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Review

Blue cotton, Blue Rayon and Blue Chitin in the analysis of heterocyclic aromatic amines—a review

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Abstract

Heterocyclic amines (HCAs) are a group of compounds formed when protein-rich foods, such as meat or fish, are prepared under normal cooking conditions, such as frying, grilling, or broiling. To evaluate and estimate the risks associated with HCAs contained in the diet, it is important to determine the levels in cooked foods, and the levels of HCAs and metabolites in the body. HCAs are normally found at low amounts in a complex matrix, which necessitates a good purification method and a sensitive detection system. The objective of this review was to briefly present the current knowledge on the use of Blue Cotton, Blue Rayon and Blue Chitin in the analysis of HCAs.
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Keywords: Blue cotton; Blue rayon; Blue chitin; Heterocyclic aromatic amines

Contents

1. Introduction

During recent years, there has been a great concern among the public about the risks and health aspects of the food we eat. Already in 1939, Professor Widmark at Lund University found that organic solvent extracts of grilled horse meat induced tumours in mammary glands when painted on the backs of mice [1]. In 1977, Japanese scientists found that the smoke and charred parts of broiled fish and beef contained significant quantities of mutagenic activity [2,3]. The mutagenic/carcinogenic compounds were found to belong to a class of compounds called heterocyclic aromatic amines (HCAs) [4,5]. HCAs are formed at ng/g levels during frying, grilling or broiling of meat and fish (for a review see [6]. Epidemiological studies point to a relationship between

Abbreviations: HCA, heterocyclic aromatic amine; IQ, 2-amino-3-methylimidazo[4,5-*f*]quinoline, CAS no. 76180-96-6; MeIQ, 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline, CAS no. 77094-11-2; IQx, 2-amino-3-methylimidazo[4,5-*f*]quinoxaline, CAS no. 108354-47-8; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline, CAS no. 77500-04-0; 7,8-DiMeIQx, 2-amino-3,7,8-trimethylimidazo[4,5-*f*]quinoxaline, CAS no. 9218-0-79-5; 4,8-DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline, CAS no. 95896-78-9; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine, CAS no. 105650-23-5; DMIP, 2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine, CAS no. 105650-23-5; AαC, 2-amino-9*H*-pyrido[2,3-*b*]indole, CAS no. 26148-68-5; MeAαC, 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole, CAS no. 68006-83-7; Norharman, 9*H*-pyrido[3,4-*b*]indole, CAS no. 244-63-3; Harman, 1-methyl-9*H*-pyrido[3,4-*b*]indole, CAS no. 486-84-0; Trp-P-2, 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole, CAS no. 62450-10-3; Trp-P-1, 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole, CAS no. 62450-06-0

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the intake of foods containing HCAs and cancer, but there are also studies showing no correlation [7]. HCA metabolites can bind to DNA, RNA and proteins by covalent bonding, and such adducts have been found in almost all kinds of tissue in studies on rodents and non-human primates [8], and even if only a small proportion of the HCA metabolites form adducts, this is presumably enough to induce tumours or other toxic effects.

For estimates of the daily intake of HCAs and for reliable risk assessments, it is important to determine the levels of HCAs in cooked foods, and the levels of HCAs and their metabolites in human urine. HCAs are normally found in low amounts in a complex matrix, which necessitates good purification methods and sensitive detection systems. The aim of this review is to briefly present the current knowledge on the use of Blue Cotton, Blue Rayon and Blue Chitin for the extraction and purification of HCAs from cooked foods, model systems, urine samples and river water. The blue pigment offers a high selectivity towards polycyclic compounds and has also been used for the extraction of other polycyclic aromatic compounds such as polycyclic aromatic hydrocarbons [9,10], but that application is outside the scope of this paper.

