al., 1989). In both studies, the NOAEC or NOAEL is very similar, namely 0.02%, equivalent to 10 mg/kg body weight/day, (Tobe et al., 1989) and 0.026%, equivalent to 15 mg/kg body weight/day (Til et al., 1989). In its assessment of formaldehyde for the oral exposure route, the International Programme on Chemical Safety (IPCS) at the WHO takes the view that the effects on the tissue of first contact following ingestion are more dependent on the concentration of the formaldehyde ingested than the cumulative (overall) formaldehyde intake itself (IPCS, 2002). As a result of formaldehyde's strongly reactive nature, the BfR considers this to be plausible, although the frequency of intake distributed over the day and its respective quantity (exposure via drinking water *ad libi-*

tum) is likely to influence the local effect, since the effective concentration at the place of effect (stomach) and the duration of this interaction depends on these factors. In addition, the local effects observed could also have been triggered independently of concentration by the daily overall intake of formaldehyde.

Accordingly, the BfR has carried out a separate risk assessment and derivation of a health-based guidance value for local effects for both parameters, namely maximum concentration and total intake.

Since both national and international institutions (ECHA, 2017a; WHO, 1996) have also discussed potential systemic effects in relation to the oral studies listed, the BfR has also completed a risk assessment for potential systemic effects.

Tolerable daily formaldehyde intake for potential systemic effects

In the assessment of formaldehyde for use as a biocide (ECHA, 2017a), the potential systemic effects stated include the increased incidence of papillary kidney necrosis (Til et al., 1989), as well as the reduced rate of increase in body weight observed in rats and dogs (Johannsen et al., 1986; Til et al., 1989). Based on the lowest NOAEL of 15 mg/kg body weight/day (Til et al., 1989), an uncertainty factor of 100 (10-fold for intra-species differences, 10-fold for inter-species differences) was applied to derive an identical acute, medium- and long-term acceptable exposure level (AEL) of 0.15 mg/kg body weight/day.

Prior to 2005, the WHO applied this same study to derive a tolerable daily intake (TDI) from this NOAEL of 0.15 mg/kg body weight/day (WHO, 1996). The EFSA also applies this value to estimate the risk to human health from formaldehyde when used as a preservative (EFSA, 2007) or as an additive in animal feed (EFSA, 2014a).

The WHO has not used this TDI value in its Guidelines for Drinking-Water Quality since 2006, however (WHO, 2005; 2006; 2017). The cases of papillary kidney necrosis and reduced increase in body weight are not further listed in the dose-response analysis or in the derivation of a health-based guidance value in relation to oral exposure in the underlying document utilised for the WHO assessment IPCS (2002). Only the histological changes in tissue on first contact (local effects) are stated as being relevant.

As a result of the metabolism of formaldehyde that already occurs in the gastrointestinal tract as well as the high *first-pass effect* due to the liver, the effects on the kidneys and body weight increase in the high-dose group appear to be secondary effects of local damage, and therefore do not represent direct systemic effects. To determine a health-based guidance value in relation to systemic effects potentially occurring at higher concentrations, the BfR therefore applies the highest tested dose of 82 mg/kg body weight/day (for male animals) (Til et al., 1989). Starting from this systemic NOAEL of 82 mg/kg body weight/day and applying the uncertainty factor of 100 (10-fold each for intra- and inter-species effects) results in a TDI of 0.82 mg/kg body weight/day for potential systemic effects. For an adult human (body weight = 60 kg), this is equivalent to a tolerable daily intake of 49 mg of formaldehyde. For an infant aged between 12 and 36 months with a body weight of 12 kg (EFSA, 2012), this results in a tolerable daily intake of 9.8 mg.

Tolerable maximum formaldehyde concentration for local effects

To derive a tolerable safe maximum concentration for formaldehyde (C_{max}) in food or drinking water, the study from Til et al. (1989) is viewed as a key study due to the higher number of animals, the superior selection of experimental conditions (dose range without increased mortality) and experiment execution (interim groups for determining the effect history), as well as its more comprehensive evaluation of adverse effects. The median formaldehyde concentration in drinking water for the highest dose group without damaging effects was 0.026% or 260 mg/l. In accordance with ECHA Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2012a), a total uncertainty factor of 25 is considered to be adequate for local effects. This results from a 10-fold factor for intra-species differences and a 2.5-fold factor for inter-species differences. Here, the BfR accounts for the fact that formaldehyde metabolism occurs at the site of first contact (mouth, throat, oesophagus, stomach) at differing speeds and degrees of efficiency with the corresponding enzyme (cf. ADH5, above) plus potential species effects. Assuming a formaldehyde concentration of 260 mg/l in drinking water and applying the uncertainty factor of 25, the resulting C_{max} is 10.4 mg/l.

The derivation of a tolerable maximum concentration for health is an approach that is usually adopted for local damage following inhalation or dermal exposure. In these cases, the direct local substance concentration applied and the frequency of application of a substance to a human or animal subject are known (e.g. concentration in air and respiratory rate). Based on the details of feed and water intake, no conclusions can be drawn about the actual formaldehyde concentration directly at the place of effect (stomach), nor about the duration or frequency of this effect. Feed/food and water intake can vary greatly in both humans and animals in terms of quantity and frequency. Food consumed by humans may also already contain formaldehyde. Selecting the factor 2.5 for toxicodynamic differences in rats and humans, and the factor 10 for intra-species variations for local effects (e.g. differences in sensitivity and toxicodynamics) nonetheless constitutes a conservative approach, since a direct local effect from formaldehyde is assumed while also remembering that ADH5 has a central role to play in providing protection from the toxic effects of endogenous formaldehyde and is therefore highly conserved in many species. The actual differences at the place of effect are presumably more minor (Schulte et al., 2006). Accordingly, the BfR considers an increased risk to health to be unlikely if the concentration of formaldehyde in food that results from the release of formaldehyde from a food contact material does not exceed the C_{max} value of 10.4 mg/l.

Tolerable daily formaldehyde intake for local effects

To derive a TDI while accounting for local effects, the BfR utilises the NOAEL of 15 mg/kg body weight/day as given in the study from Til et al. (1989). By applying a total uncertainty factor of 25 for local effects (see derivation of a tolerable maximum formaldehyde concentration), this results in a TDI of 0.6 mg/kg body weight/day. For an adult human (body weight = 60 kg), this is equivalent to a tolerable daily intake of 36 mg of formaldehyde. For an infant aged between 12 and 36 months with a body weight of 12 kg (EFSA, 2012), this produces a tolerable daily intake of 7.2 mg. Since the TDI (0.6 mg/kg body weight/day) is lower than the TDI for potential systemic effects (0.82 mg/kg body weight/day, see above), the BfR considers this value to be sufficiently protective for both local and potentially systemic effects.

The derivation of a tolerable intake value for human health based on body weight is an approach that is usually adopted for systemic effects only. Alongside body weight, the only other parameter considered in this approach is the quantity of a substance ingested over a certain period of time (such as one day). The concentration at the place of effect is not accounted for by this approach. However, since this is very important for local effects, the application of the TDI model to the present case involves a degree of uncertainty. An assessment of the health risks in relation to the formaldehyde concentration has been completed in the above section.

Working from the assumption that the effect is dependent on total intake, the BfR believes that an increased risk to health is unlikely if daily formaldehyde intake does not exceed the

TDI value of 0.6 mg/kg body weight/day. This applies both to local effects and to potential systemic effects.

3.1.2.3 Toxicological characterisation of melamine

As a result of its use in kitchen utensils, and its occurrence in foodstuffs such as meat and cereals, melamine is orally ingested (Zhu et al., 2019). Melamine is re-absorbed rapidly in the gastrointestinal tract and, with a half-life in plasma of 3 to 5 hours in vertebrates (Li et al., 2019; Liu et al., 2010), is predominantly excreted unchanged in urine (WHO, 2009). Research has shown that systemically available melamine can pass the blood-brain, blood-testis and placental barriers (Chan et al., 2011; Mannoni et al., 2017; Zheng et al., 2013). In rats, the dispersal of melamine administered intravenously into various organs, including the brain, kidneys and bladder, has been shown (Wu et al., 2009). With an LD_{50} value ranging from 3.1 g/kg to over 6.4 g/kg in rats and from 3.2 g/kg to 7.0 g/kg in mice, melamine has low acute toxicity (Melnick et al., 1984). Following subchronic and chronic exposure, melamine can cause dose-dependently the formation of urinary stones (NTP, 1983).

Following the melamine scandal in China in 2008, during which thousands of children fell ill with kidney stones as a result of consuming follow-on formula contaminated with melamine, a number of new studies were performed on melamine toxicity. Besides melamine's nephrotoxic effects, as research has repeatedly confirmed, a growing number of studies now also report other adverse effects. The following section summarises the state of knowledge here.

Renal toxicity
Epidemiological data show that the intake of high amounts of melamine leads to precipitation in the lower urinary tract and to melamine-associated formation of urinary stones (Yang et al., 2013). Structurally, melamine forms highly insoluble complexes via hydrogen bonds with endogenous uric acid (Dalal et al., 2011) that then precipitate once the saturation concentration is exceeded[1]. Urinary stones may also form in conjunction with cyanuric acid, which is structurally very similar to melamine. Some bacteria are capable of metabolising melamine into cyanuric acid (Zheng et al., 2013). Cyanuric acid is also a trace substance in food products of plant origin (EFSA, 2010; Zhu et al., 2019). There is discussion as to whether the simultaneous intake of cyanuric acid and melamine promotes the formation of urinary stones in humans (Dalal et al., 2011; Dominguez-Estevez et al., 2010; Sathyanarayana et al., 2019). *In vivo* findings of kidney stones formed from melamine-cyanuric acid complexes have previously been recorded only in rats, pets and livestock following co-exposure to both substances (Dorne et al., 2013). Examinations of infants (aged 6 to 36 months) following the consumption of follow-on formula contaminated with melamine have shown that kidney stones consisted solely of melamine and uric acid (Sun et al., 2010). Moreover, it has been reported that the amount of melamine excreted with the urine positively correlates with the size of kidney stones formed (Dalal et al., 2011; Lam et al., 2009). Another retrospective evaluation of cases of illness associated with melamine-contaminated follow-on formula in China revealed indications that gender and urinary pH affect the risk of kidney stone formation (Lu et al., 2011). In this study, the risk of forming melamine-associated kidney stones was calculated in boys twice as high as in girls. Due to the solubility profile of melamine with a minimal saturation concentration at pH 5.5 (Dominguez-Estevez et al., 2010) urinary stone formation is facilitated in correspondingly acidic urine (Dorne et al., 2013; Skinner et al., 2010). Dependent on size a proportion of these precipitates are passed as gravel or smaller-sized stones with urine. Larger concretions can be deposited in the urinary tract. Deposition

[1] Concentration of a substance in a solvent, above which point no more substance can be dissolved.

of kidney stones in the renal pelvis can lead to urinary retention with subsequent damage to the kidneys and even renal failure (Guan et al., 2016). In addition, smaller crystals can be mechanical irritants to tissue, and lead to tissue changes involving necrosis, nephritis and kidney tubule degeneration (Bhalla et al., 2009). In rats, it has been shown that tissue damage occurs both directly via deposition in the proximal convoluted tubule as well as indirectly via the resulting blockage in the distal convoluted tubule (Bhalla et al., 2009; Chen et al., 2014; Guan et al., 2016).

In a further study, rats exposed to melamine exhibited typical signs of nephropathy in conjunction with reduced renal blood flow (Tian et al., 2016). No stone formation was observed here. However, the authors themselves point to weaknesses in the imaging technology used; hence, it cannot be concluded from this study that melamine exhibits renal toxicity without the involvement of urinary tract stones.

The formation of stones in the kidneys or in the efferent urinary system represents the most sensitive end point for the investigation of melamine-induced effects. Reflecting this, the current derivation of a tolerable daily intake (TDI) for melamine is based on studies investigating renal toxicity (EFSA, 2010). Utilising dose-response relationship data from a chronic feeding study in rats (NTP, 1983), a *benchmark dose lower confidence limit* for an additional 10% risk of falling ill ($BMDL_{10}$) of 19 mg/kg body weight/day was calculated by EFSA (EFSA, 2010). This value has been reproduced and confirmed by the BfR using the recently revised EFSA Guidance for BMD Modelling (EFSA, 2017) (see section 5.1 in the annex). The value serves as the starting point for deriving a health-based guidance value for melamine (see section 3.1.2.4).

Genotoxicity and carcinogenicity
Melamine is neither genotoxic *in vivo* nor in *in vitro*(WHO, 2009). A classification as a carcinogen is currently being evaluated (ECHA, 2019). Studies in rats indicate that melamine has carcinogenic potential as a result of the initial stone formation described above. In animal experiments, the subchronic and chronic administration of melamine in high doses led to the formation of crystalline deposits (urinary tract stones) and, in some cases, to a statistically significant increase in the incidence of bladder tumours (NTP, 1983; Ogasawara et al., 1995; Okumura et al., 1992; Skinner et al., 2010). An increased incidence of cancer occurred only together with stone formation. In this context, chronic inflammatory processes that occur as a result of prolonged mechanical irritation of the tissue by the stones are assumed to induce carcinogenesis (Ogasawara et al., 1995; Skinner et al., 2010). Melamine-induced stone formation is dose-dependent.Accordingly, stones only form once a certain quantity of melamine is present that exceeds the saturation concentration in urine (Hazleton Raltech Inc., 1983). As a result, the carcinogenic potential of melamine is subject to a threshold mechanism.

For stones not induced by melamine, a Swedish cohort study involving 60,000 patients also showed a link between an increased risk of renal pelvic cancer or bladder cancer and initial stone formation (Chow et al., 1997). Another cohort study involving over 21,000 patients also discovered a positive correlation between the presence of stones in the lower efferent urinary system and the presence of bladder tumours (Sun et al., 2013). Overall, the presence of stones in patients is associated with a higher risk of developing cancer of the urinary tract.

Reproduction toxicity
Several animal studies have shown that melamine can have reprotoxic effects. In mice and piglets, for example, damage to the ultrastructure of the blood-testis barrier has been demonstrated. Amongst other functions, the blood-testis barrier keeps exogenous substances away from the reproductive cells in the seminiferous tubules. This barrier function is achieved by

specific cell-to-cell junctions. Piglets and mice exposed to melamine exhibited histopathological lesions in testicular tissue and germ cell abnormalities after ten weeks and three days of exposure, respectively (Chang et al., 2018; 2014). Piglets were exposed to melamine via the feed containing 100–1,000 mg of melamine/kg of feed. Since the study provides no data about the quantity of feed administered per dose group or animal, an approximation of the melamine dose intake per piglet is calculated in the following. According to the guidance from the Bavarian State Research Centre for Agriculture, which prescribes a feed quantity of 1.8 kg/day for piglets weighing 30 kg or more (Bayerische Landesanstalt für Landwirtschaft, 2014), the melamine exposure for the piglets in the above mentioned study was approximately 6–60 mg/kg body weight/day. In another experiment, mice were exposed to melamine within a range of 30–700 mg melamine/kg body weight/day. Using transmission electron microscopy and the lanthanum tracer technique, the authors could show that melamine reduces the barrier function of the blood-testis barrier by disrupting the cell-to-cell junctions. As one consequence the permeability for melamine increases, which can permeate as far as the seminiferous tubules, where it can disrupt processes of steroidogenesis and germ cell maturation (Chang et al., 2018; Chen et al., 2014). In another study, mice were administered 2, 10 and 50 mg/melamine body weight/day via gavage for 28 days. Significant reductions in sperm quantity and quality were observed in all dose groups. In the median- and high-dose group, morphological changes of testes were also observed, as well as reduced levels of testosterone in the blood (Sun et al., 2016). However, whether the effects observed are actually capable of producing health impairments (reduced fertility, malformation, behavioural disorders, etc.) has not been clarified so far.

As they all have weaknesses, none of the studies described above are suitable for deriving health-based guidance values. For example, they were neither conducted under the rules for good laboratory practice nor in accordance with internationally established guidelines. In some cases, only one concentration of the test substance was investigated, which is why it is not possible to draw any conclusions about a potential dose-response relationship. In others, it is not clear whether the effects observed are relevant for health. Notwithstanding this, they do at least indicate that melamine has the potential to be a reprotoxin. At present, a study conforming to OECD guidance and conducted under the rules of good laboratory practice (OECD TG 443, *Extended One-Generation Reproductive Toxicity Study*) is being performed to clarify these open issues (ECHA, 2016).

As well as the blood-testis barrier, melamine has also been shown to cross the placental barrier in animal experiments. A study with pregnant and nursing rats demonstrated the maternal transfer of melamine into amniotic fluid and the foetus. Melamine was also detected in the dam's milk (Chan et al., 2011). In a further study in rats, experimental animals as well as their offspring exhibited impaired renal function, indicated by reduced renal blood flow and increased levels of inflammatory markers in consequence of melamine exposure of the dams (Tian et al., 2016). Since only one single dose was tested (600 mg/kg body weight/day) for prenatal exposure, a critical dose for the F1 generation cannot be derived.

No data are currently available on the reprotoxic effects of melamine in humans. Further studies are required in order to estimate the relevance of the effects described to humans.

Neurotoxicity
It has been shown in rats that melamine can pass the blood-brain barrier (Mannoni et al., 2017). Following intravenous administration of melamine, its dispersal to various organs, including the brain, was demonstrated (Wu et al., 2009). Various studies in rats have identified the hippocampus as target tissue of neurotoxic effects. *In vitro* experiments on cell cultures

have also observed changes in synaptic excitation, as well as indications of melamine-induced oxidative stress. Overall, the available data confirm that melamine can impair the synaptic plasticity of the hippocampus in the rat brain (Mannoni et al., 2017). This is of decisive importance for memory and learning processes in spatial contexts. In behavioural tests with rats the neurotoxic effects of melamine result in cognitive deficiencies with regard to spatial orientation and spatial memory (Bolden et al., 2017; Chu et al., 2013; Mannoni et al., 2017). In most studies, only a single melamine dose of 300–400 mg/kg body weight/day was administered, which equates to 10–20% of the LD_{50} dose. This high level of exposure is of no relevance for the assessment of consumer goods under investigation here. No dose-response relationship has been determined for these end points to date. Whether or not these neurotoxic effects of melamine are transferable to humans is unclear, since no corresponding epidemiological investigations are available.

