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Preface

Heterocyclic aromatic amines—still a challenge for scientists

Heterocyclic aromatic amines (HAs) were discovered in the early 1970s by Sugimura [1]. Since these chemicals are formed during cooking of meat and fish [2], humans all over the world are continuously exposed to these compounds. The fact that HAs are potent inducers of DNA damage and cause cancer in different organs of laboratory animals [3], has stimulated intense research in regard to their formation, occurrence and biological effects. A number of findings suggest that HAs are involved in the aetiology of various forms of human cancer. In particular the incidence of colon cancer, which is increasing in industrialised countries, might be causally related to exposure to these food borne carcinogens [4]. It is also notable that recent findings indicate that HAs are also released into the environmental and contaminate aquatic ecosystems [5,6]. Within the last 30 years, approximately 2100 articles have been published on HAs (assessment based on a computer aided search in PubMed), nevertheless their investigation is still a challenge to scientists of different disciplines. The analytical determination of these compounds is complicated and currently strong efforts are made to improve the chemical determination of HAs in human foods. It became also clear that the formation of HAs depends strongly on the cooking conditions [7]. These leads to problems in the assessment of the human exposure levels. On the basis of a comparison of different studies, Felton et al. [8], stated that the estimated exposure of humans differs by a factor of 10^3. HAs undergo a complex metabolism and a panel of different phase I and phase II enzymes is involved in their activation/detoxification [9]. At present, strong efforts are made to better understand the human biotransformation pathways of the HAs. This information is required for risk assessments based on the extrapolation of results of animal studies to humans. Numerous studies have been carried out in order to identify dietary constituents which protect against adverse health effects of HAs (for review, see [10]). All these topics are addressed by the articles contained in this special issue. The first section on analytical aspects comprises papers concerning the formation, chemical determination and exposure of humans; the section on biological effects contains contributions on the metabolism, excretion, and on genotoxic and carcinogenic effects of HAs; in the last part experimental data are described which deal with protective effects of dietary constituents.

The formation of the compounds were studied in different model systems (Bordas et al.; Lan et al.; Messner et al.; Murkovic) to be able to control the experimental parameters, e.g. temperature and heating time exactly. Of special interest were reaction mechanisms and the identification of the precursors. It was found that amino acids and carbohydrates were precursors and the presence of creatine/creatinine is a necessary prerequisite for the formation of the polar HAs like MeIQ, 4,8-DiMeIQx and PhIP. From creatinine the imidazo moiety is formed; the quinoline and quinoxaline moiety is a result of the Maillard reaction. However, the exact mechanism of formation is still under investigation [11].

Due to the polar nature of HAs, liquid chromatography is the method of choice for analysing these substances. Different reversed phase columns were compared (Barcelo et al.) to find out which column is the most appropiate. Today for detection mainly MS and MS/MS (Barcelo et al., Busquets et al.) are used but for the less polar amines also fluorescence detection (Ristic et al.) offers enough sensitivity and selectivity. Amperometric and electrode array detectors (Gerbl et al.) are suitable to detect some but not the whole spectrum of polar and less polar amines. A cruical point in the analysis of HAs is multi-step sample preparation (Skog) but as it is shown in the interlaboratory studies (Santos et al.) reliable results are obtained by experienced analysts. The concentration of the HAs are generally in the low ppb-range (Busquets et al.; Warzecha et al.) if meat or fish is prepared under gentle conditions, but especially when beef is fried or grilled under vigorous conditions, concentrations of about 20 ng/g can be found for HAs. Only in the case of PhIP even much higher concentrations were observed. Based on the now available data estimates of the daily intake (Keating et al.) were made.

The ß-carbolines norharman and harman are not only formed in heated proteinous food but have been shown to be normal body constituents and are also alkaloids ingested with edible or medicinal plants. The several exposure routes and toxicokinetics of these HAs are comprehensively summarised in the review by Pfau and Skog. The contribution of Tosuka et al. describes the information of amino-biphenyl-β-carbolines and contains interesting data on the DNA damaging and carcinogenic effects of these novel type of endogenously formed amines which are also generated in humans.

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The contribution of Majer and co-workers concerns the DNA damaging effects of AαC. To date, only a few data on the genotoxic effects of this carboline are available, although this compound is frequently found in fried meats in higher amounts than most other amines [12]. Duc and Leong-Morgenthaler report on a molecular investigation into the effects of p53 protein and DNA mismatch repair on PhIP-induced damage.

The articles of Turesky et al. and Kulp et al. focus on methods which will contribute to an improved risk assessment. The first describes the detection and quantitation of DNA adducts as critical biomarkers for interspecies extrapolations, the second concerns a new method which allows to monitor urinary deoxification products of PhIP, the most abundant HA, in humans. This approach will be also a valuable tool for future intervention trials. The contribution concerning the polymorphisms of enzymes involved in the metabolism of HAs (Airoldi et al.) gives an overview on the current state of knowledge to which extent inter-individual differences in the activity of enzymes involved in xenobiotic metabolism may affect the health risks of HAs in man. The article of Fekadu et al. shows that also the intestinal microflora has a strong impact on the genotoxic effects caused by HAs which has been underestimated in the past.

Most investigations concerning the identification of dietary constituents which protect against the DNA damaging effects of HAs were carried out with experimental models which do not reflect the situation in humans [13]. In the present issue, results of in vivo studies are described which have a better predictive value in regard to human protection. Uhl et al. describe the effects of *Brassica* vegetables on IQ induced preneoplastic lesions in a two organ animal model with rats; in the study of Humblot and colleagues, the single cell comet assay was used to monitor protection towards HA induced DNA damage in inner organs of rats by yoghurt constituents and attempts were made to elucidate the underlying mechanisms of protection. Several earlier studies indicate that dietary fibres are protective towards HAs [14] but data on the effects of non starch polysaccharides and resistant starch are scarce. The paper of Kestell et al. describes detailed investigations on the impact of non-starch polysaccharides and resistant starch on the metabolism of HAs. There is also increasing evidence that dietary antioxidants reduce the formation of HAs and interfere with their metabolic activation; the current state of knowledge on these effects is summarised in the contribution of Vitaglione and Fogliano. The findings of Boyce et al. show that resveratrol, a phytoalexin which prevents cancer formation via different mechanisms [15] is also protective towards certain HAs.

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