1.1. HCA structures

To date, more than 20 HCAs have been identified in heat-treated foods [4,5]. The molecular structures of some of them are shown in Fig. 1. Depending on their structure, HCAs can be divided into different sub-classes (examples are given in parenthesis): amino-imidazo-quinolines denoted IQ compounds (IQ and MeIQ), amino-imidazo-quinoxalines denoted IQx compounds (IQx, MeIQx and DiMeIQx), amino-imidazo-pyridines denoted IP compounds (DMIP and PhIP) and amino-carbolines (AαC, MeAαC, Harman, Norharman, Trp-P-1 and Trp-P-2). HCAs normally have planar structures and consist of three fused aromatic rings with at least one nitrogen atom in the ring structure and with

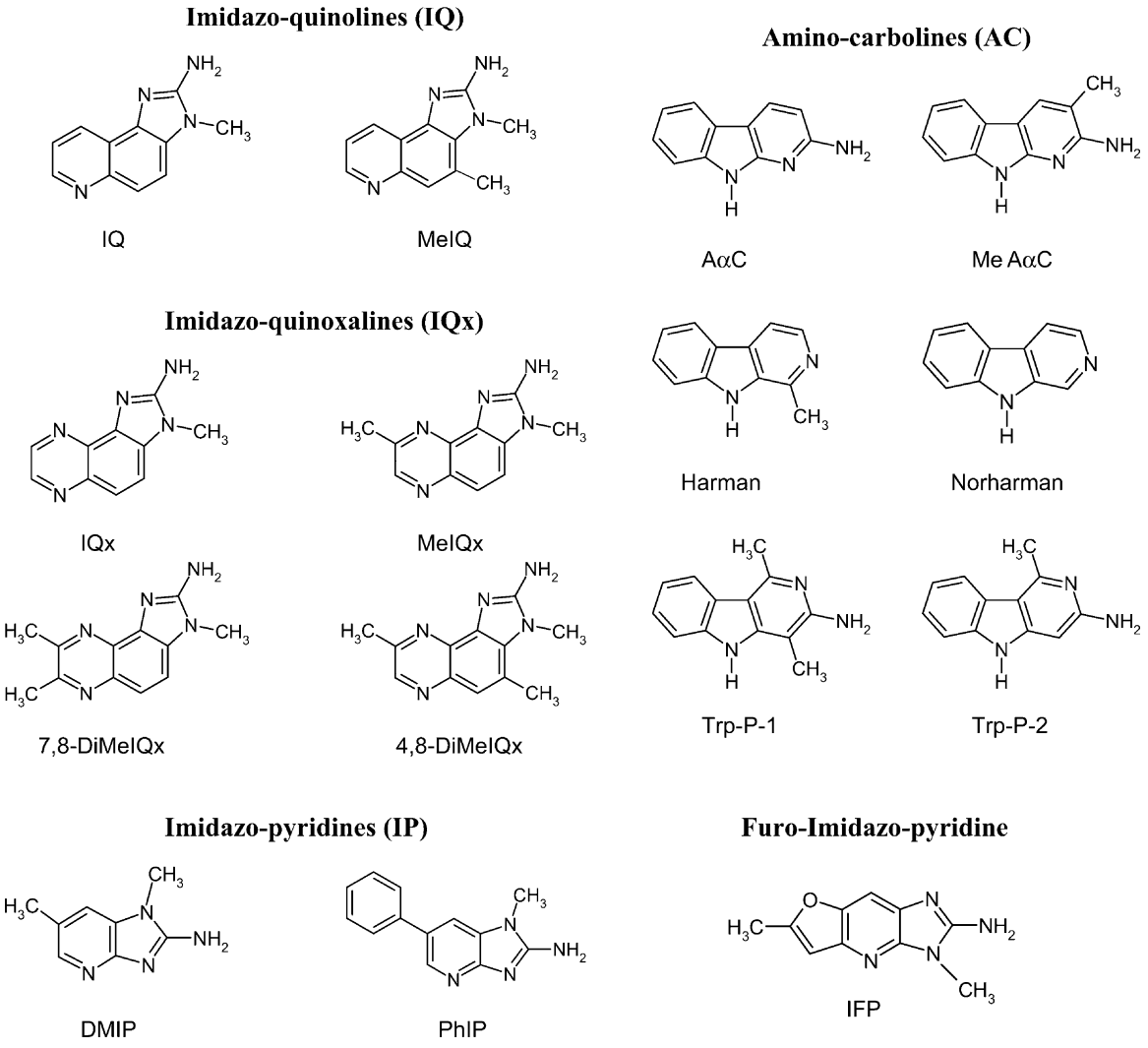

Fig. 1. Molecular structures and common names for some HCAs.

one exocyclic amino group, and up to four methyl groups as substituents. There are, however, some exceptions, for example, PhIP and DMIP have only two fused rings, while harman and norharman have no exocyclic amino group, and IFP has an oxygen atom in its ring structure.

1.2. Occurrence in cooked foods

The amount of HCAs in cooked foods is highly dependent on the type of meat and the cooking method, and is positively correlated to the cooking time and temperature [6,11–14]. The most common HCAs found are PhIP, at levels up to 480 ng/g in barbecued chicken [15], and MeIQx at levels commonly below 30 ng/g [6,16]. For the other HCAs, the levels normally range from not detectable to about 10 ng/g. Generally, low or undetectable levels of HCAs are found in commercially cooked food products [6,17].

1.3. Extraction and purification