Other aspects
There is one study examining melamine effects in rats indicating that microbial processes in the gut can play a role in the formation of kidney/urinary tract stones (Zheng et al., 2013). Specific gut bacteria of the *Klebsiella* genus convert melamine into cyanuric acid both *in vivo* and *in vitro*. It is suggested that even a small amount of the cyanuric acid formed from melamine is sufficient to form crystallisation nuclei with melamine, which then facilitate the formation of complexes (stones) with uric acid (Zheng et al., 2013). This hypothesis is supported by a study examining rats that were colonised by Klebsiella. In these animals, the combined administration of melamine and antibiotics led to a significant reduction of the melamine-induced stone formation (Zheng et al., 2013).

The composition of gut flora can differ significantly between individuals of a species. The occurrence of *Klebsiella terrigena* has been determined in rat faeces (Zheng et al., 2013). An earlier study identified *K. terrigena* in 50 of 5,377 human stool samples (0.9%) (Podschun, 1991). Since there are no reports of mixed crystals of cyanuric acid, uric acid and melamine in humans, the relevance of microbial processes for the formation of melamine-induced kidney/urinary tract stones is unclear.

3.1.2.4 Deriving a health-based guidance value for melamine

EFSA (2010) has derived a tolerable daily intake (TDI) for melamine of 0.2 mg/kg body weight/day. This is based on a chronic toxicology study in rats (NTP, 1983) in which stones were found in the efferent urinary system and especially in males. By using *benchmark dose modelling* (BMD modelling), EFSA calculated a *benchmark dose lower confidence limit* for an additional 10% risk of falling ill ($BMDL_{10}$) of 19 mg/kg body weight/day. By applying an uncertainty factor of 100 (10-fold for intra-species and inter-species differences, respectively), this produced a (rounded) TDI of 0.2 mg/kg body weight/day (EFSA, 2010).
This value has been reproduced and confirmed by the BfR using the recently revised EFSA Guidance for BMD Modelling (EFSA, 2017). To do so, the web-based software PROAST[2] was used (software version 66.38). Details are provided in the annex in section 5.1. The calculated $BMDL_{10}$ of 16 mg/kg body weight/day is very close to the $BMDL_{10}$ value of 19 mg/kg body weight/day defined by EFSA (2010), and therefore confirms, with the application of an uncertainty factor of 100 (10-fold each for intra-/inter-species differences), the TDI of EFSA (2010) von 0.2 mg/kg body weight/day.

The formation of bladder or kidney stones takes place if the saturation concentration of melamine in final urine is exceeded. This concentration is strongly dependent on pH of the final

[2] https://shiny-efsa.openanalytics.eu/app/bmd

urine (Dominguez-Estevez et al., 2010). One study in rats and human urine has investigated the impact of pH on melamine solubility revealing in human urine the minimum concentration of 15 mg/l at pH 5.5. Typically, pH of human urine ranges between 5.2 and 6.2. In the rat urine used by Dominguez-Estevez et al. (2010) with a physiological pH between 8.3 and 8.5, the saturation concentration for pure melamine is almost 100 times higher, at 1,400 mg/l. In a sample of human urine artificially raised to pH 8.3, the saturation concentration of melamine was 833 mg/l (Dominguez-Estevez et al., 2010). In addition, the uric acid concentration in human urine is much higher than in rat urine, since humans, unlike rats, do not possess the enzyme uricase that breaks down uric acid. Uric acid combines with melamine thereby forming the crystals and stones as described. The significant differences seen between melamine solubility in human and rat urine, together with the higher uric acid concentration in human urine, raise the question of whether the TDI derived from a rat study is safe enough to be applied to humans.In Order to address this issue, EFSA (2010) also analysed the available data on Chinese children (Li et al., 2009) who had consumed contaminated follow-on formula during the 2008 melamine scandal. BMD modelling was applied to determine that their $BMDL_{10}$ was 0.74 mg/kg body weight/day. Since this modelling was also not compliant with current (EFSA, 2017) guidance, the BfR repeated the modelling in accordance with current specifications (see section 5.2 in the annex). In doing so the $BMDL_{10}$ of 0.74 mg/kg body weight/day was confirmed. Since infants represent a very sensitive population group, no further uncertainty factor is required. The TDI derived from animal experiments of 0.2 mg/kg body weight/day is significantly lower than the $BMDL_{10}$ value from the stated human study and hence considered as adequately conservative.

3.1.3 Exposure assessment

In section 3.1.2.2, the BfR has derived health-based guidance values both for the concentration of formaldehyde in food products and for total daily intake. In the following section, the corresponding exposure values are evaluated in relation tothese reference values . In addition, the daily melamine exposure values are evaluated in relation to the TDI derived in section 3.1.2.4.

The concentrations of formaldehyde and melamine in food products—here specifically hot beverages—are represented herein by the contents of the substances in food simulants resulting from migration experiments. In order to estimate the total daily intake values for adult consumers over a longer period of time, the daily quantities of coffee beverages consumed have been linked with the results of the third consecutive migration test (which has to be used according to Regulation (EU) No 10/2011 for testing the conformity of materials intended for repeated use) for formaldehyde and for melamine from the fillable food contact materials investigated. In conformance to the stated regulation, it is assumed that the formaldehyde/melamine content in the food simulant corresponds to the content in real-life food products. By drawing on comparative investigations with melamine, the BfR has shown that this correspondence is indeed very high for coffee beverages (Bradley et al., 2010). Consumption data have been taken from the German National Food Consumption Study II (NVS II) conducted by the Max Rubner Institute (MRI, 2008), as summarised in the EFSA *consumption database* [3].

Reusable mugs made from MFR (e.g. *coffee-to-go* cups) are primarily targeted at adult consumers. Notwithstanding this, MFR is also a typical material for the production of children's tableware: it is therefore foreseeable that the fillable objects investigated (mugs, cups and bowls) will also be used by children. Accordingly, an additional estimate of total daily intake values for formaldehyde and melamine has been calculated for infants. To do so, the BfR

[3] https://www.efsa.europa.eu/de/food-consumption/comprehensive-database

has utilised consumption data from EFSA, which have been derived from the risk assessment of substances capable of migrating from food contact materials (EFSA, 2016).

3.1.3.1 Content/concentration of formaldehyde and melamine in food (migration values)

The BfR has analysed the results of investigations from the German food monitoring authorities from 2014 to 2019, as well as its own data. Only samples, which met the following conditions, were included in the assessment. :

(1) The respective articles are typically filled with (hot) liquids during daily use. Such articles include mugs, cups and bowls, for example. Since reusable *coffee-to-go* cups are currently very popular with consumers, and these cups are often made from MFR, these articles were of particular interest for the BfR. To expand the available dataset on formaldehyde/melamine released from these products, other fillable articles not explicitly referred to as coffee cups/mugs were also included in the assessment.
(2) For the sample investigated, the fact of whether an article was made from 'conventional' MFR or ''bambooware'' had to be clearly and unambiguously stated.
(3) For the migration investigation, 3% acetic acid was used as the food simulant and the test was conducted in accordance with the provisions of Regulation (EU) No 10/2011 three times in succession at 70 °C for two hours each.
(4) The results were available for the third migrate and could be unambiguously related to the volume (or mass) of the food simulant.

Formaldehyde migration
The results for formaldehyde are summarised in Table 1 and illustrated by the bar chart in Figure 1. A total of 138 samples from 'conventional' MFR and 228 samples from 'bambooware' were identified according to the criteria mentioned above, and included in the assessment.

It is noticeable, that the migration of formaldehyde from the articles made from 'conventional' MFR is significantly lower than migration from 'bambooware'. For the articles made from 'conventional' MFR, all results from the third formaldehyde migration test are lower than 50 mg/l and are approximately log-normal distributed. The median is 4.45 mg/l (Figure 1a). For 8 objects (5.8%), the migration exceeds the SMLT for formaldehyde of 15 mg/kg of food product as set out in Regulation (EU) No 10/2011. For 'bambooware' items, the formaldehyde migration results below 50 mg/l are also approximately log-normal distributed (Figure 1b, 173 samples, median 6.75 mg/l). However, the formaldehyde migration for 55 'bambooware' articles (24%) investigated exceeds the value of 50 mg/l (Figure 1c) and significantly so in some cases. As a result, these articles cannot be represented in a log-normal distribution along with those articles that release less than 50 mg formaldehyde/l. The articles that release considerably greater amounts of formaldehyde are therefore considered separately for the exposure assessment. The median value for formaldehyde migration from 'bambooware' items that release more than 50 mg/l is 242 mg/l and is therefore roughly 16 times higher than the SMLT. The very high standard deviation of 236 mg/l shows the high level of variation in formaldehyde migration from the individual articles. If all 'bambooware' articles are considered together, then formaldehyde migration exceeds the SMLT in 31% of the samples (70 objects).

Table 1: Release of formaldehyde from fillable food contact materials made from 'conventional' melamine formaldehyde resin (MFR) and 'bambooware'; migration conditions: 2 h at 70 °C in 3% acetic acid, 3rd migrate; LOQ = limit of quantification

		'Bambooware'

	‘Conventional’ MFR	Total	Migration <50 mg/l simulant	Migration >50 mg/l simulant
No. of samples	138	228	173	55
Result in mg/l simulant				
Minimum	**<LOQ**	**<LOQ**	**<LOQ**	**54.8**
Maximum	**32.7**	**912**	**33.0**	**912**
Median	**4.45**	**9.25**	**6.75**	**242**
75th percentile	7.39	31.9	10.8	388
95th percentile	**15.3**	**442**	**19.7**	**808**
Mean value	**5.69**	**85.9**	**8.07**	**331**
Standard deviation	5.47	180	6.15	236
Relative standard deviation (dimensionless)	0.96	2.1	0.76	0.71
No. of samples >15 mg/l (SMLT)	8 (5.8%)	70 (31%)	15 (8.7%)	55 (100%)

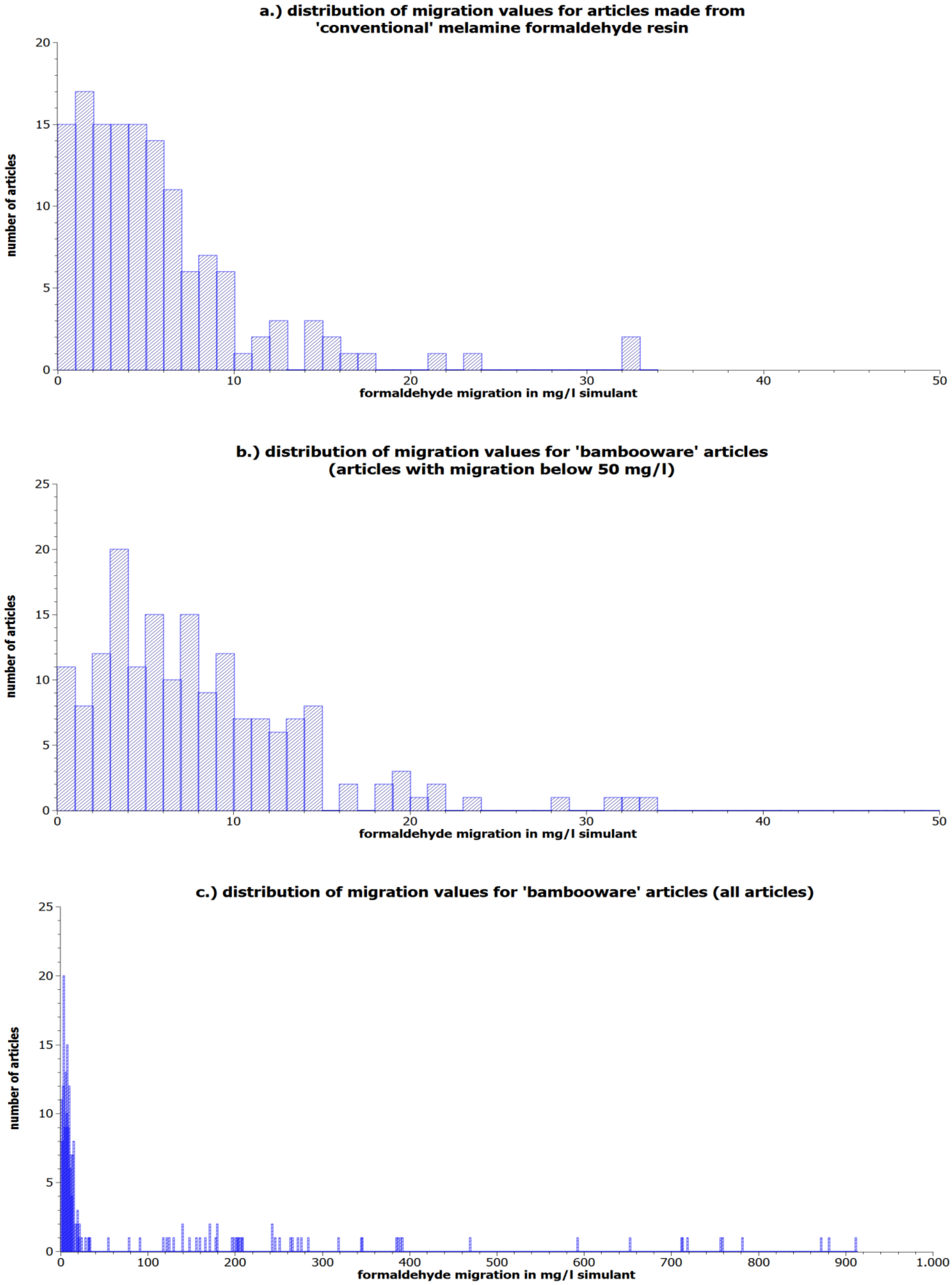


Figure 1: **Illustration of the respective number of objects with formaldehyde migration values in a specific range**

Melamine migration
The results for melamine are summarised in Table 2 and illustrated by the bar chart in Figure 2. A total of 111 samples from ‘conventional’ MFR and 180 samples from ‘bambooware’ were identified according to the criteria mentioned above, and included in the assessment.

All results from the third melamine migration test are below 25 mg/l and are approximately log-normal distributed. For 19 samples made from ‘conventional’ MFR and 18 ‘bambooware’ samples, the melamine released was below the limit of quantification/detection. For the calculation of statistical values (mean, median, standard deviation, etc.), a release value of 0 mg/kg was used for these samples (lower bound approach). The migration of melamine from articles made from ‘conventional’ MFR is, with a median of 0.69 mg/l (Figure 2a), slightly lower on average than the migration from ‘bambooware’ articles, which have a median of 1.55 mg/l (Figure 2b). For 17 articles (15%) made from ‘conventional’ MFR and for 63 ‘bambooware’ articles (35%), the migration exceeds the SML for melamine of 2.5 mg/kg of food as set out in Regulation (EU) No 10/2011.

Table 2: Release of melamine from fillable food contact materials made from ‘conventional’ melamine formaldehyde resin (MFR) and ‘bambooware’; migration conditions: 2 h at 70 °C in 3% acetic acid, 3rd migrate; LOQ = limit of quantification

	‘Conventional’ MFR	‘Bambooware’
No. of samples	111	180
Result in mg/l simulant		
Minimum	**<LOQ**	**<LOQ**
Maximum	**8.37**	**20.7**
Median	**0.69**	**1.55**
75th percentile	1.88	3.53
95th percentile	**4.29**	**7.71**
Mean value	**1.27**	**2.64**
Standard deviation	1.58	3.06
Relative standard deviation (dimensionless)	1.24	1.16
No. of samples >2.5 mg/l (SML)	17 (15 %)	63 (35 %)

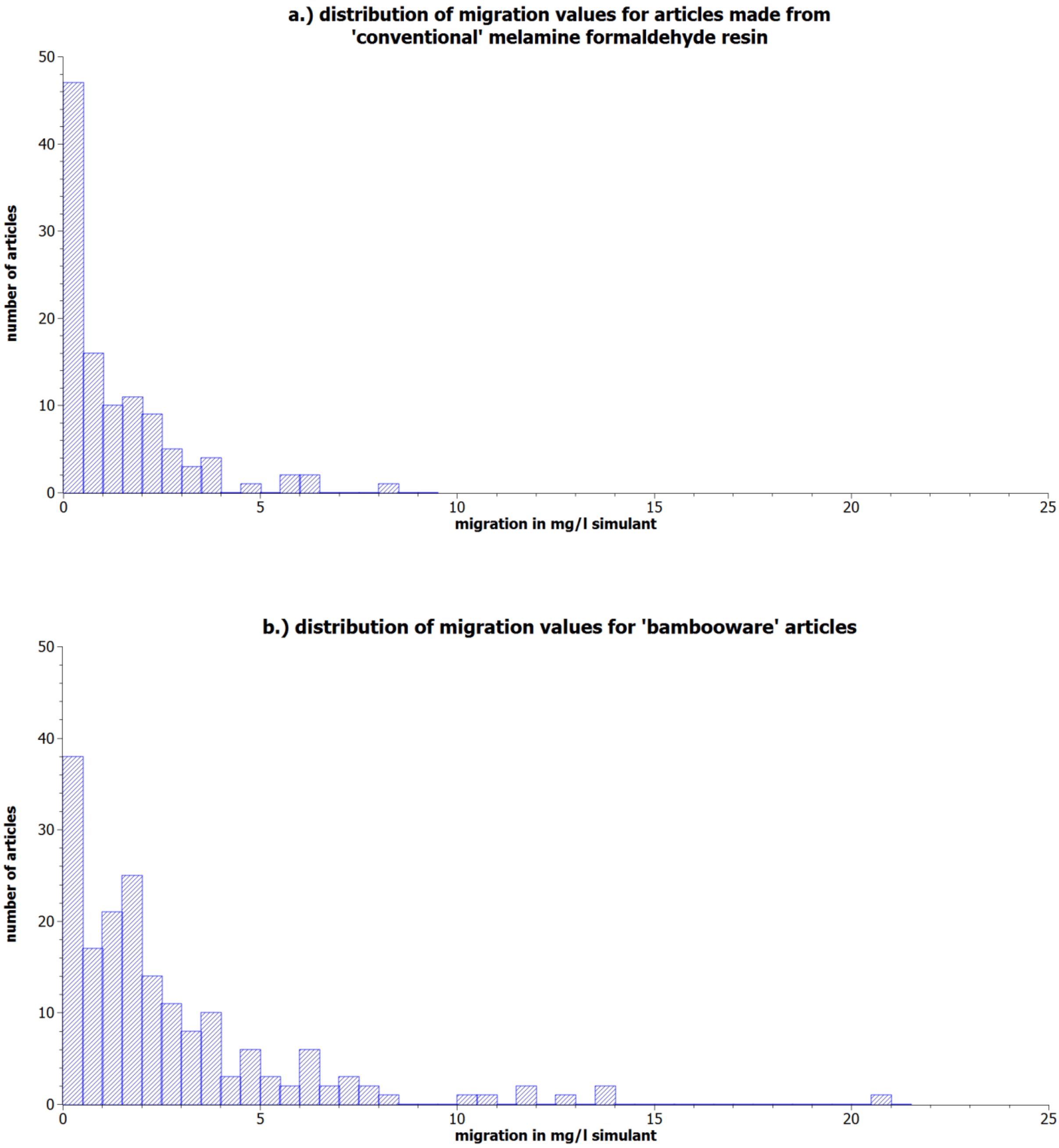


Figure 2: Illustration of the respective number of objects with melamine migration values in a specific range

3.1.3.2 Consumption data

<u>For adults</u>, consumption data were taken from the results of the German National Food Consumption Study II (NVS II) for coffee beverages (MRI, 2008), since reusable *coffee-to-go* cups are currently highly popular with consumers and these cups are often manufactured from MFR. This focus on just a single food group leads to an underestimation of the exposure of consumers, who use the corresponding cups on a daily basis, as there may be other sources of intake, such as the consumption of other foods hot-filled into MFR articles (soups,

semolina pudding, etc.). Data on the daily usage of objects made from MFR for the consumption of these other food products by the adult population are not available, however. The BfR estimates that this usage is more typical for (young) children.

