

Primary aromatic amines from printed food contact materials such as napkins or bakery bags

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Some substances in the group of primary aromatic amines (PAAs) are carcinogenic. PAAs can, for example, occur as contaminants in colour pigments. They can pose a health risk in colour-printed paper napkins and bakery bags as well as other food contact materials if they migrate into food. The Federal Institute for Risk Assessment (BfR) has assessed whether the current limit values for the migration of these substances into food provide adequate protection.

Based on its model calculations, the BfR comes to the conclusion that it is advisable to review the limit for the migration of PAAs (not detectable in total with a detection limit of 0.01 milligrams (mg) per kilogram (kg) of food or food simulant) in the case of PAAs classified as carcinogenic. The contact of consumers with these substances should be minimised. The BfR believes that the ALARA principle should apply for these PAAs; in other words, it should be ensured that their occurrence in materials that come into contact with food is as low as is technically possible. The migration of these PAAs into food or food simulants should not be detectable with an analytical detection limit of 0.002 milligrams (mg) per kilogram (kg) of food or food simulant. The BfR recommends that only colour pigments be used that do not contain any carcinogenic aromatic amine component.

1 Subject of the assessment

Following inquiries from various federal laender, the Federal Institute for Risk Assessment (BfR) was requested by the Federal Ministry of Food, Agriculture and Consumer Protection (renamed the Federal Ministry of Food and Agriculture in March 2014) to state its opinion on the:

- toxicological assessment of the migration of primary aromatic amines (PAAs) from food contact materials made of paper (in this case napkins and bakery bags)
- applicability of a migration limit for PAAs of 4 µg/l in cold water extract, derived from the limit of 0.1 mg per kg of paper for PAAs classified as carcinogenic and/or mutagenic defined in the Council of Europe Resolution on paper and board materials (ResAP (2002) 1) for recycled fibres
- application of this limit solely to PAAs of categories 1A and 1B according to the CLP Regulation¹ (EC) 1272/2008 or also to PAAs of category 2, respectively on the maximum amount of substance that is considered acceptable for PAAs of category 1 and 2 for release from napkins into the cold water extract

¹ CLP Regulation (Regulation on Classification, Labelling and Packaging of Substances and Mixtures)

2 Assessment

From a toxicological point of view, PAAs are a heterogeneous class of substances. Some PAAs such as 2-naphthylamine are known to be human carcinogens (CLP classification 1A). Based on the result of animal experiments, various PAAs are seen as being carcinogenic in humans (CLP classification 1B). These include o-anisidine and o-toluidine. N,N-dimethylaniline, on the other hand, is a substance that gives cause for concern due to its suspected carcinogenic effect in humans (CLP classification 2). Then there are numerous PAAs that do not give any cause for concern with regard to carcinogenic effects, such as 2,5-diaminotoluene.

Different PAAs can occur in materials that come into contact with food. In napkins and bakery bags, the main source of PAAs is in the form of contaminants in the azo pigments used in the printing inks. Assessments exist for some PAAs, and a specific migration limit has been stipulated on the basis of these assessments.

In the case of plastics that come into contact with food, Regulation (EU) 10/2011 states that PAAs that have not been specifically assessed may not migrate into food or food simulants in a detectable amount. The detection limit is 0.01 mg/kg and applies to the sum of released PAAs.

Using the example of **o-anisidine**, the BfR has investigated whether this limit is sufficient from the point of view of risk assessment. This investigation was based on an EU Risk Assessment Report on o-anisidine compiled by the former European Chemicals Bureau (ECB) in 2002 [1], the ECHA Guidance Document [3] and the expert opinion of the three scientific committees of the EU Commission on the risk assessment of genotoxic carcinogens [4]. In its risk assessment with regard to carcinogenic effects, the ECB used as toxicological reference value an HT25 value (chronic daily dose in mg/kg bodyweight at which 25% of the animals developed a tumour in an animal experiment, converted for humans) of 9.9 mg/kg bodyweight. The underlying T25 value from a study on rats was 39.7 mg/kg bodyweight and day.

Based on the assumptions that

- the aggregate limit is exhausted by o-anisidine alone
- a burden is present in food at the detection limit of 0.01 mg/kg
- a person with a bodyweight of 60 kg consumes 1 kg of a contaminated food every day for life

it is possible to derive a daily exposure of 0.00017 mg o-anisidine/kg bodyweight in a worst-case scenario. The HT25 value and this exposure level form the basis for the following risk observations:

- Calculation of the lifetime cancer risk [4]
 $\text{Exposure}/[\text{HT25}/0.25] = 0.00017 \text{ mg/kg BW} / [9.9 \text{ mg/kg BW} / 0.25] \approx 4 \times 10^{-6}$
- Calculation of a margin of exposure
 $\text{HT25}/\text{Exposure} = 9.9 \text{ mg/kg BW} / 0.00017 \text{ mg/kg BW} \approx 6 \times 10^4$