As HCAs are found at low levels (ng/g) in cooked foods, i.e. in a complex sample matrix, there is a need for extraction, purification and concentration of the HCAs before analysis, and this is often achieved with liquid–liquid extraction, solid-phase extraction, or column liquid chromatography [18–20]. A method was developed by Gross et al. [21] using liquid–liquid extraction on a solid support, followed by solid-phase extraction with cation exchange and C_{18} columns. This method has been widely used for the extraction of HCAs from cooked food samples, however it is laborious and involves many different columns and steps.

Other and simpler methods for the extraction and concentration of HCAs from various type of samples employ *copper phthalocyanine trisulphonate*, a common blue pigment widely used as a dye. In 1983, Hayatsu and co-workers discovered that this pigment had a high affinity for aromatic compounds with three or more fused rings in their structure [22]; the planar structure can form a 1:1 hydrophobic complex with the blue pigment that has a large planar structure in the molecule. This ability was used for the manufacture of Blue Cotton, i.e. cotton bearing covalently bound copper phthalocyanine trisulphonate. Blue Cotton is commercially available (Funakoshi Co. Ltd., Japan); its molecular structure is shown in Fig. 2. The content of the pigment in Blue Cotton is around 10 μmol per g dry weight [23]. As most HCAs have a planar structure and easily form bonds with the blue pigment, Blue Cotton has been used for the adsorption of different HCAs from aqueous extracts of various samples. The HCAs adsorbed on Blue Cotton can be recovered by elution with hydrophilic organic solvents, most effectively by methanol containing a small amount of ammonia [23]. Probably the ammonia helps to dissociate the complex by coordinating itself to the central metal ion in the ligand. The extraction procedure is very simple, typically a piece of Blue Cotton is inserted into an aqueous sample solution (20 mg/100 ml), and the solution is then stirred for

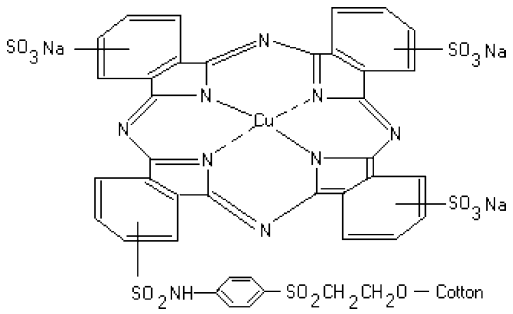

Fig. 2. Molecular structure of Blue Cotton.