In the NVS II study, retrospective consumer surveys on two separate days about their consumption behaviour over the last 24 hours were conducted. The data on the consumption of coffee beverages are summarised below. The values in Table 3 take into account only those days on which coffee beverages were consumed, while the values in Table 4 also include days without coffee consumption. The broadest dataset is available for young and middle-aged adults (19 to 50 years old), with responses for 20,838 days. Respondents stated coffee beverages were consumed on 15,895 of these days (76.3%, Table 3). Calculated over all available days, the average level of consumption is around 441 g/coffee per person and day. The median is 380 g per person and day. The 95th percentile is 1,200 g per person and day (for full details, see Table 4).

Table 3: **Data from the German National Food Consumption Study II on the consumption of coffee beverages in various age groups. Mean, median and 95th percentile values are calculated by taking into account data for days on which consumption took place.**

Age group	No. of days with consumption (% of all reported days)	Mean in g/day	Relative standard deviation	Median in g/day	95th percentile in g/day
Adolescents (14–18 years)	308 (15.2)	320	0.71	300	678
Adults (19–50 years)	15,895 (76.3)	578	0.69	500	1200
Older adults (50–65 years)	3,442 (85.8)	516	0.58	490	1060
Elderly adults (65–80 years)	804 (82.0)	453	0.56	386	900

If consumption days are considered only, then average consumption is slightly higher. Here, the mean is 578 g per person and day, the median is 500 g per person and day and the 95th percentile is 1,200 g per person and day (Table 3). For older and elderly adults, the percentage number of days, on which coffee beverages are consumed, is 85.8% and 82%, respectively, and so higher than for adults in the 19–50 age group. The respective quantities consumed calculated for all days are very similar, however, and actually somewhat lower for high consumers (95th percentile) (Table 4).

Table 4: **Data from the German National Food Consumption Study II on the consumption of coffee beverages in various age groups. Mean, median and 95th percentile values are calculated by accounting for data from all days (not just those with consumption).**

Age group	No. of days with consumption (% of all reported days)	Mean in g/day	Relative standard deviation	Median in g/day	95th percentile in g/day
Adolescents (14–18 years)	308 (15.2)	48.7	2.0	0	300
Adults (19–50 years)	15,895 (76.3)	441	0.93	380	1200
Older adults (50–65 years)	3,442 (85.8)	443	0.74	380	1000

Elderly adults (65–80 years)	804 (82.0)	372	0.75	380	900

For infants (12–36 months), EFSA (2016) has evaluated the data from the *consumption database* and derived corresponding consumption quantities for foods in contact with certain kinds of food contact materials. For fillable articles, Category 2 (milk, milk products and other non-alcoholic drinks) is to be applied. Since infants (12 to 36 months) in this category represent the population group with the highest level of consumption in relation to their body weight (80 g of food product per kg of body weight for high consumers) and since a low level of variation in the articles used each day (cups, bowls, etc.) is also typical for this group, the following exposure calculations focus on this specific group. An average body weight of 12 kg is assumed (EFSA, 2012; 2016). In the case of exclusive use of the exact same article or various articles of the same type, this would result in a figure for daily consumption of 960 g of hot food products that come into contact with the respective article(s).

3.1.3.3 Calculation of daily intake

Formaldehyde

For adults, an exposure assessment was made using a Monte Carlo simulation[4]. To do so, the program ‘ConsExpo Web’[5] (version 1.0.6, released 13 Feb 2019) was used. The content in food (results from the migration experiments, see above) were specified as *substance concentration* in the form of log-normal distributions with the respective median and relative standard deviation (see Table 1). For ‘bambooware’ articles, only the migration values <50 mg/l were used in the initial step. The migration values >50 mg/l do not fit into the log-normal distribution of the values <50 mg/l (cf. Figure 1b and c) and therefore needed to be considered separately. For the *ingested amount,* the consumption quantities were specified also as log-normal distributions (median and relative standard deviation, see Table 3). According to the reported subset of days where consumption took place (76.3%, see Table 3), 278 consumption days per year were assumed. Both *migration from packaging* and *instant release* were selected as simulation parameters. To convert exposure values to body weight values, a body weight of 60 kg was assumed, in accordance with Regulation (EU) No 10/2011. The results of the Monte Carlo simulation are shown in Table 5 as well as in Figure 8, and in Figure 9 (in the annex).

In accordance with the distributions of migration data from ‘conventional’ MFR and from ‘bambooware’ (values <50 mg/l), the resulting daily intake values are within a similar order of magnitude: for normally exposed (mean/median) and highly exposed individuals (95th percentile), the level of exposure resulting from the use of ‘bambooware’ is between 30% and 50% higher when compared to the use of ‘conventional’ MFR (Table 5).

[4] A Monte Carlo simulation is a method that attempts to find numerical solutions to complex, stochastic problem scenarios. For the problem scenario in question, a value is drawn randomly from the distribution of formaldehyde content values and multiplied by a consumption quantity value, also drawn randomly from the respective distribution. By repeating this process many times, a distribution curve is generated of the respective individual exposures, for which various percentiles and a standard deviation can then be calculated.

[5] https://www.consexpoweb.nl

Table 5: **Daily levels of formaldehyde exposure for adults (19–50 years) who use reusable coffee cups made from melamine formaldehyde resin. The calculation was done using a Monte Carlo simulation. For ‘bambooware’ articles, only the migration values <50 mg/l were included in the calculation (76% of all values).**

Exposure to	No. of days with consumption per year	Exposure in terms of all days in mg/kg bw*/day		
		Mean value	Median	95th percentile
Objects made from ‘conventional’ MFR**	278	**0.056**	**0.036**	**0.17**
‘Bambooware’	278	**0.079**	**0.055**	**0.22**
Ratio of ‘bambooware’ to ‘conventional’ MFR**	–	1.4 (140%)	1.5 (150%)	1.3 (130%)

* Body weight = 60 kg
** Melamine formaldehyde resin

For ‘bambooware’ articles, however, in addition to the objects discussed above, 24% of the samples investigated exhibited migration values (substantially) higher than 50 mg/l (Table 1). These could not be represented by a normal/log-normal distribution. To estimate the level of exposure resulting from the usage of these objects, the 25th percentile, the median, the 95th percentile and the maximum value from the migration results were each multiplied by the median and 95th percentile of the consumption values for coffee beverages for adults. The daily intake values so obtained represent the range of exposure values (Table 6). The values exceed the daily intake values resulting from the use of ‘bambooware’ with formaldehyde migration values <50 mg/l significantly (being from 4 to 326 times higher, cf. Table 5).

Table 6: **Daily formaldehyde exposure for adults (19–50 years, body weight = 60 kg) in mg/kg body weight/day, depending on the individual’s consumption behaviour and the formaldehyde migration from the respective ‘bambooware’ article used; to calculate the percentiles, only the migration values >50 mg/l were used.**

Consumption behaviour / Migration	Normal consumers (median 380 g/day)	High consumers (95th percentile 1,200 g/day)
25th percentile (171 mg/l)	1.1	3.4
Median (242 mg/l)	1.5	4.9
95th percentile (808 mg/l)	5.1	16
Maximum value (912 mg/l)	5.8	18

For infants (12–36 months), an exposure assessment was also carried out by means of a Monte Carlo simulation using ‘ConsExpo Web’ (version 1.0.6). For the values for migration into food, the same approach was applied as was previously used in the calculation for adults. A value of 960 g of food product/day was used as the quantity consumed (see section 3.1.3.2). A body weight of 12 kg was assumed (EFSA, 2012; 2016). The daily intake is much higher for infants than for adults (Table 7, Figure 10 and Figure 11 in the annex). Even if taken into account that the quantity consumed for infants has already been calculated for high consumers (95th percentile), their average daily intake (0.50 and 0.67 mg/kg body weight/day) is more than three times higher than for the highly exposed adult group (95th percentile, see Table 5). This applies both to articles made from ‘conventional’ MFR and to ‘bambooware’.

Also for infants, daily formaldehyde exposure was estimated that would result from the use of ‘bambooware’ articles that release formaldehyde in significantly higher amounts than 50 mg/l (Table 8). These values exceed the level of exposure resulting from the use of ‘bambooware’ with formaldehyde migration values <50 mg/l (see Table 7) about 8 to 134 times. Also compared to adult high consumers (cf. Table 6), daily formaldehyde intake for infants is roughly four times higher.

Table 7: **Daily formaldehyde exposure for infants (12–36 months) who consume heated food products from fillable objects made from melamine formaldehyde resin. The calculation was done using a Monte Carlo simulation. For ‘bambooware’ items, only the migration values <50 mg/l were included in the calculation (76% of all values).**

Exposure to	Exposure in terms of all days in mg/kg body weight*/day		
	Mean value	Median	95th percentile
Objects made from ‘conventional’ MFR**	**0.50**	**0.35**	**1.3**
‘Bambooware’	**0.67**	**0.54**	**1.6**
Ratio of ‘bambooware’ to ‘conventional’ MFR**	1.4 (140%)	1.5 (150%)	1.2 (120%)

* Body weight; daily quantity consumed = 80 g of food/kg body weight
** Melamine formaldehyde resin

Table 8: **Daily formaldehyde exposure for infants (12–36 months), depending on formaldehyde migration from the respective ‘bambooware’ article used; to calculate the percentiles, only the migration values >50 mg/l were used; daily quantity consumed 80 g of food product/kg body weight.**

Migration	Resulting formaldehyde intake in mg/kg body weight/day for high consumers (80 g/kg body weight/day)
25th percentile (171 mg/l)	14
Median (242 mg/l)	19
95th percentile (808 mg/l)	65
Maximum value (912 mg/l)	73

Melamine
For adults, an exposure assessment was done using the same approach as for formaldehyde (Table 9, Figure 12 and Figure 13 in the annex). The melamine contents in food used in the calculation are shown in Table 2.

Similarly to the distributions of migration data from ‘conventional’ MFR and from ‘bambooware’, the resulting daily intake values are within a similar order of magnitude. Nevertheless, for normally exposed (mean/median) and highly exposed individuals (95th percentile), the daily intake resulting from the use of ‘bambooware’ is roughly twice as high (Table 9).

Table 9: Daily melamine exposure for adults (19–50 years) who use reusable coffee cups made from melamine formaldehyde resin. The calculation was done via Monte Carlo simulation.

Exposure to	No. of days with consumption per year	Exposure in terms of all days in mg/kg body weight*/day		
		Mean value	Median	95th percentile
Objects made from ‘conventional’ MFR **	278	**0.010**	**0.006**	**0.033**
‘Bambooware’	278	**0.021**	**0.013**	**0.069**
Ratio of ‘bambooware’ to ‘conventional’ MFR **	-	2.1 (210%)	2.2 (220%)	2.1 (210%)

* Body weight = 60 kg
** Melamine formaldehyde resin

<u>For infants (12–36 months)</u>, an exposure assessment was also carried out via Monte Carlo simulation using ‘ConsExpo Web’ (version 1.0.6). For the values for migration into food, the same approach was applied as was previously used in the calculation for adults. A value of 960 g of food/day was used as the quantity consumed (see section 3.1.3.2). A body weight of 12 kg was assumed (EFSA, 2012; 2016). The daily intake for infants (Table 10, Figure 14 and Figure 15 in the annex) is considerably higher than for adults (Table 9). Even if taken into account that the quantity consumed for infants has already been calculated for high consumers (95th percentile), their average daily intake is nearly three times higher than for highly exposed adults (95th percentile). This applies both to articles made from ‘conventional’ MFR and to ‘bambooware’.

Table 10: Daily melamine exposure for infants (12–36 months) who consume heated food products from fillable articles made from melamine formaldehyde resin. The calculation was done using a Monte Carlo simulation.

Exposure to	Exposure in terms of all days in mg/kg body weight*/day		
	Mean value	Median	95th percentile
Objects made from ‘conventional’ MFR **	**0.090**	**0.057**	**0.28**
‘Bambooware’	**0.19**	**0.12**	**0.56**
Ratio of ‘bambooware’ to ‘conventional’ MFR **	2.1 (210%)	2.2 (220%)	2.0 (200%)

* Body weight; daily quantity consumed = 80 g of food/kg body weight
** Melamine formaldehyde resin

3.1.3.4 Summary of exposure data

Formaldehyde

Table 11 shows the daily oral formaldehyde exposure for adults (19–50 years) and for infants (12–36 months), both for normally exposed (median) and highly exposed (95th percentile) individuals.

Table 11: Daily formaldehyde intake calculated from migration data and consumption data in mg/kg body weight/day for adults (body weight = 60 kg) and infants; q.c. = quantity consumed

	Adults (19–50 years)		Infants (12–36 months)	
	Normally exposed individuals (median)	Highly exposed individuals (95th percentile)	Normally exposed individuals (median)	Highly exposed individuals (95th percentile)
'Conventional' melamine formaldehyde resin articles				
	0.036	0.17	0.35	1.3
'Bambooware' articles with migration <50 mg/l				
	0.055	0.22	0.54	1.6
'Bambooware' articles with migration >50 mg/l				
Migration value	**Normal consumers (q.c. = 380 g/day)**	**High consumers (q.c. = 1,200 g/day)**	**High consumers (q.c. = 80 g/kg body weight/day)**	
Median	1.5	4.9	19	
95th percentile	5.1	16	65	
Maximum value	5.8	18	73	
Article with maximum migration allowed (SMLT) of 15 mg/kg of food product	0.095	0.30	1.2	

The data were calculated using a Monte Carlo simulation. For 'bambooware' articles that release significantly more than 50 mg formaldehyde/l, this approach was not possible, since the respective migration values were not normal or log-normal distributed (see Figure 1, Table 1). For these articles, an exposure assessment was done by multiplying various percentiles of the migration results with the quantities consumed by normal consumers (adults only) and high consumers (adults and infants).

For both adults and infants, the daily exposure is also given that would result from exhaustion of the migration limit specified in Regulation (EU) No 10/2011.

Melamine
Table 12 shows the daily oral melamine exposure for adults (19–50 years) and for infants (12–36 months), both for normally exposed (median) and highly exposed individuals (95th percentile). The data were calculated via Monte Carlo simulation.

For both adults and infants, the exposure is also given that would result if migration from an article would exhaust the migration limit specified in Regulation (EU) No 10/2011. For infants, a quantity consumed of 80 g/kg body weight/day was used for calculations (equals 960 g/day at 12 kg body weight (EFSA, 2016)).

Table 12: Daily melamine intake calculated from migration data and consumption data in mg/kg body weight/day for adults (body weight = 60 kg) and infants

	Adults (19–50 years)		**Infants (12–36 months)**	
	Normally exposed individuals (median)	**Highly exposed individuals (95th percentile)**	**Normally exposed individuals (median)**	**Highly exposed individuals (95th percentile)**
'Conventional' melamine formaldehyde resin articles				
	0.006	0.033	0.057	0.28
'Bambooware' articles				
	0.013	0.069	0.12	0.56
Article with maximum level of migration allowed (SML) of 2.5 mg/kg of food product	0.020	0.059	0.20	

3.1.3.5 Other sources of exposure

Formaldehyde
Formaldehyde is present in many kinds of food, such as fruit and vegetables, products of animal origin, soft drinks and coffee. In 2005, the Joint Research Centre (JRC) was commissioned by the European Commission to determine the formaldehyde content in foods and to use these data for an exposure assessment. The JRC concluded that adults take up between 4 and 40 mg of formaldehyde every day through food, depending on their eating habits (JRC, 2005). At a body weight of 60 kg, this corresponds to an exposure of 0.067–0.67 mg/kg body weight/day. As a result, the TDI of 0.6 mg/kg body weight/day can already be exhausted or even exceeded by exposure via food. In a more recent study, EFSA (2014b), with reference to a study published by the French Agence Francaise de Securite Sanitaire des Aliments (AFSSA, 2004), estimated the average daily intake for adults from food with around 11 mg per person/day (0.18 mg/kg body weight/day) to be significantly lower. The National Toxicology Program run by the U.S. Department of Health and Human Services has also calculated a lower exposure of between 2 and 14 mg/day, i.e. 0.033 to 0.23 mg/kg body weight/day (NTP, 2010). No corresponding data are available for children.