For **2,4-toluyldiamin**, the following risk observations are based on the T25 value of 2 mg/kg bodyweight and day (from a study using rats) in the EU Risk Assessment Report [2],

from which it is possible to calculate by analogy with o-anisidine an HT25 value of 0.5 mg/kg bodyweight, and on the assumptions outlined above:

- Calculation of the lifetime cancer risk [4]
 $\text{Exposure}/[\text{HT25}/0.25] = 0.00017 \text{ mg/kg BW} / [0.5 \text{ mg/kg BW} / 0.25] \approx 8 \times 10^{-5}$
- Calculation of a margin of exposure
 $\text{HT25}/\text{Exposure} = 0.5 \text{ mg/kg BW} / 0.00017 \text{ mg/kg BW} \approx 3 \times 10^3$

These hypothetical risks are in border ranges or lower than the risks that are generally considered tolerable.

Nevertheless, exposure to these PAAs should be minimised to the greatest possible extent.

These observations apply not only to napkins and food packagings like bakery bags but are generally also transferrable to the migration of PAAs into food from sources such as plastics and other printed food contact materials.

Based on the methods currently used to determine PAAs (LC-MS/MS, HPLC-DAD following enrichment) and on the current knowledge of the BfR, a detection limit of 0.002 mg/kg is analytically feasible. Moreover, achieving this detection limit for individual PAA is also necessary in order to monitor the aggregate detection limit of 0.01 mg/kg.

3 Framework for action/Recommended measures

The ALARA principle should be applied to migrations of genotoxic carcinogenic PAAs (categories 1A and 1B of the CLP Regulation). In terms of good manufacturing practice, this could primarily be achieved by replacing substances classified as carcinogens of classes 1A and 1B (cf. German Consumer Goods Ordinance, Annex 1 No. 7) with less problematic amines or by further reducing their concentrations in the pigments.

In addition to the aggregate detection limit of 0.01 mg/kg, the BfR believes that the migration of class 1A and 1B PAAs into food or food simulants as individual substances should not be detectable with a detection limit of 0.002 mg/kg.

In view of the fact that in food contact materials made of paper the pigments used in printing inks constitute the main source of PAAs, the BfR recommends to review this procedure also with regard to the restriction of the migration of PAAs outlined in the draft version of the German Printing Inks Ordinance dated 18 January 2013.

The requirement of Regulation (EU) 10/2011 with regard to the migration of PAAs which have not been specifically assessed is based on the occurrence of these PAAs as hydrolysis products or contaminants of the substances used. In this connection, the migration of PAAs from polyurethanes and polyamides is of particular significance. The following PAAs classified as carcinogens in category 1B according to the CLP Regulation are examples of hydrolysis products of isocyanates used in the production of polyurethanes:

Table 1: PAAs as hydrolysis products of isocyanates approved under Regulation (EU) 10/2011 and categorised as carcinogens of category 1B (CLP Regulation)

Amine	CAS	Source
4,4'-methyldianiline	101-77-9	Diphenylmethane-4,4'-diisocyanate, FCM substance no. 198
2,4-diaminotoluene	95-80-7	2,4-toluene diisocyanate, FCM substance no. 354
4,4'-oxydianiline	101-80-4	Diphenylether-4,4'-diisocyanate, FCM substance no. 476
3,3'-dimethylbenzidine	119-93-7	3,3'-dimethyl-4,4'-diisocyanatobiphenyl, FCM substance no. 169

4,4'-methyldianiline is also found in substances released by kitchen utensils made of polyamide.

In the opinion of the BfR, therefore, it should be assessed at EU level whether the exhaustion of the aggregate limit value for PAAs as outlined in Regulation(EU) 10/2011 (not detectable with a detection limit of 0.01 mg/kg) solely by PAAs classified as carcinogens in classes 1A and 1B of the CLP Regulation constitutes an adequate level of protection, or whether it would not be better to apply the proposed procedure of additionally defining a detection limit of 0.002 mg/kg for the migration of these substances as individual substances.

4 References:

- [1] ECB (2002) European Union Risk Assessment Report on o-anisidine
<http://echa.europa.eu/documents/10162/c556ccd6-05be-41ab-a896-058ca6b8fae3>
- [2] 4-Methyl-m-phenylenediamine (toluene-2,4-diamine), CAS No: 95-80-7, EINECS No: 202-453-1 Summary Risk Assessment Report (2008)
<http://echa.europa.eu/documents/10162/a306907a-8401-4a75-8a84-88b9f225d5cf>
- [3] ECHA (2008) Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health.
<http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>
- [4] SCHER/SCCP/SCENIHR (2009) Scientific opinion on risk assessment methodologies and approaches for genotoxic and carcinogenic substances, *adopted on the 19th plenary meeting of the SCCP of 21 January 2009*.
http://ec.europa.eu/health/ph_risk/committees/04_scher/docs/scher_o_113.pdf