30 min. This procedure is repeated once or twice with new pieces of Blue Cotton. The pieces of cotton are washed with water and the adsorbed HCAs are then eluted using a solution of methanol–ammonia (usually in the ratio 50:1). The solutions are combined and evaporated to dryness and then dissolved in a small volume of solvent before further analysis. Literature data on recoveries are few, but for pure reference compounds the recoveries have been reported to be 57–98% for IQ, MeIQx, PhIP, Trp-P-1, Trp-P-2, AαC and MeAαC [22–24]. For cooked meat samples, the recoveries have been 40 and 75% for IQ, MeIQ, MeIQx, 4.8-DiMeIQx and PhIP [18,25].

Literature data on the use of Blue Cotton in the analysis of HCAs from various sample mixtures are summarised in Table 1. Also the detection system is given in Table 1. Modelling experiments are useful tools for studying the influence of different physical parameters and various precursors on formation of HCAs; several HCAs, for example IQ, MeIQx and DiMeIQx have been identified in model systems after extraction with Blue Cotton [26–29]. Using Blue Cotton, IQ, MeIQx, DiMeIQx, PhIP have often been detected, but also some HCAs that are not commonly found in fried foods have been identified, for example 4-OH-PhIP in broiled beef [30], 4-CH_2OH-8-MeIQx in beef extract [31] and 7,9-DiMe*ig*Qx in beef extract [28]. Blue Cotton has been used for HA extraction from both human urine [32–34], and rat urine [35,36]. In addition, but not included in the table, there are also some reports on the use of Blue Cotton for the extraction of HCAs from dialysis fluids, human plasma and human cataract lenses [37–39]. Blue cotton has been used for the isolation of HCAs (IQ, Trp-P-1 and AαC) from river water [40]. There are also several reports in which the mutagenic activity has been measured but no HCAs have been identified [41].

An improved method uses rayon as the supporting material instead of cotton, as rayon can contain two to three times more blue pigment, making Blue Rayon (Funakoshi Co. Ltd., Japan) a more efficient adsorbent than Blue Cotton [23,41]. The content of the pigment in Blue Rayon is around 30 μmol per g dry weight [23]. Although the mechanistic strength of Blue Rayon is lower than that of Blue Cotton, bags containing Blue Rayon (0.5 g) have often been used for adsorption of HCAs from river water [40,42,43]. The

Table 1
Literature data on the extraction of HCAs from model systems and cooked food samples using Blue Cotton

Blue Cotton/sample	Identified HCAs	Detection	Reference
Model system	MeIQx	MS, NMR, UV	[27]
Model system	7,8-DiMeIQx	MS, UV	[26]
Model system	4,8-DiMeIQx	MS, UV	[26]
Model system	IQ	MS, UV	[29]
Model system	7,9-DiMe*ig*Qx	MS, NMR, UV, X-ray crystallography	[28]
Model system	MeIQx, PhIP	UV, MS	[48]
Cooked minced beef, Beef extract	IQ, MeIQx	UV	[32]
Beef extracts	IQ, MeIQx	EC	[49]
Cooked minced beef	MeIQx	–	[50,51]
Heat-dried and grilled fish	MeIQx, 4,8-DiMeIQx	MS, UV	[52]
Smoked, dried fish	MeIQx, 4,8-DiMeIQx	UV	[53]
Broiled salmon	IQ, MeIQ	MS	[54]
Fried walleye pollack (fish)	IQ, MeIQ, MeIQx, 4,8-DiMeIQx, PhIP	UV	[25]
Charred egg yolk	IQ, MeIQ, Glu-P-1	Fluorescence, UV	[55]
Broiled beef	4′-OH-PhIP	UV	[30]
Beef extract	4-CH_2OH-8-MeIQx	MS, NMR, UV	[31]
Beef extract	7,9-DiMe*ig*Qx	MS, NMR, UV, X-ray crystallography	[28]
Beef extract, Cooked meat and fish	IQ, MeIQ, 4,8-DiMeIQx, MeIQx, 7,9- DiMe*ig*Qx, PhIP, 4′-OH-PhIP, Trp-P-1, AαC, MeAαC	–	[56]
Cooked meat, Beef extract	Harman, Norharman	Fluorescence, UV	[57]
Fried beef	IQ, MeIQ, 4,8-DiMeIQx, MeIQx, PhIP	EC	[58]
Roast pork	IQ, MeIQ, MeIQx, PhIP, 4,8-DiMeIQx	MS, UV	[18]
Rat urine and faeces	MeIQx, metabolites	MS, NMR, UV	[36]
Rat urine	IQ, metabolites	Scintillation, UV	[35]
Human faeces	MeIQx	–	[51]
Human urine	MeIQx, PhIP, Trp-P-1, Trp-P-2	Fluorescence, UV	[33]
Human urine	MeIQx, 4,8-DiMeIQx, PhIP, 4′-OH-PhIP	MS, UV	[34]

