BfR removes anthraquinone from its list of recommendations for food packaging

BfR opinion No. 005/2013, 12 February 2013

The substance anthraquinone can be used for the production of cellulose. Any traces of the substance that remain in the cellulose can transfer to foods from packaging papers or cardboards manufactured from it. The Federal Institute for Risk Assessment (BfR) took the publication of an expert opinion of the European Food Safety Agency (EFSA) published in 2012 as an opportunity to reassess the use of anthraquinone in the manufacture of paper intended for food contact.

In its opinion on anthraquinone as an active pesticide ingredient, the EFSA concludes that carcinogenic effects cannot be ruled out for anthraquinone and that the hazard potential for mammals cannot be determined unequivocally. Animal experiments show that anthraquinone can have a carcinogenic effect on the kidneys and liver. The International Association for Research and Cancer (IARC) classifies the substance as a possible carcinogen for humans (“Group 2B”).

For the presence of anthraquinone in food, a maximum residue level of 0.01 mg per kilogramme of food has been defined for Europe, irrespective of whether the residue originated from a pesticide or some other source.

The BfR has estimated that anthraquinone contamination from paper and cardboard can exceed the permitted residue limit of 0.01 mg per kilogramme of food. In addition, the BfR has information on cases where the permitted residue limit value for anthraquinone was exceeded in tea which can be attributed to the anthraquinone levels contained in the paper and cardboard used as packaging materials.

In consequence, the BfR withdraws its recommendation for the use of anthraquinone in the manufacture of paper intended for food contact. In addition, the institute will lobby for a harmonised categorisation of the health hazard posed by the substance as part of the European chemicals legislation (REACH regulation).

1 Subject of the assessment

In the BfR recommendations XXXVI “Paper, cardboard and paperboard intended for food contact” and XXXVI/2 “Paper, cardboard and paperboard for baking purposes”, anthraquinone (CAS No. 84-65-1) is listed as a raw material additive (accelerator for the separation of lignin and cellulose in the extraction of cellulose fibre). Recent toxicological data and current assessments by the European Food Safety Agency (EFSA) have prompted the Federal Institute for Risk Assessment (BfR) to evaluate whether it is justifiable to uphold the recommendation for the use of anthraquinone in the manufacture of food packaging materials.

2 Findings

Since the substance has been shown to be carcinogenic in animal experiments, anthraquinone may have carcinogenic potential for humans as well. For this reason, the BfR cannot continue to recommend the use of anthraquinone as an accelerator for the separation of lignin and cellulose in the extraction of cellulose fibre. Accordingly, the institute will remove the entries for this substance from recommendations XXXVI and XXXVI/2.

3 Statement of Reasons

3.1 Risk assessment

3.1.1 Possible source of danger

Anthraquinone is used as an accelerator for the separation of lignin and cellulose in the preparation of cellulose fibres. For this intended purpose, the substance is listed in the BfR recommendations XXXVI “Paper, cardboard and paperboard intended for food contact” and XXXVI/2 “Paper, cardboard and paperboard for baking purposes”. The substance may be used at a maximum quantity of 0.15 % of the finished paper. Dry paper must not contain more than 30 mg of anthraquinone per kilogramme.

In addition, anthraquinone has been requested to be included, as a bird repellent, in the annex of Directive 91/414/EEC on the placing of plant protection products on the market. Due to clear indications of the harmful effects on human health and the absence of data to establish a reliable acceptable daily intake (ADI), an acute reference dose (ARfD) and a reliable acceptable operator exposure level (AOEL), the request was rejected. (Decision 2008/986/EC of the Commission on the non-intake of anthraquinone and the revocation of approvals of pesticides containing this substance).

Accordingly, in the annexes of Regulation (EC) No. 396/2005 on limit values for pesticide residue originating from plants or animals in or on food and feed, no specific residue limit value has been defined for anthraquinone, i.e. in accordance with Art 18(1)(b) of the mentioned regulation, the limit of 0.01 mg/kg food applies.

For manufacturing anthraquinone, different methods are known. The most important ones are:

- Oxidation of anthracene, AQ-OX (with HNO_3)
- Friedel-Crafts acylation AQ-FC (from phthalic acid anhydride and benzene)
- Diels-Alder reaction, AQ-DA (from p-benzoquinone and 1,3-butadiene)

In the first procedure, 9-nitroanthracene is formed as an impurity.

3.1.2 Hazard potential

In 2012, the EFSA published an opinion on the permissible residue limit value for anthraquinone in food. Due to the lack of data on toxicity in mammals and on the metabolism in plants and animals and also on account of the data on the substance’s carcinogenic potential, the EFSA was unable to establish whether the permissible residue limit value in accordance with Regulation (EC) No. 396/2005 of 0.01 mg/kg of food sufficiently protects consumers.