Another relevant exposure route for consumers is the inhalation intake pathway after formaldehyde release from furniture, carpets, toys or insulation material, for example, or via cigarette smoke (BfR, 2006; BfR, 2007; BfR, 2010; JRC, 2005; NTP, 2010). Since intake via inhalation leads to tumours of the nose and throat whereas the oral route induces lesions in the (fore)stomach, a reduced increase in body weight and papillary kidney necrosis, different toxicological end points are present here. No data are available on the release of formaldehyde from filled food contact materials into the ambient air under the application conditions considered here. Accordingly, this opinion only assesses effects resulting from oral exposure.

Melamine
Foods contain only low levels of melamine from natural sources. Accordingly, in almost all food groups the melamine contents reported by EFSA (2010) were generally (80% of samples) below the respective limit of quantification. Detectable levels of melamine were most frequently reported for cereals, highly sugared products, fats and dairy products. To obtain a conservative exposure estimate, all samples with release values below the limit of quantification were assigned the value of this limit ('upper bound' approach). For adults, this resulted in an exposure of less than 11 µg/kg body weight/day and for infants, fed exclusively on follow-on formula, in an exposure of less than 2 µg/kg body weight/day (EFSA, 2010). In a recent study (Zhu et al., 2019), a total of 121 samples from six different food categories were investigated to determine their content of melamine and its degradation products (ammeline, ammelide and cyanuric acid). These chemical content data were then combined with daily food intake values by the U.S. EPA in order to estimate daily exposure for various age groups. The two substances that dominated in the food samples were melamine and cyanuric acid. The melamine intake calculated for children was between 0.029 and 0.53 µg/kg body weight/day and for adults between 0.013 and 0.16 µg/kg body weight/day, respectively. Intake of cyanuric acid was similarly low, calculated as between 0.12 and 2.6 µg/kg body weight/day for children and between 0.075 and 0.60 µg/kg body weight/day for adults (Zhu et al., 2019), respectively.

3.1.4 Risk characterisation

3.1.4.1 Risk characterisation for formaldehyde release

Since the BfR considers both the formaldehyde concentration in food and the total daily intake to be relevant for assessing a potential health risk, the BfR has derived health-based guidance values for both of these factors (section 3.1.2.2). In the following section the exposure calculated in section 3.1.3 is compared with these health-based guidance values.

Risk characterisation in relation to the formaldehyde concentration found in the food simulant
For chronic exposure, the BfR has derived a maximum tolerable formaldehyde concentration (C_{max}), resulting from migration out of food contact materials, of 10.4 mg/l of foodstuff (section 3.1.2.2). The results of the migration investigations on fillable articles made from 'conventional' MFR and from 'bambooware', respectively, are presented in Table 13 and Figure 3 (see section 3.1.3.1).

Table 13: **Results of investigations on the release of formaldehyde from fillable food contact materials made from 'conventional' melamine formaldehyde resin (MFR) and from 'bambooware'; migration conditions: 2 h at 70 °C in 3% acetic acid, 3rd migrate; LOQ = limit of quantification; values in brackets are the % of the tolerable maximum concentration (C_{max}) of 10.4 mg/l food (simulant); values highlighted in red and bold exceed C_{max}**

	'Conventional' MFR	'Bambooware'	'Bambooware', migration <50 mg/l simulant	'Bambooware', migration >50 mg/l simulant
No. of samples	138	228	173	55
Result in mg/l simulant				
Minimum	<LOQ (-)	<LOQ (-)	<LOQ (-)	**54.8 (527)**
Median	4.45 (43)	9.25 (89)	6.75 (65)	**242 (2330)**
Mean value	5.69 (55)	**85.9 (826)**	8.07 (78)	**331 (3178)**
75th percentile	7.39 (71)	**31.9 (307)**	**10.8 (104)**	**388 (3732)**
95th percentile	**15.3 (147)**	**442 (4252)**	**19.7 (190)**	**808 (7771)**
Maximum	**32.7 (314)**	**912 (8764)**	**33.0 (318)**	**912 (8764)**
No. of samples >10.4 mg/l (C_{max})	17 (12 %)	101 (44 %)	46 (27 %)	55 (100 %)

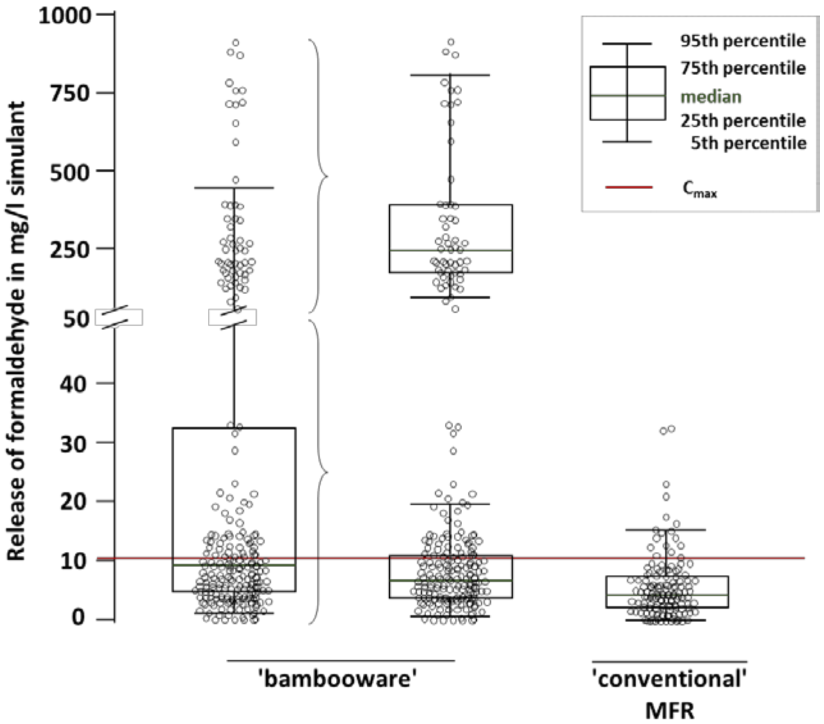


Figure 3: **Distribution of formaldehyde release from 'bambooware' and articles made from 'conventional' MFR. In addition to the representation of the entirety of 'bambooware' samples (left), the results also shown individually for the groups of articles with a formaldehyde release of less or more than 50 mg/l food simulant, respectively (centre). For individual percentiles, see Table 13.**

In addition, for all values, the percentage of exhaustion or exceedance of C_{max} is specified. For the various materials, the number and the proportion of samples are specified for which the formaldehyde migration exceeds C_{max}. As can be seen from these results, there are large differences in formaldehyde migration from the materials. For articles made from 'conventional' MFR, migration exceeded C_{max} for 12% of the samples, but for 44% of the samples from 'bambooware'. Even if only the 'bambooware' articles with a formaldehyde release <50 mg/l are considered, C_{max} is still exceeded by 27% of the samples. The differences become even more pronounced if the various percentiles for the migration values are regarded. For articles made from 'conventional' MFR, both the maximum value and the 95th percentile of formaldehyde release exceed the C_{max} value. However, the figures for the median, mean and 75th percentile are all significantly lower than C_{max}. For 'bambooware' articles, only the median value for formaldehyde release is (just) lower than C_{max}. The mean, 75th percentile and 95th percentile are all higher or significantly higher than C_{max}. While the maximum value for formaldehyde release from 'conventional' MFR is approximately three times C_{max}, the maximum value and the 95th percentile for the formaldehyde release from 'bambooware' are 87 and 42 times higher than C_{max}, respectively. Even the mean release is approximately eight times higher than C_{max}.

As a result of the daily consumption of foodstuffs with a formaldehyde concentration above the C_{max} of 10.4 mg/l an increased risk to health is possible. These high release values are therefore not acceptable from a health perspective.

Consumers who use 'bambooware' articles that have formaldehyde migration levels above 50 mg/l are consuming foodstuffs whose formaldehyde concentration is much higher than the C_{max} value. Even the average formaldehyde release from 'bambooware' articles in this group (331 mg/l of food simulant) actually exceeds the NOAEL in the animal experiment from which the C_{max} value was derived (260 mg/l). This means that there is no longer a safety margin to this concentration. The 75th and 95th percentile and maximum value for formaldehyde release from 'bambooware' articles in this group significantly exceed this concentration, and approach the concentration at which injurious effects such as inflammatory lesions of the forestomach and stomach have been observed in animal experiments (1,900 mg/l). The BfR therefore advises against the use of these articles as food contact materials (especially in contact with hot liquid foods).

However, C_{max} is also exceeded by the valid SMLT of 15 mg/kg food set out in the Regulation (EU) No 10/2011. The BfR therefore concludes that this SMLT value is too high to ensure that food contact materials do not pose a health risk. In section 3.2.1 of this opinion, the BfR has derived a toxicologically justified release value for formaldehyde from food contact materials that are intended for daily use of 6.0 mg/kg food.

Risk characterisation in relation to the total daily intake of formaldehyde
The BfR has derived a TDI of 0.6 mg/kg body weight/day for formaldehyde (section 3.1.2.2). This value is considered protective of health both for local effects and for potential systemic effects following oral intake.

As shown in Table 1, high amounts of formaldehyde can migrate from some of the food contact materials investigated into foods. The daily consumption of the quantities of food products as described in section 3.1.3.2 (coffee beverages for adults, or milk, dairy products or other non-alcoholic beverages for infants) therefore results in correspondingly high daily intake values. If these intake values are converted with regard to the average body weight of the respective population group, the total daily intake values in mg per kg of body weight are obtained as shown in Table 11 and Table 14. Table 14 also presents these daily intake values in comparison to the TDI of 0.6 mg/kg body weight/day.

Table 14: **Daily formaldehyde exposure calculated from migration data and consumption data, shown in relation to the tolerable daily intake (TDI) value of 0.6 mg/kg body weight/day for adults (body weight = 60 kg) and infants (body weight = 12 kg); values highlighted in red and bold exceed the TDI; q.c. = quantity consumed**

	Formaldehyde intake for adults (19–50 years) as a percentage of TDI (and in mg/kg body weight)		Formaldehyde intake for infants (12–36 months) as a percentage of TDI (and in mg/kg body weight)	
	Normally exposed individuals (median)	Highly exposed individuals (95th percentile)	Normally exposed individuals (median)	Highly exposed individuals (95th percentile)
'Conventional' melamine formaldehyde resin articles				
	6.0% (0.036)	28% (0.17)	59% (0.35)	**223% (1.3)**
'Bambooware' articles with migration <50 mg/l				
	9.2% (0.055)	37% (0.22)	89% (0.54)	**270% (1.6)**
'Bambooware' articles with migration >50 mg/l				
Migration value	**Normal consumers (q.c. = 380 g/day)**	**High consumers (q.c. = 1,200 g/day)**	**High consumers (q.c. = 80 g/kg body weight/day)**	
Median (242 mg/l)	**256% (1.5)**	**808% (4.9)**	**3231 % (19)**	
95th percentile (808 mg/l)	**853% (5.1)**	**2694 % (16)**	**10775 % (65)**	
Maximum value (912 mg/l)	**962% (5.8)**	**3038 % (18)**	**12153 % (73)**	
Article with maximum level of migration allowed (SMLT) of 15 mg/kg of food product	16% (0.095)	50% (0.30)	**200% (1.2)**	

If one considers only the articles made from 'conventional' MFR and the 'bambooware' articles with a formaldehyde migration below 50 mg/l, the resulting daily intake value does not exceed the TDI value either in the case of adults or in the case of normally exposed infants (median). However, for adults formaldehyde exposure through food can already exhaust or even exceed the TDI (see section 3.1.3.5). Accordingly, the BfR considers an intake through food contact materials of 100% of the TDI in this population group as not acceptable from a health point of view. In the opinion of the BfR, the daily formaldehyde intake from 'conventional' MFR and 'bambooware' should therefore not exceed 20% of the TDI. This value is exceeded by the intake for highly exposed adults (95th percentile; intakes of 28% and 37%). For highly exposed infants (95th percentile), the daily intake significantly exceeds the TDI (by up to 170%, see Table 14), both for articles made from 'conventional' MFR and for 'bambooware' articles.

If the TDI of 0.6 mg/kg body weight/day is exceeded for a prolonged period of time, an increased risk to health in the form of malignant changes in the upper sections of the digestive tract (up to and including the stomach) is possible. These high release values are not acceptable from a health perspective.

For consumers who use ‘bambooware’ articles with formaldehyde migration above 50 mg/l, daily intake results that is very much higher than the TDI. Adult normal consumers who use one of these articles with average formaldehyde release (median = 242 mg/l, see Table 1) on a daily basis are taking up formaldehyde at approximately 2.5 times the TDI. High consumers who use one of these articles with a high level of formaldehyde release (95th percentile = 808 mg/l, maximum value = 912 mg/l) are taking up formaldehyde at levels up to 30 times higher than the TDI. This is equivalent to a daily exposure of 16 or 18 mg/kg body weight/day and exceeds the NOAEL from the animal experiment that was used to derive the TDI (15 mg/kg body weight/day). This means that there is no longer a safety margin to this NOAEL. Even though the use of an article with a very high level of formaldehyde release on a daily basis by a high consumer is a highly conservative assumption, these high release values are toxicologically not acceptable. The BfR considers an increased risk to health to be likely from the daily use of an article of this kind. The exposure for an infant resulting from the use of this kind of article is equivalent to 12,000% of the TDI and is so high that it corresponds to 65 or 73 mg/kg body weight/day. This is almost as high as the dose at which adverse health effects such as inflammatory lesions of the forestomach and stomach were observed in the animal study (82 mg/kg body weight/day). The BfR therefore advises against the use of these articles as food contact materials (especially in contact with hot liquid foods).

In the exposure scenarios selected, the TDI can also be significantly exceeded in some cases where the level of formaldehyde release complies with the SMLT of 15 mg/kg food, as set out in Regulation (EU) No 10/2011 (Table 14). The BfR therefore concludes that the SMLT value is too high to ensure that food contact materials do not pose a health risk. In section 3.2.1 of this opinion, the BfR applies the TDI of 0.6 mg/kg body weight/day to derive a release value for formaldehyde from food contact materials that are intended for daily use of 6.0 mg/kg food, which is justified on health grounds.

3.1.4.2 Risk characterisation for melamine release

EFSA (2010) has derived a TDI of 0.2 mg/kg body weight/day for melamine, basing this figure on a study in rats in which the formation of stones in the efferent urinary system was observed (section 3.1.2.4). In the following section, this TDI is contrasted with the exposure values calculated in section 3.1.3.

High levels of melamine can migrate from some of the food contact materials investigated into food (Table 2). The resulting daily intakes do not exceed the TDI either in the case of adults or in the case of normally exposed infants (see Table 15). For highly exposed infants (95th percentile), the daily intake significantly exceeds the TDI (by up to 180%), both for articles made from ‘conventional’ MFR and for ‘bambooware’ articles.

If the TDI of 0.2 mg/kg body weight/day is exceeded for a prolonged period of time, an increased risk to health in the form of damage to the kidneys and the efferent urinary system is possible. These high release values are therefore not acceptable from a health perspective.

Table 15: **Daily melamine exposure calculated from migration data and consumption data, shown in relation to the tolerable daily intake (TDI) of 0.2 mg/kg body weight/day for adults (body weight = 60 kg) and infants; values highlighted in red and bold exceed the TDI**

	Melamine intake for adults (19–50 years) as a percentage of TDI (and in mg/kg body weight/day)		Melamine intake for infants (12–36 months) as a percentage of TDI (and in mg/kg body weight/day)	
	Normally exposed individuals (median)	Highly exposed individuals (95th percentile)	Normally exposed individuals (median)	Highly exposed individuals (95th percentile)
'Conventional' melamine formaldehyde resin articles				
	3.0% (0.006)	17% (0.033)	29% (0.057)	**140% (0.28)**
'Bambooware' articles				
	6.5% (0.013)	35% (0.069)	60% (0.12)	**280% (0.56)**
Article with maximum level of migration allowed (SML) of 2.5 mg/kg of food product	10% (0.02)	30% (0.059)	100% (0.2)	

In the exposure scenarios selected, the TDI is not exceeded as long as the level of melamine release complies with the SML of 2.5 mg/kg food, as set in Regulation (EU) No 10/2011 (Table 15). The BfR concludes that no health risk results from the 100% exhaustion of the TDI for infants, because the exposure scenario has been conservatively selected (95th percentile of quantity consumed) and there is a negligible level of exposure from other sources such as food (see section 3.1.3.5). The BfR therefore concludes that the SML value is suitable to ensure that food contact materials do not pose a health risk. In the exposure scenario for children selected here, melamine release above this SML would lead to the TDI being exceeded. The BfR concludes that this would present a potential risk to health. The melamine release from fillable articles intended for use by children should therefore not exceed the SML of 2.5 mg/kg food. For adults (body weight = 60 kg), the BfR considers a release of melamine of up to 10 mg/kg food as safe (= 0.2 mg/kg body weight/day × 60 kg body weight / 1.2 kg food/day) in terms of the exposure scenario adopted here (95th percentile of daily coffee consumption, 1.200 kg per person/day, see Table 4).

3.2 Other aspects

3.2.1 Derivation of a release value for formaldehyde acceptable from a health perspective

Regulation (EU) No 10/2011 defines a group restriction (total specific migration limit, SMLT) for the release of formaldehyde of 15 mg per kg of food. This SMLT applies for the total of formaldehyde, 1,4-butanediol formal and urotropin calculated as formaldehyde. The scientific basis for this migration limit derivation is not known to the BfR. The BfR has not seen any toxicological justification of the SMLT by perusing the available studies. The value exceeds the maximum tolerable concentration of formaldehyde in foodstuffs (C_{max}) of 10.4 mg/l as derived herein (section 3.1.2) significantly. As Table 14 shows, in the exposure scenario for infants described herein a formaldehyde release of 15 mg/kg food also significantly exceeds (200%) the TDI of 0.6 mg/kg body weight/day as derived in section 3.1.2.2. The–in the opinion of the BfR–toxicologically acceptable formaldehyde intake of 20% of the TDI would also be significantly exceeded (50% of the TDI) by high consumers. Lastly, the 'accepted exposure level' (AEL[6]) of 0.15 mg/kg body weight/day (ECHA, 2017a) derived as part of approving formaldehyde as a biocide (according to Regulation (EU) No 528/2012) would also be considerably exceeded in the exposure scenarios described here. From a health perspective, the SMLT should be considerably lower.