(–) not specified.

extraction procedure using Blue Rayon is the same as for Blue Cotton. Blue Rayon has mainly been used for the adsorption of HCAs from river water [40,42–44]. Recoveries for pure reference compounds have been reported to be 75–94% for IQ, MeIQx, PhIP, Trp-P-1 [23]. Both Blue Cotton and Blue Rayon can be packed into glass columns or disposable plastic columns, which facilitate the extraction and purification procedure [18,22,23,34,43,45]. When pure reference compounds were dissolved in ethyl acetate and added onto a columns of Blue Rayon, the recovery was 82–110% for IQ, IQx, MeIQ, MeIQx, PhIP, Trp-P-1 and Trp-P-2, but when the HCAs instead were dissolved in water, the recovery was markedly reduced except for Trp-P-1 and Trp-P-2 [46].

By using chitin powder (poly-*N*-acetylglucosamine) as the supporting material, the content of the blue pigment can be doubled compared with rayon and increased by four times compared with cotton [47]. The content of the pigment in blue chitin is around 40 μmol per g dry weight [47]. The powder form makes blue chitin suitable for packing in small columns. Blue Chitin columns have been developed especially for extracting planar polycyclic compounds, for example mutagens such as HCAs, and are commercially available (Funakoshi Co. Ltd., Japan). The procedure is simple; the sample solution is applied to a preconditioned column at a flow rate of 5–10 ml/min, then the column is washed with water and purged with air to remove the water before the HCAs are eluted with methanol containing a small amount of ammonia. The eluent is evaporated to dryness under reduced pressure and the residue is dissolved in a small volume of solvent. Methods based on Blue Chitin columns are simpler and less time-consuming than methods based on Blue Cotton or Blue Rayon, and higher recoveries of HCAs are usually obtained [47]. The adsorption of IQ was not affected by pH in the range of 7–9, but it was somewhat lower at pH 3 [47]. In another study, the adsorption was markedly higher when pure HCAs were dissolved in NaOH than in water or HCl [46]. Furthermore, the recoveries of HCAs from a spiked cooked food sample were around 50% for MeIQx and PhIP and 72% for Trp-P-1 and Trp-P-2 [46]. In the same study, using Blue Chitin columns, several HCAs were detected in fried chicken and hamburgers (IFP, PhIP, MeIQx, DiMeIQx, harman, norharman, Trp-P-2 and AαC) [46].

2. Conclusions

Accurate assessment of the human exposure to HCAs requires reliable methods for the analysis of HCAs in various types of cooked meat samples and urine samples. Methods

based on Blue Cotton, Blue Rayon and Blue Chitin have been developed especially for extracting planar polycyclic compounds such as HCAs. The methods show recoveries comparable to or better than existing solid phase extraction methods, and are faster and simpler than most of them. Thus, Blue Cotton, Blue Rayon and Blue Chitin offer simple procedures for selective adsorption of HCAs from various samples such as cooked foods, model systems, urine, faeces and river water.

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