A two-year feeding study (NTP, 2005) on rats and mice is available on the carcinogenic potential of anthraquinone. The purity of the substance used was 99.8 %; and it contained 9-nitroanthracene as an impurity (manufactured using the AQ-OX process). The results of this study reported, among other things, increased incidents of tubular neoplasms in the kidneys of female rats and liver neoplasms in both male and female mice.

As regards the carcinogenicity of anthraquinone, IARC (2012) concludes that there is “inadequate evidence” in humans but that there is “sufficient evidence” of it in experimental

animals. For this reason, IARC classifies anthraquinone as “possibly carcinogenic to humans” (“Group 2B”).

Apart from 9-nitroanthracene as an impurity, another possible cause of the carcinogenic effect mentioned was the main metabolite of anthraquinone, i.e. 2-hydroxy-anthraquinone (NTP, 2005). This metabolite is formed in the liver and secreted via the kidneys. Liver and kidneys are the most important target organs of the tumorigenic effect of anthraquinone. In the bacterial mutagenecity test, both 2-hydroxy-anthraquinone and 9-nitroanthracene are positive. However, the former is contained in the urine of test animals in much higher concentrations than 9-nitroanthracene. Another metabolite found in the urine of experimental animals was the carcinogenic substance 1-hydroxy-anthraquinone, though in lower quantities. Hydroxy-anthraquinones are formed in the animals irrespective of impurities resulting from the manufacturing process of the anthraquinone. Therefore, the metabolites seem to be a plausible cause of the carcinogenic effect of anthraquinone.

3.1.3 Exposure

Assuming the maximum permitted residue level of anthraquinone in paper and cardboard amounting to 30 mg/kg in accordance with recommendations XXXVI and XXXVI/2, calculations would result in an anthraquinone level of 0.45 mg/kg of food as the worst foreseeable case (assuming contact of 6 dm² of cardboard material with a grammage of 250 g/m² with 1 kg of food and complete transfer from the packaging to the food).

The test results of the National Council for Air and Steam Improvement (NCASI, 2008) showed that during storage (1h/74-80°C + 48h/4°C), pizza absorbs up to 5 % of the anthraquinone contained in the pizza carton. Taking into account the permissible limit value and a contact of 5 dm² pizza carton (250 g/m²) with 500 g pizza, this results in a transfer from packaging to food of 0.04 mg anthraquinone/kg of pizza. This value exceeds the permitted residue limit value for anthraquinone laid down in Regulation (EC) No. 396/2005.

In addition, the BfR has information on cases where the permitted residue limit value for anthraquinone was exceeded in tea which can be attributed to the anthraquinone levels contained in the paper and cardboard used as packaging materials.

3.1.4 Risk characterisation

The use of anthraquinone in the manufacture of paper and cardboard can lead to exposure of consumers (>0.01 mg/kg of food). Since there are indications that the substance is potentially carcinogenic, safe application cannot be guaranteed: due to the results of the NTP study (2005), it is to be assumed that anthraquinone has carcinogenic potential. As a cause of the tumorigenic effect, the formation of hydroxy-anthraquinones is assumed. These metabolites are formed independently of the anthraquinone manufacturing process and have been tested as mutagenic and / or carcinogenic.

3.2 Framework for action

The residue limit value that applies to anthraquinone in accordance with Regulation (EC) No. 396/2005 on limit values for pesticide residue originating from plants or animals in or on food and feed of 0.01 mg/kg of food can be exceeded when cellulose fibres are prepared for the manufacture of paper and cardboard intended for food contact. Since there are indications that the substance has a carcinogenic potential, the BfR cannot recommend the continued

use of anthraquinone and will remove the entry for this substance from recommendations XXXVI and XXXVI/2.

If the use of anthraquinone in fibre manufacture is indispensable, the BfR points out that due to the current provisions in Regulation (EC) No. 396/2005 on the presence of anthraquinone in food, a residue limit value of 0.01 mg/kg of food applies, irrespective of whether this residue originated from pesticides or another source.

In the opinion of the BfR, the harmonised classification and labelling of anthraquinone should be evaluated under REACH in accordance with the CLP Regulation (Regulation on classification, labelling and packaging of substances and mixtures, (EC) No 1272/2008).

4 References

EFSA (European Food Safety Authority), 2012, Reasoned opinion on the review of the existing maximum residue levels (MRLs) for anthraquinone according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2012; 10(6):2761.

NTP, 2005, Technical report on the toxicology and carcinogenesis studies of anthraquinone (CAS NO. 84-65-1) in F344/N rats and B6C3F1 mice (feed studies). http://ntp.niehs.nih.gov/GGTSPU-argusgate02.bfr.bund.de-2559-1334870-KWmEDXPaE4s2DaEh-DAT/ntp/htdocs/LT_rpts/TR494.pdf

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