For adults, a body weight of 60 kg (according to Regulation (EU) No 10/2011) is used as the basis for the derivation of a toxicologically acceptable release value. The TDI of 0.6 mg/kg body weight/day therefore corresponds to an acceptable daily oral intake of 36 mg of formaldehyde. According to the cited regulation, a daily consumption of 1 kg food, which was in contact with the respective food contact material, is assumed. Since the daily consumption quantity of coffee beverages for adult high consumers, as determined in section 3.1.3.2, is 1,200 g, as a precautionary measure this higher value is used for calculating a toxicologically acceptable maximum formaldehyde migration. This results in an acceptable migration value of 30 mg formaldehyde/kg food. However, it should be noted that adults also take up relevant quantities of formaldehyde through foods. Depending on the study consulted (see section 3.1.3.5), the TDI can already be exhausted or even exceeded. As a result, food contact materials should contribute only modestly to the daily formaldehyde uptake. Using an allocation factor of 20% would result in a toxicologically acceptable release of 6.0 mg formaldehyde/kg food from food contact materials for adults.

For infants (12–36 months), a body weight of 12 kg (EFSA, 2012) is used as the basis for the derivation of a toxicologically acceptable release value. The TDI of 0.6 mg/kg body weight/day therefore corresponds to an acceptable daily oral intake of 7.2 mg formaldehyde. Assuming a daily consumption of 960 g food that was in contact with the food contact material (see section 3.1.3.2), would result in a toxicologically acceptable migration of 7.5 mg formaldehyde/kg food. The BfR does not consider the application of an allocation factor to be necessary in this age group.

This is for the following reasons:
(1) The assumptions made, namely that a child consumes 960 g of hot-filled liquid food from an MFR article (bowl, mug, etc.), are highly conservative and already incorporate an additional margin of safety.
(2) A conservative approach has also been taken by using the uncertainty factor of 25 to derive the TDI (see section 3.1.2.2). The release value of 6.0 mg/kg food derived from that TDI and considered acceptable for adults also offers adequate protection for (young) children.

The BfR considers a migration limit of 6.0 mg/kg food to be protective of health in terms of both local effects and potential systemic effects within all age groups. This limit also ensures that no formaldehyde release from food contact materials into foodstuffs takes place that exceeds the maximum tolerable formaldehyde concentration (C_{max}) of 10.4 mg/l. From a health perspective, the BfR therefore concludes that the migration of formaldehyde from food contact materials into food should not exceed a value of 6.0 mg/kg food. The BfR considers this value to guarantee an adequate level of protection for all population groups.

3.2.2 MFR and repeated contact with hot liquid foods

The BfR has conducted a long-term test investigating the release of melamine from five 'bambooware' cups and three cups made from 'conventional' MFR. In course of that, 12 successive migration tests on the cups were conducted (3% acetic acid, 2 h, 70 °C ±2 °C over

[6] Defines the external dose up to which exposure to the substance is acceptable in terms of health.

the entire duration of migration). Melamine migration increased in each test, both in cups made from ‘conventional’ MFR and also—at a much higher rate—for ‘bambooware’ cups (Figure 4). This indicates progressive material degradation under the applied test conditions. MFR is a polycondensate. It can be broken down again by reacting with water, resulting in the release of its monomers (melamine and formaldehyde). At room temperature, this reaction does not take place to any significant degree. This reaction is accelerated, however, at higher temperatures and by contact with liquid media (such as coffee, fruit juices or tea). As a result of this, articles manufactured from MFR are essentially unsuitable for contact with hot liquid foodstuffs, since the polymer is not stable under these conditions. In addition, in the case of MFR starting monomers with toxicological relevance are produced.

Formaldehyde release does not increase throughout the 12 migration tests (Figure 5). Due to the chemical conditions present when manufacturing MFR, a surplus of formaldehyde is used compared with melamine. Melamine is therefore always bound covalently in the resulting polymer and can be released almost exclusively by degradation (hydrolysis) of these covalent bonds. The hydrolysis of the polymer leads to an increase in its surface area, which is also visible at the macroscopic scale: the surface appears matt and roughened. This increased surface area leads to an increase in the area that can be targeted by hydrolysis, and should therefore accelerate the rate of release for both melamine and formaldehyde. It is unclear why the release measured for formaldehyde does not rise as well. Further investigation of this matter is required.

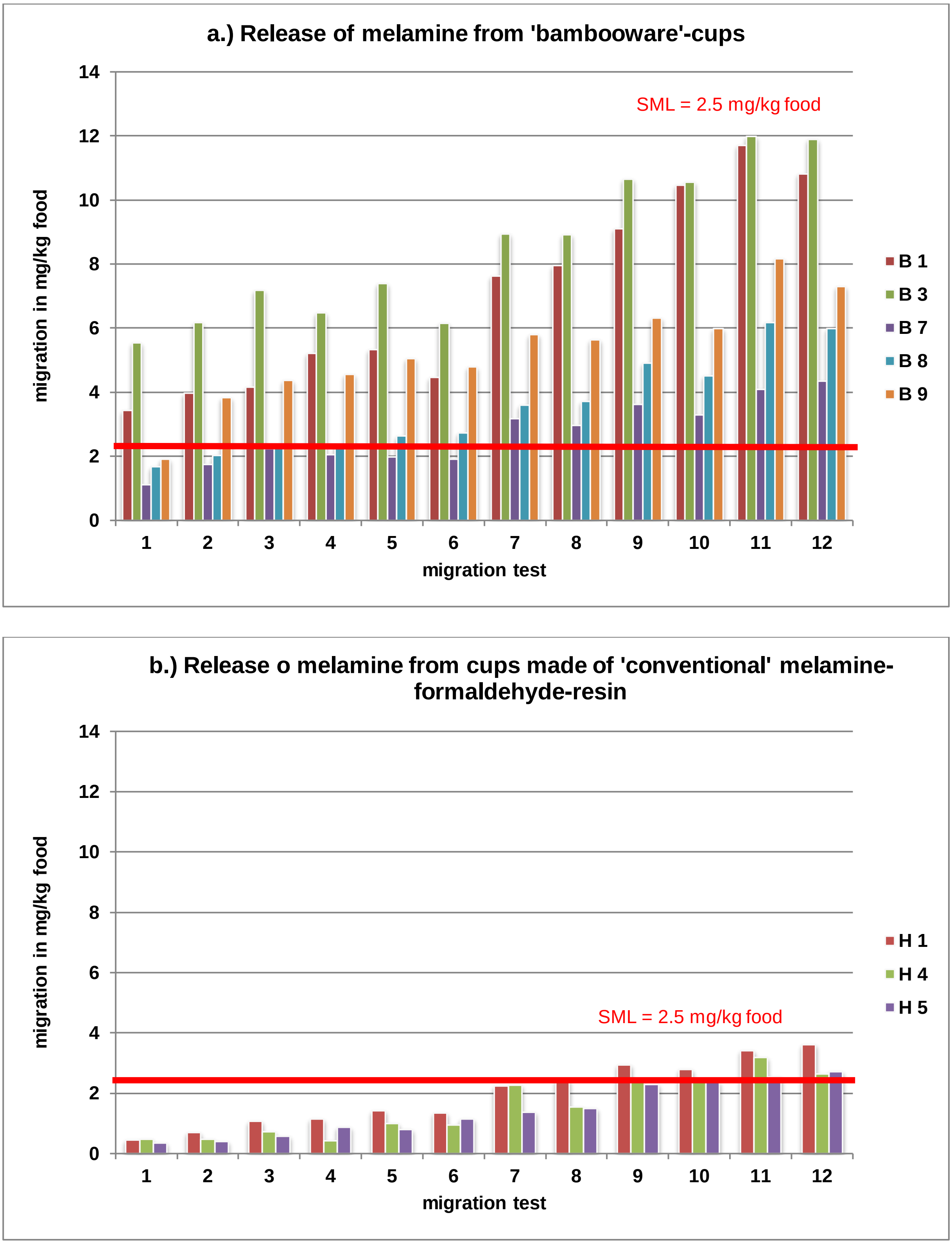
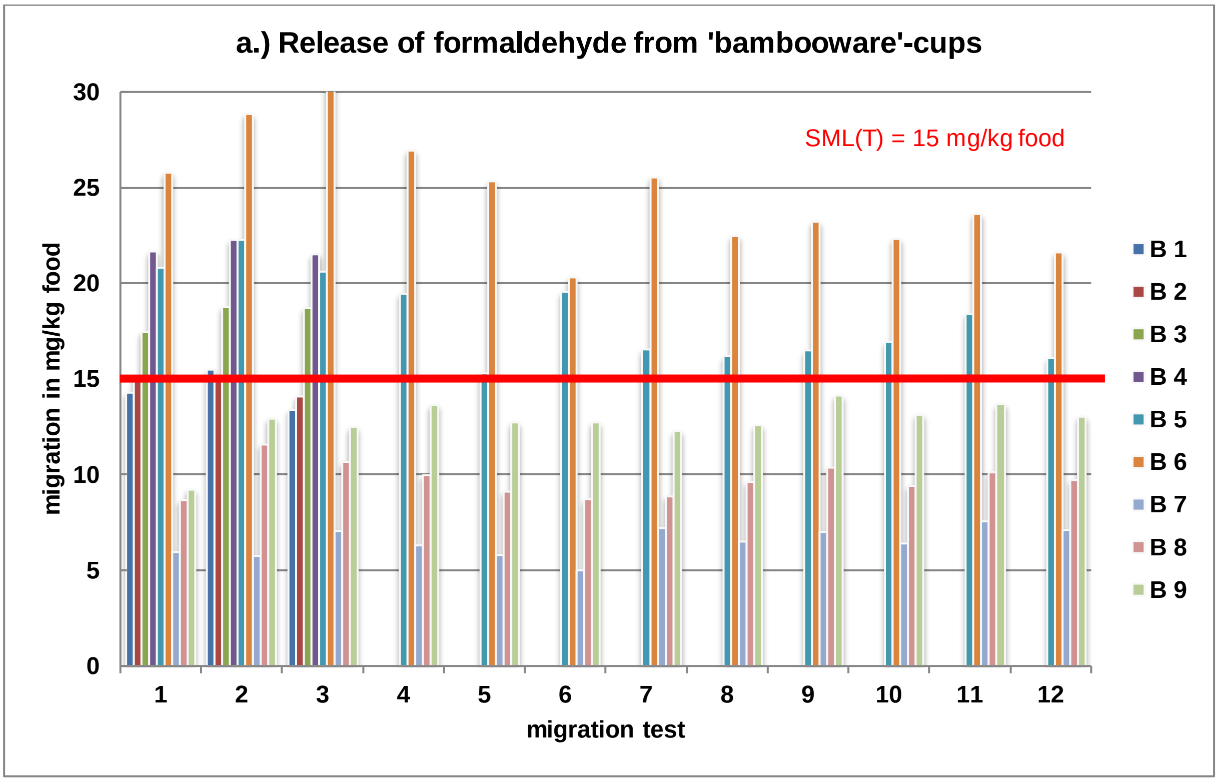


Figure 4: Results of tests on the migration of melamine from 'bambooware' drinking cups (a) and 'conventional' melamine formaldehyde resin cups (b). Migration conditions: 2 h at 70 °C, 3% acetic acid solution; B = 'bambooware' cups, H = 'conventional' MFR cups



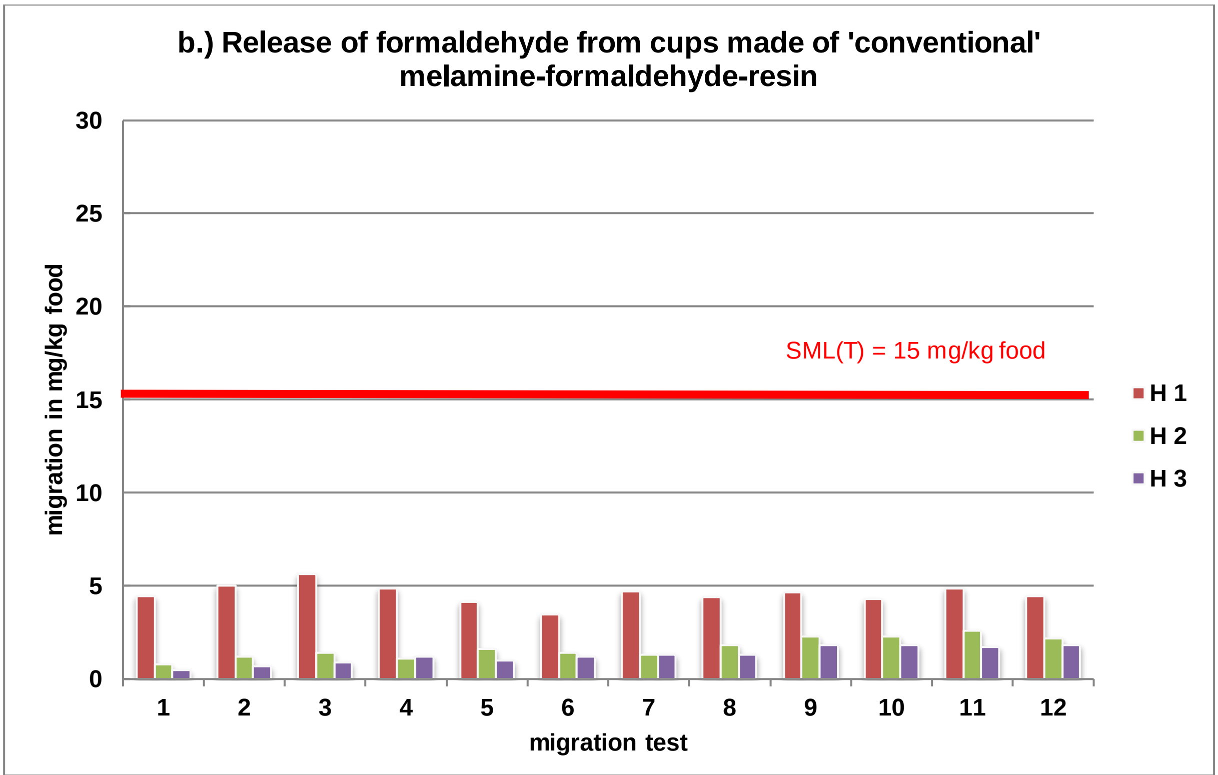


Figure 5: **Results of tests on the migration of formaldehyde from 'bambooware' drinking cups (a) and 'conventional' melamine formaldehyde resin cups (b). Migration conditions: 2 h at 70 °C, 3% acetic acid solution; B = 'bambooware' cups, H = 'conventional' MFR cups**

3.2.3 Uncertainty analysis

3.2.3.1 Uncertainties in the toxicological analysis

Formaldehyde
As regards local effects following chronic oral exposure to formaldehyde, empirical values are lacking that would permit a more detailed estimate to be made of suitable uncertainty factors when extrapolating animal study results to humans. Accordingly, the BfR has applied the factors from concepts used to evaluate systemic effects following oral chronic intake of a substance as well as for the evaluation of local effects (ECHA, 2012a; ECHA, 2017b). This approach is intended to ensure that both the formaldehyde concentration in a consumed foodstuff and the overall formaldehyde uptake are taken into account for the risk assessment. There is nonetheless a certain degree of uncertainty as to whether the standard uncertainty factors applied are adequate for deriving a health-based guidance value from animal study data.

Whether or not formaldehyde can trigger cancer in humans following oral ingestion has not been conclusively clarified yet. Inflammatory changes in the forestomach and stomach occurred in animal studies, but no tumours were found. In any case, the effect is based on a threshold mechanism. Hence, the derivation of tolerable concentrations and intake values is appropriate.

Melamine
The TDI of 0.2 mg melamine/kg body weight/day was derived by EFSA (2010) based on a study in rats (NTP, 1983) in which the formation of stones in the efferent urinary system was observed, particularly in male animals. Since the formation of these stones is heavily dependent on pH and uric acid concentration, and since rats and humans differ considerably in this regard (Dominguez-Estevez et al., 2010), there is some uncertainty as to whether the uncertainty factor selected for the derivation of the TDI adequately reflects the stated differences (see section 3.1.2.4). Modelling based on human data has produced a $BMDL_{10}$ of 0.74 mg/kg body weight/day (Li et al., 2009), which is considerably higher than the TDI. Nevertheless, uncertainties present in the exposure assessment of the cited study as well as other epidemiological studies (Li et al., 2009; Li et al., 2019; Liu et al., 2011; Sathyanarayana et al., 2019) indicate that health impairments could potentially also occur even below the TDI. Since the studies named exhibit a series of uncertainties, such as the inadequate determination of melamine exposure, unsuitable control groups or insufficient statistical certainty due to subject groups being too small, further data will be required to clarify this issue.

Further research is also required with regard to the potential reproduction toxicity of melamine. Multiple studies have provided indications of adverse effects—such as damage to the testes and reduced sperm count—and some of these studies were able to show that these adverse effects occurred at comparatively low doses. Whether or not melamine does indeed induce toxicity to the reproduction system at doses below the $BMDL_{10}$ applied for the derivation of the TDI could be answered by the OECD guidance study currently being conducted (ECHA, 2016). In addition, the question of the transferability of these results to humans should be addressed by mechanistic investigations.

3.2.3.2 Uncertainties in the exposure assessment

As is accustomed for food contact materials (Regulation (EU) No 10/2011), the formaldehyde release values determined by migration tests in food simulants were regarded as content in foods. In comparable investigations with melamine the BfR was able to demonstrate that this approach under the same conditions (time, temperature) for coffee beverages does not lead to overestimation of actual content values (Bradley et al., 2010). However, since migration tests are intended to represent the 'worst-case' scenario, the actual content in food in real use may be lower from case to case. The BfR has no information as to whether the 366 samples considered here accurately represent the kinds of fillable MFR articles available on the market in Germany.

As regards the samples with formaldehyde migration exceeding 50 mg/l, there is uncertainty as to whether all these articles are actually made from MFR (see section 5.3 for details). However, this issue is not relevant for a health-based assessment of the levels of formaldehyde and melamine released from these articles.

The results of the German NVS II survey for coffee beverages (for all consumers of these drinks), as summarised in the EFSA Consumption Database, have been used as consumption data. The data were incorporated into the exposure assessment as a log-normal distribution. However, no data is available as to whether the quantities of coffee beverages consumed by users of reusable *coffee-to-go* cups made from MFR also correspond to this log-normal distribution. For example, it is conceivable that the group of users of such cups consists to a larger proportion of high consumers or that they use several cups whose release levels differ from one another.

3.3 Recommendations and measures

Melamine and formaldehyde release from articles made from melamine formaldehyde resin (MFR) can be too high from a toxicological perspective when they come into contact with hot liquid food. For 12% of the articles tested made from 'conventional' MFR and 44% of the 'bambooware' articles tested, formaldehyde release exceeded the maximum tolerable formaldehyde concentration of 10.4 mg/l.

Similarly, for 15% of the articles tested made from 'conventional' MFR and for 35% of the 'bambooware' articles tested, melamine release was higher than the SML of 2.5 mg/kg food as defined in Regulation (EU) No 10/2011. In the exposure scenario chosen herein, a melamine release of 2.5 mg/kg food corresponds to a daily exposure of 100% of the TDI for infants. A higher melamine release would exceed the TDI by a corresponding amount. The release of melamine from fillable articles intended for use by children should therefore—in accordance with the exposure scenario chosen herein—not exceed the SML of 2.5 mg/kg food. For adults (body weight = 60 kg), the BfR considers a release of melamine of up to 10 mg/kg food as safe in terms of the exposure scenario adopted here.

As a consequence, the BfR considers an increased health risk for consumers to be possible for some articles or—in the case of 'bambooware' articles with a very high formaldehyde release—to be likely. Hence, these articles should not be used in contact with hot liquid foods. In this context, the BfR appreciates the continuous routine testing of melamine and formaldehyde release from food contact materials made from MFR as performed by the German food monitoring authorities. This also and especially applies for MFR using alternative fillers such as bamboo fibres, rice husks and others. For such articles, the German food monitoring authorities also report cases of consumer deception if these products are advertised as being 'environmentally friendly', 'made from renewable materials' or 'biodegradable', and in circumstances where the fact that the material is actually a plastic is not mentioned or in some way concealed (CVUA, 2017). The BfR believes more work needs to be done on raising consumer awareness about this issue, and welcomes initiatives by the German food monitoring authorities to provide information about this topic on their websites, for example.

In the opinion of the BfR, the current total specific migration limit (SMLT) for formaldehyde of 15 mg/kg food defined in Regulation (EU) No 10/2011 does not offer consumers an adequate level of protection. The BfR concludes that an SMLT of 6.0 mg formaldehyde/kg food would be an appropriate value to protect consumer health.

In addition, the steadily increasing melamine release during consecutive tests (12 successive migration tests) indicates that articles made from MFR are not stable under the migration conditions as selected (2 h, 70 °C, 3% acetic acid), which is very likely to be the result of the successive degradation of the polymer. As a result, articles made from MFR should be considered as unsuitable for use in contact with hot liquid foods and should therefore be utilised at low temperatures only (such as room temperature).

In 2011, the BfR published an opinion (BfR, 2011) showing that, as a general rule, very large quantities of formaldehyde and melamine migrate from MFR tableware at temperatures above 70 °C, and this could therefore represent a health risk. Accordingly, articles made from MFR should not be used to heat food in microwave ovens. Consumers should always follow instructions provided by the manufacturer of the respective MFR article.

Work should be completed with international experts on devising a coherent approach to the assessment of the health risks that arise from exposure to substances that lead exclusively to local adverse effects following their chronic oral intake.

Further information on the subject from the BfR website

BfR publications on the release of melamine and formaldehyde from tableware and kitchen utensils

https://www.bfr.bund.de/en/a-z_index/melamine-130058.html

BfR "Opinions app"

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5. Annex

5.1 Updated benchmark dose modelling from a subchronic study in rats(NTP, 1983) that is used to derive the TDI

The underlying data are presented in Table 16. The calculation of the doses based on melamine contents in feed as well as the individual quantities consumed and animal subject body weights has been taken from EFSA (2010).

Table 16: Data from a subchronic study in Fischer rats (NTP, 1983); doses were calculated from feed intake, melamine content in the feed and animal body weight (EFSA, 2010); male animal subjects.

Dose in mg/kg body weight/day	Number of animals with bladder stones	Total no. of animals
0	1	10
73	2	10
144	5	10
292	7	10
576	9	10
1221	9	9

The results are presented in Table 18 and Table 17, and the modelled curves are shown in Figure 6. When the same models are used, the results are in agreement with those from EFSA (2010). Today, however, many more models are available. Another evaluation criterion, the *Akaike information criterion* (AIC), has also become established for assessing model quality, and placing a bound on the parameter for model slope, as was typical at the time, is now no longer permitted according to recent EFSA Guidance (EFSA, 2017). The selection of a suitable $BMDL_{10}$ now also uses a different approach to that from 2010. According to the current Guidance, the results of all models should be weighted in order to obtain an average $BMDL_{10}$ (*model averaging*), while EFSA (2010) has selected the lowest BMDL from all of the models weighted according to certain criteria. This makes direct comparisons between results very difficult. The results of the *model averaging* are shown in Table 17. The calculated $BMDL_{10}$ of 16 mg/kg body weight/day is virtually identical to the value obtained by EFSA (2010) of 19 mg/kg body weight/day.

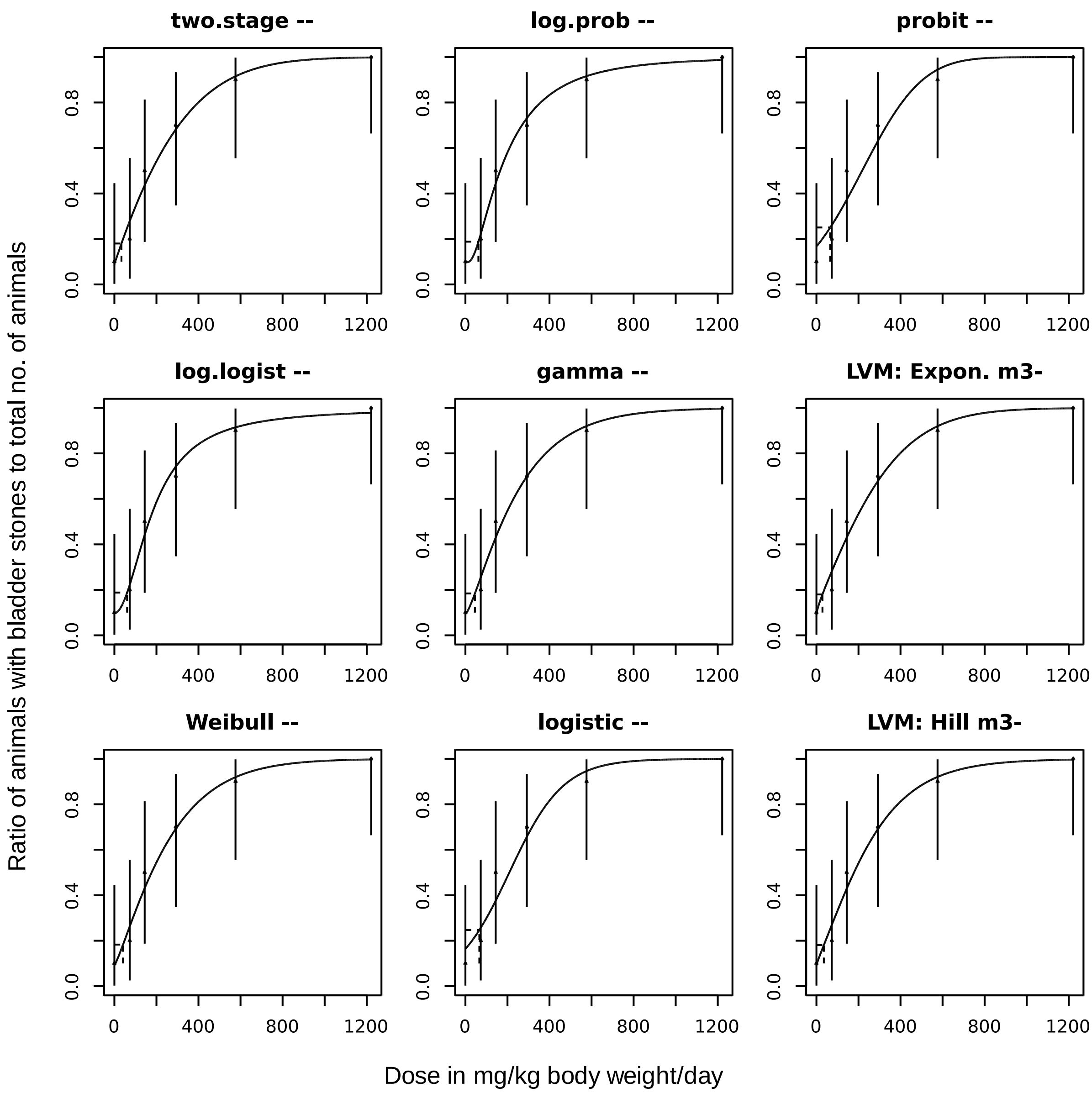

Figure 6: Results of modelling the data of a subchronic study in Fischer rats (NTP, 1983)

Table 17: Weighting factors for the individual models and results from model averaging, $BMDL/U_{10}$ = benchmark dose lower/upper confidence limit for an additional 10% risk

Model	two.stage	log.logist	Weibull	log.prob	gamma	logistic	probit	EXP	HILL
Weighting factor	0.1	0.09	0.1	0.1	0.1	0.16	0.15	0.09	0.1

Calculated parameters	$BMDL_{10}$	$BMDU_{10}$
Value in mg/kg body weight/day	**16**	**148**

Table 18: **Results of modelling the data of a subchronic study in Fischer rats (NTP, 1983) in mg/kg body weight/day, AIC = Akaike information criterion, $BMDL/U_{10}$ = benchmark dose lower/upper confidence limit for an additional 10% risk, BMD_{10} = benchmark dose for an additional 10% risk**

Model	AIC	Model accepted	$BMDL_{10}$	$BMDU_{10}$	BMD_{10}
null	82.96		**n/a**	n/a	n/a
full	61.10		**n/a**	n/a	n/a
two.stage	55.68	Yes	**19.1**	124	33.7
log.logist	55.76	Yes	**19.0**	147	60.7
Weibull	55.60	Yes	**8.22**	123	41.1
log.prob	55.56	Yes	**20.6**	143	61.9
gamma	55.58	Yes	**5.32**	136	45.3
logistic	54.68	Yes	**45.6**	96.6	66.3
probit	54.86	Yes	**46.8**	92.7	65.6
LVM: Expon. m3-	55.76	Yes	**3.98**	109	28.7
LVM: Hill m3-	55.68	Yes	**6.25**	116	35.4

5.2 Updated benchmark dose modelling from a study in Chinese infants (Li et al., 2009) who were fed with follow-on formula contaminated with melamine

The underlying data are presented in Table 19. The exposure in each case was calculated from the melamine content in the follow-on formula, the individual quantities consumed as reported by the parents and the body weights of the children at the time of the investigation (Li et al., 2009).

Table 19: **Data from a study in Chinese infants (Li et al., 2009); exposure values were calculated with reference to the body weight of the children at the time of the investigation.**

Exposure in mg/kg body weight/day	No. of children with nephrolithiasis	Total no. of children
0.0	115	3062
0.1	98	1334
0.3	59	542
0.6	76	590
1.2	58	340
2.4	37	235
4.8	25	182
9.6	54	305
19.2	81	342
38.4	64	202
76.8	16	47

The calculation results are presented in Table 20 and Table 21, and the modelled curves are shown in Figure 7. When the same models are used, the results are in agreement with those from EFSA (2010). Today, however, many more models are available. Another evaluation criterion, the *Akaike information criterion* (AIC), has also become established for assessing model quality, and placing a bound on the parameter for model slope, as was typical at the time, is now no longer permitted according to recent EFSA Guidance (EFSA, 2017). The selection of a suitable $BMDL_{10}$ now also uses a different approach to that from 2010. According to the current Guidance, the results of all models should be weighted in order to obtain an average $BMDL_{10}$ (*model averaging*), while EFSA (2010) has selected the lowest BMDL from all of the models weighted according to certain criteria. This makes direct comparisons between results very difficult. The results of the *model averaging* are shown in Table 21. The calculated $BMDL_{10}$ of 0.74 mg/kg body weight/day is identical to the value obtained by EFSA (2010) of 0.74 mg/kg body weight/day.

Table 20: Results of modelling the data from a study in Chinese infants (Li et al., 2009) in mg/kg body weight/day, AIC = Akaike information criterion, $BMDL/U_{10}$ = benchmark dose lower/upper confidence limit for an additional 10% risk, BMD_{10} = benchmark dose for an additional 10% risk, non-accepted models with fit to the data that is too poor (AIC > lowest AIC +2)

Model	AIC	Model accepted	$BMDL_{10}$	$BMDU_{10}$	BMD_{10}
null	4514.66		n/a	n/a	n/a
full	4161.84		n/a	n/a	n/a
two.stage	4286.58	No	n/a	n/a	11.0
log.logist	4158.24	Yes	0.792	1.77	1.19
Weibull	4158.24	Yes	0.811	1.84	1.23
log.prob	4157.92	Yes	0.741	1.60	1.09
gamma	4158.26	Yes	0.838	1.91	1.28
logistic	4343.34	No	n/a	n/a	22.0
probit	4333.92	No	n/a	n/a	20.2
LVM: Expon. m3-	4160.96	No	n/a	n/a	1.23
LVM: Hill m3-	4163.36	No	n/a	n/a	1.95

Table 21: Weighting factors for the individual models and results from model averaging, $BMDL/U_{10}$ = benchmark dose lower/upper confidence limit for an additional 10% risk

Model	two.stage	log.logist	Weibull	log.prob	gamma	logistic	probit	EXP	HILL
Weighting factor	0	0.22	0.22	0.26	0.22	0	0	0.06	0.02

Calculated parameters	$BMDL_{10}$	$BMDU_{10}$
Value in mg/kg body weight/day	**0.74**	**1.79**

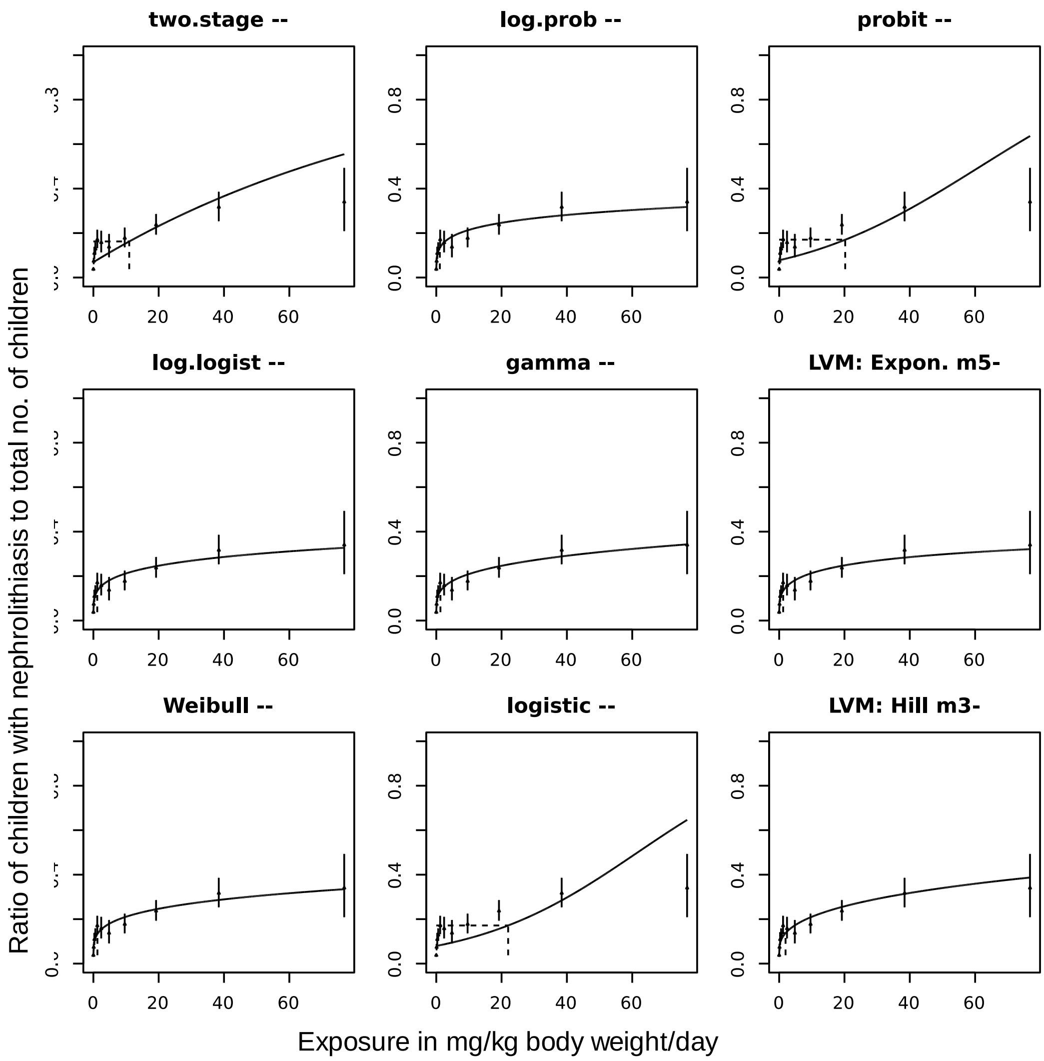

Figure 7: **Results of modelling the data from a study in Chinese infants (Li et al., 2009)**

5.3 Figures for estimating the daily levels of formaldehyde intake

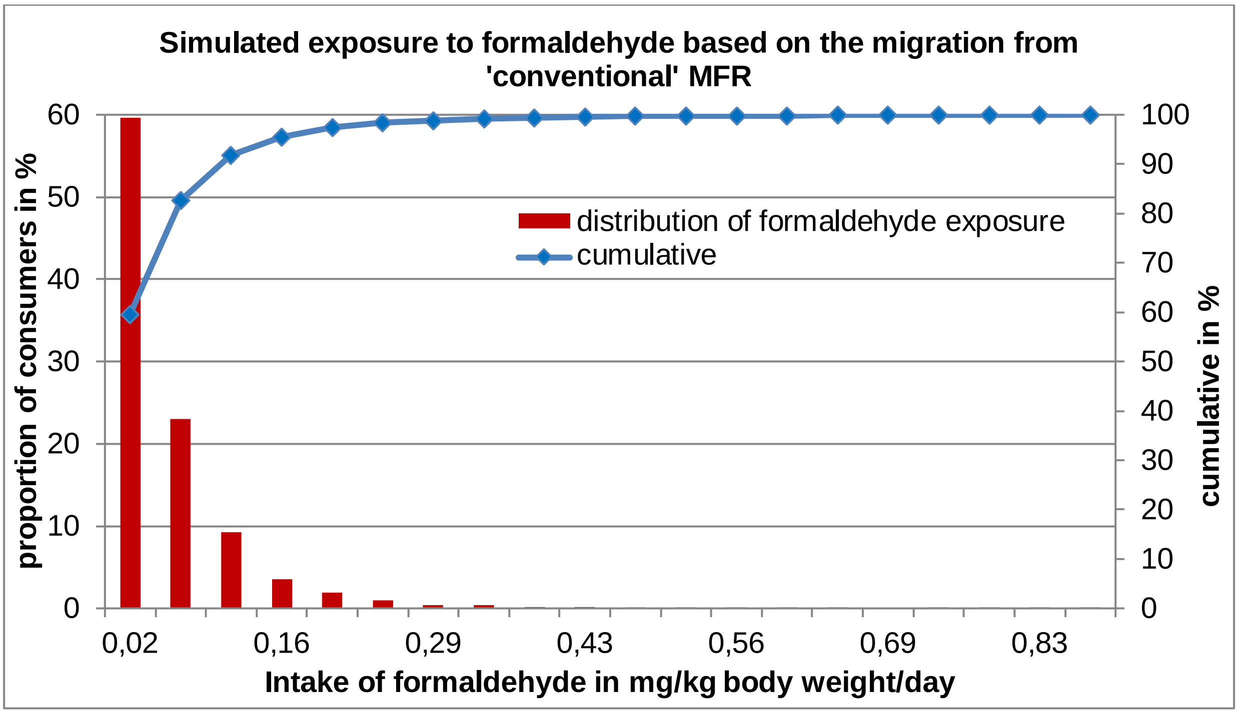

Figure 8: Daily formaldehyde intake, calculated using a Monte Carlo simulation and resulting from the formaldehyde release from fillable articles (e.g. cups) made from 'conventional' melamine formaldehyde resin for adult consumers (19–50 years)

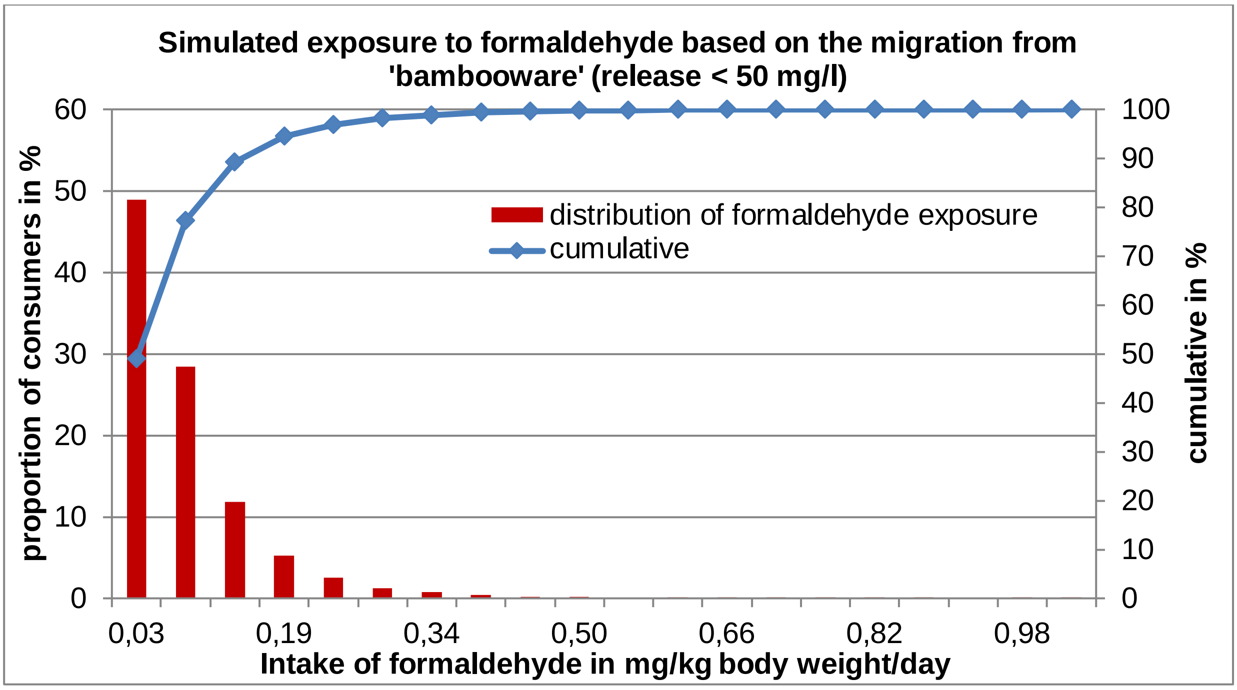

Figure 9: Daily formaldehyde intake, calculated using a Monte Carlo simulation and resulting from the formaldehyde release from fillable 'bambooware' articles (e.g. cups) for adult consumers (19–50 years); only migration data <50 mg/l used

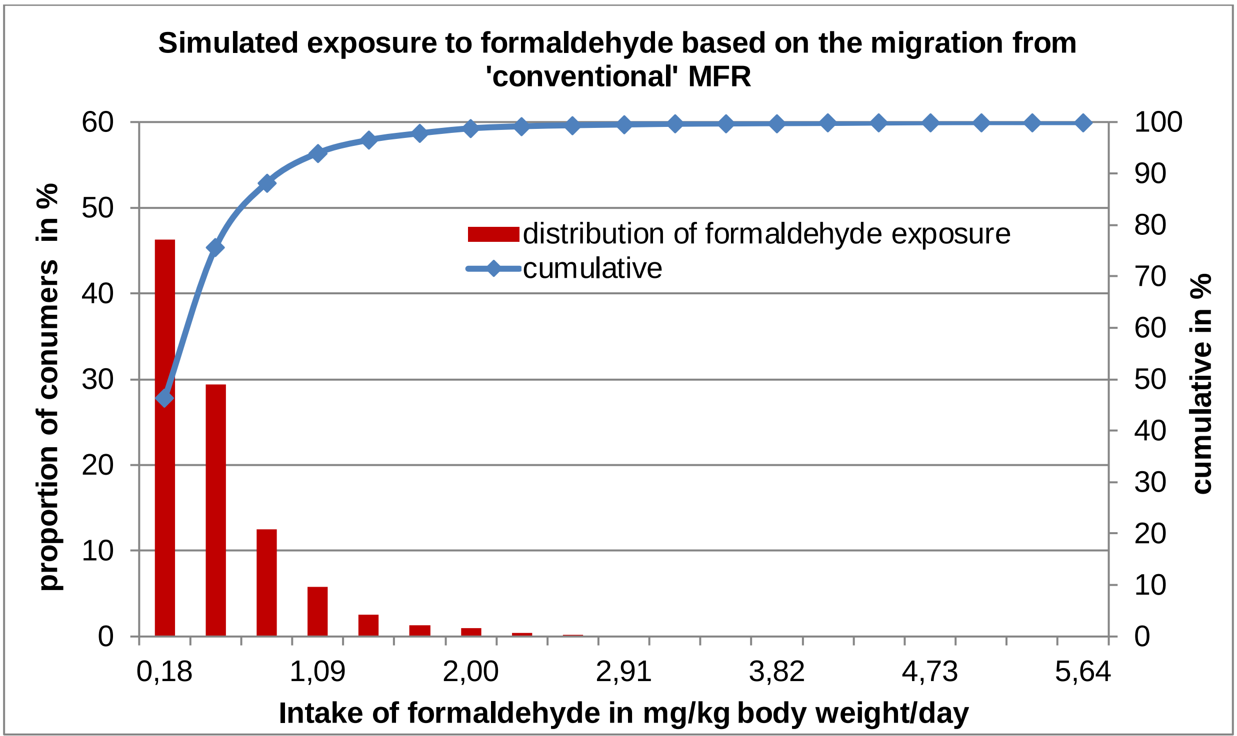

Figure 10: Daily formaldehyde intake, calculated using a Monte Carlo simulation and resulting from the formaldehyde release from fillable articles (e.g. cups) made from 'conventional' melamine formaldehyde resin for infants (12–36 months)

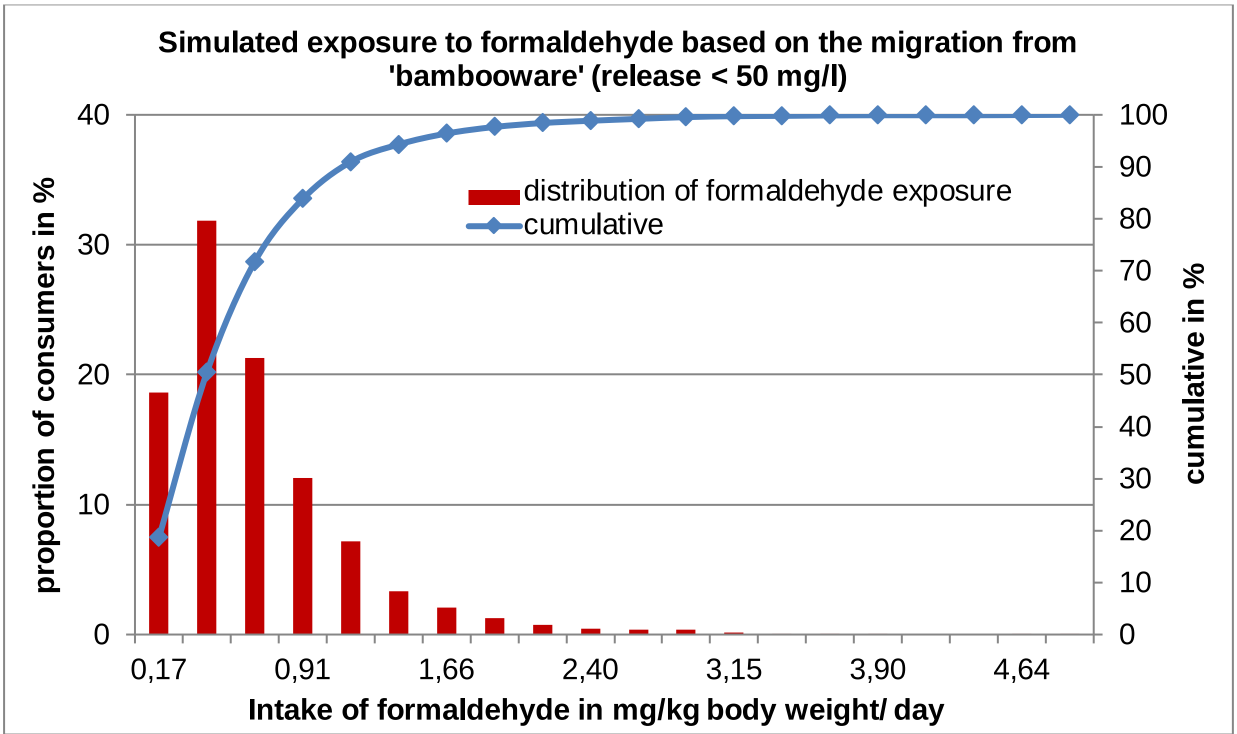

Figure 11: Daily formaldehyde intake, calculated using a Monte Carlo simulation and resulting from the formaldehyde release from fillable 'bambooware' articles (e.g. cups) for infants (12–36 months); only migration data <50 mg/l used

5.4 Figures for estimating the daily levels of melamine intake

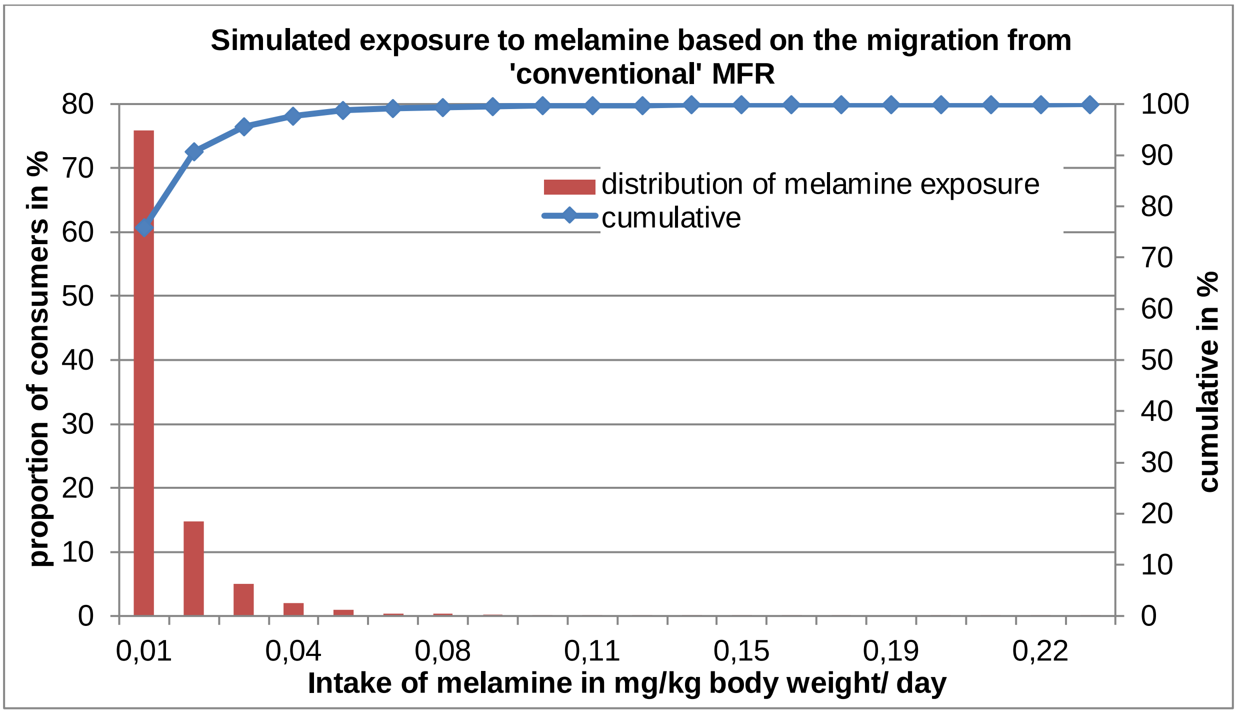

Figure 12: Daily melamine intake, calculated using a Monte Carlo simulation and resulting from the melamine release from fillable articles (e.g. cups) made from 'conventional' melamine formaldehyde resin for adult consumers (19–50 years)

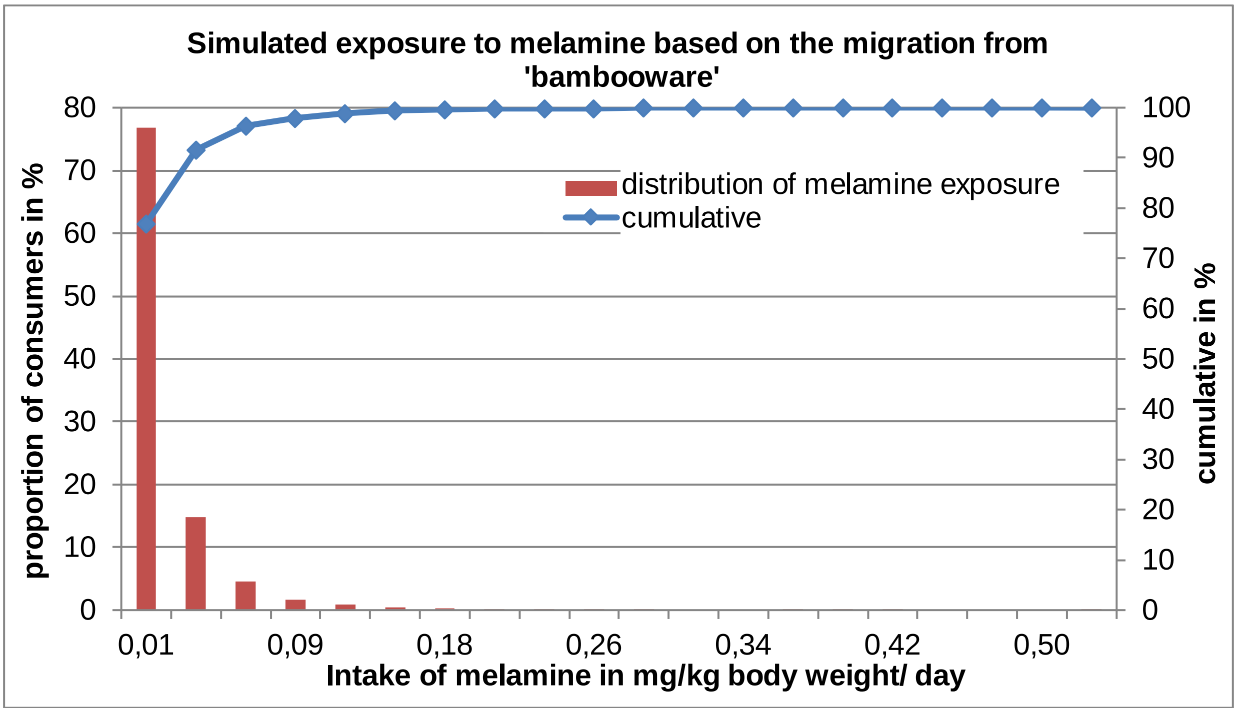

Figure 13: Daily melamine intake, calculated using a Monte Carlo simulation and resulting from the melamine release from fillable 'bambooware' articles (e.g. cups) for adult consumers (19–50 years)

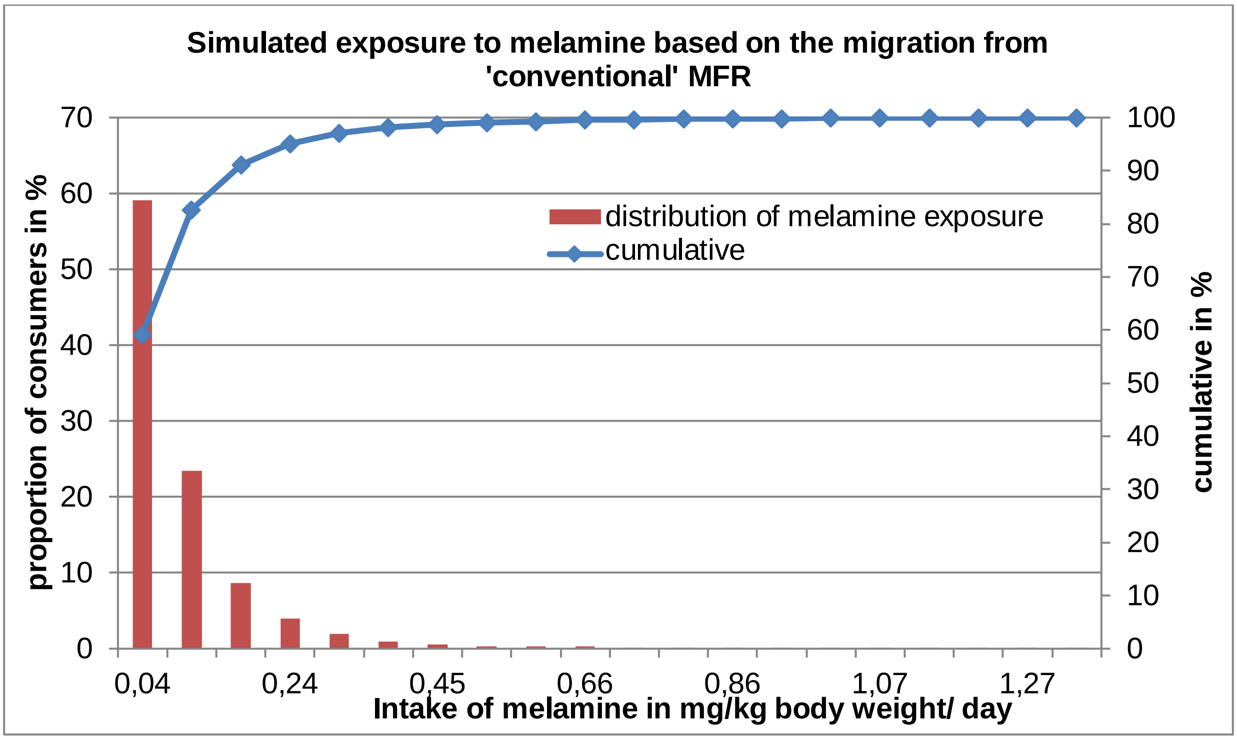

Figure 14: Daily melamine intake, calculated using a Monte Carlo simulation and resulting from the melamine release from fillable articles (e.g. cups) made from 'conventional' melamine formaldehyde resin for infants (12–36 months)

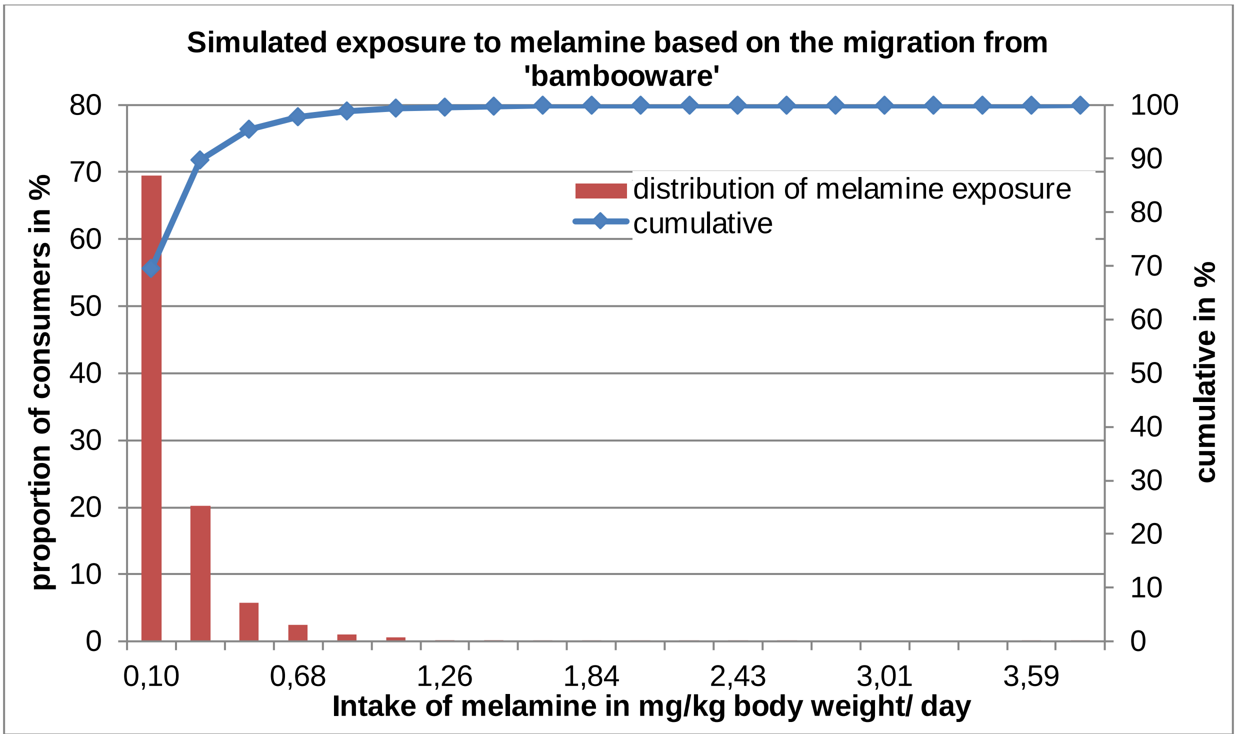

Figure 15: Daily melamine intake, calculated using a Monte Carlo simulation and resulting from the melamine release from fillable 'bambooware' articles (e.g. cups) for infants (12–36 months)

5.5 Identification of material differences by using the correlation between melamine and formaldehyde release from one and the same object

By utilising the objects that were tested both for their release of melamine and of formaldehyde, the BfR has investigated whether these release values exhibit a similar relation to one another. This would indicate strong similarities between the materials. In this context, there is also the question as to whether there are differences between ‘conventional’ MFR and ‘bambooware’. The BfR identified 87 samples of ‘conventional’ MFR and 139 ‘bambooware’ samples for which both parameters were investigated. The results are presented in Figure 16, Figure 17 and Figure 18. As can be seen, objects made from ‘conventional’ MFR and ‘bambooware’ articles with formaldehyde migration below 50 mg/l do not differ significantly from one another, and that for both there is correlation with the corresponding melamine release (Figure 17).

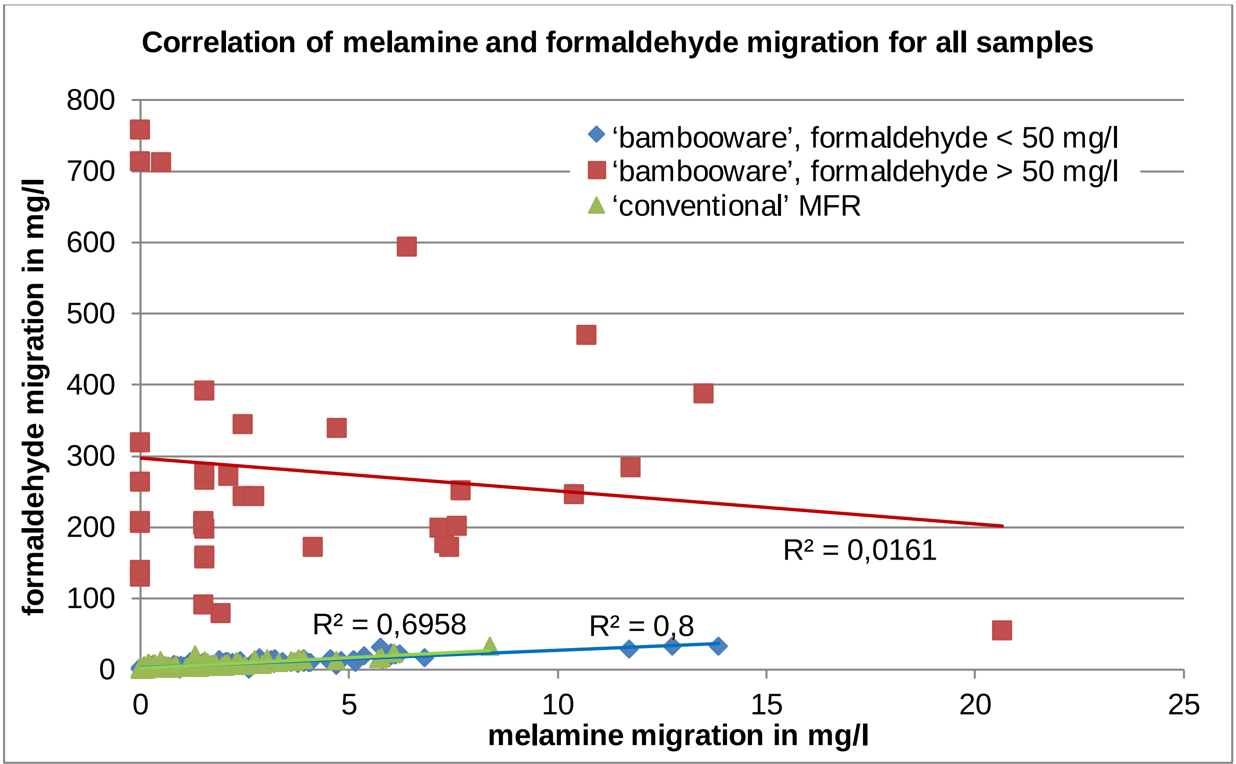

Figure 16: **Migration values for melamine (x-axis) plotted against the migration values for formaldehyde (y-axis) from the same articles. The graph shows all articles for which both migration results were available. The respective coefficient of determination for the correlation (R^2) is also given.**

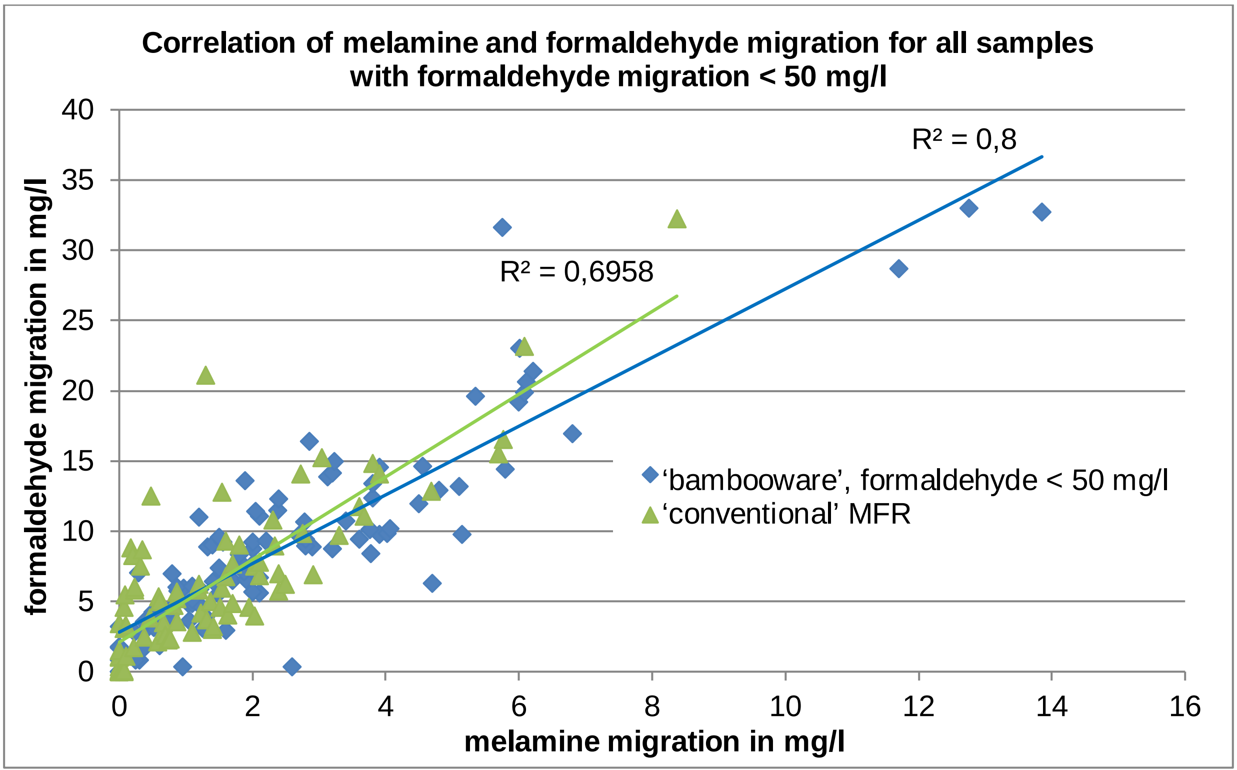

Figure 17: **Migration values for melamine (x-axis) plotted against the migration values for formaldehyde (y-axis) from the same articles. The graph shows all articles with formaldehyde migration levels <50 mg/l for which both migration results were available. The respective coefficient of determination for the correlation (R^2) is also given.**

For 'bambooware' articles with formaldehyde release above 50 mg/l, no correlation with the corresponding melamine release (Figure 18) is observed, nor do these articles (with the exception of one sample) fit to the series of the other articles (Figure 16). For some of these samples, only a very low melamine release was detected (or none at all) although formaldehyde release was very high at the same time. These results indicate that the material from which the articles with formaldehyde release above 50 mg/l are made differs from the material used to make the other articles. Possibly, this material is not in fact (pure) MFR but contains other components such as urea or phenol. However, there is no analytical proof of this. However, the presence of melamine urea formaldehyde resin would explain the differences in the migration behaviour and the high level of formaldehyde release in particular (Mannoni et al., 2017; Poovarodom et al., 2011).

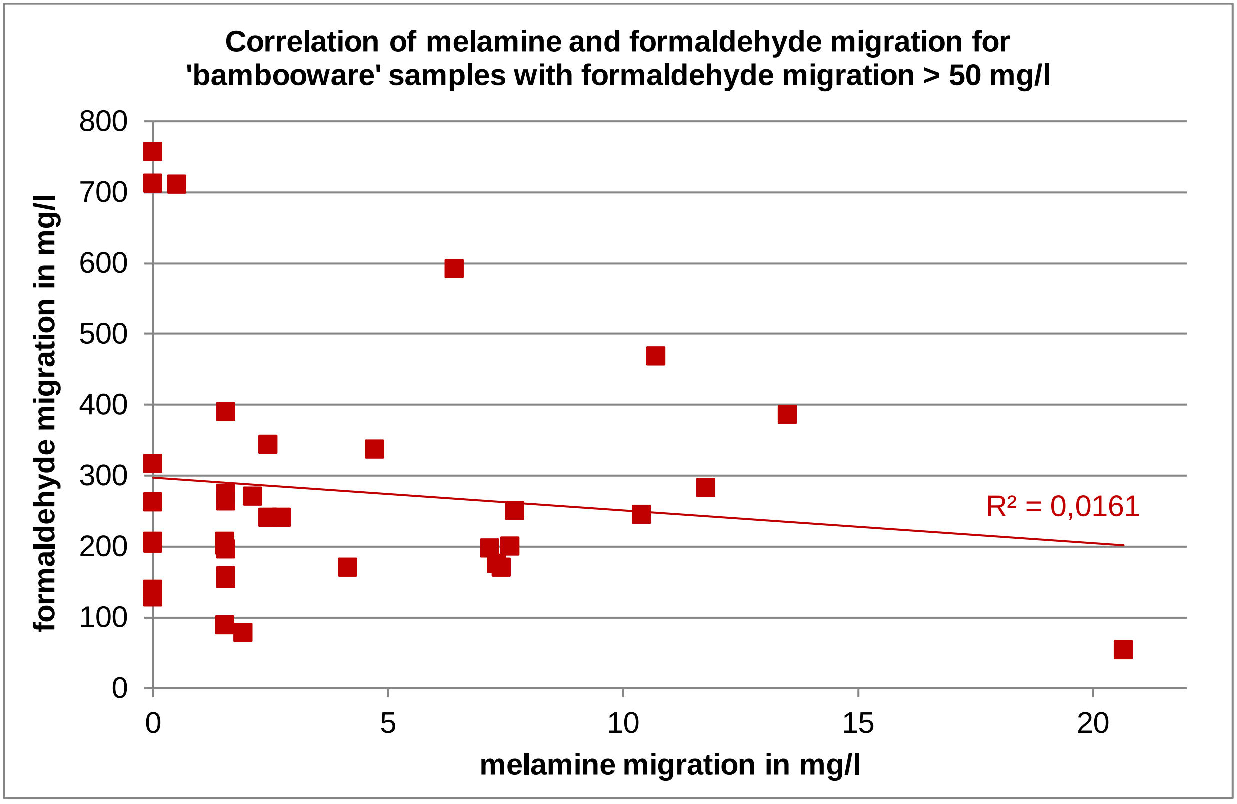

Figure 18: Migration values for melamine (x-axis) plotted against the migration values for formaldehyde (y-axis) from the same articles. The graph shows all articles with formaldehyde migration levels >50 mg/l for which both migration results were available ('bambooware' samples only). The respective coefficient of determination for the correlation (R^2) is also given.