

Food Borne Carcinogens: A Dead End?

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1. Introduction

One of the major challenges in biomedicine is to find strategies to prevent cancer. It is among the top 10 causes of death in middle and high income countries (WHO, 2004) and accounts for a major economic expenditure; for instance, £5.86 billion were spend on cancer care in 2009-2010 in the UK, which is 5.6% of the UK's total annual health spending (Sullivan et al., 2011). The pathogenesis of this condition involves a series of complex and interwoven mechanisms ranging from genetic to environmental and/or behavioral factors. Some of the causes and risk factors of cancer are smoking, infection/inflammation, dietary factors, sunlight exposure, and pollution (Sugimura, 2002). Radiofrequency electromagnetic fields have also been recently classified as "possibly carcinogenic" by the World Health Organization's International Agency for Research on Cancer (IARC) (IARC, 2011). This chapter is going to focus mainly on diet as a risk factor for cancer.

Diet can play an important role in the onset of cancer since apparent harmless meals, to which we are exposed daily, can bring mutagens in close proximity to our DNA, certainly a bad combination. The formation of the "cooking mutagens" takes place in the framework of the Maillard reaction when thermally treating food. These mutagens are products of the reaction of common food components such as aminoacids, fatty acids or creatine and have to be metabolically activated to acquire the potential to alter DNA. For instance, melanoidins, the polymers that give the brownish colour when cooking (Arnoldi et al., 1997; Tehrani et al., 2002), are other products of the Maillard reaction with which we are more familiar.

Study in cooking mutagens was pioneered at Lund University, in 1939, where E.M.P Widmark reported that organic solvent extracts from grilled horse meat caused tumours in mice mammary glands when they were repeatedly applied to mouse skin (Widmark, 1939). Some years later, Druckrey and Preussman (Druckrey et al., 1962) reported the presence of carcinogenic N-nitrosamines in tobacco smoke, which were identified in food in the 1990s (Drabik-Markiewicz et al, 2011; Tricker et al., 1991). The presence of polycyclic aromatic hydrocarbons was also found on the crust of well-done charcoal-grilled steaks by Lijinsky and Shubick. These compounds were formed from the pyrolysis of fat drippings into flames and the adherence of this pyrolysate to the surface of food (Chung, 2011; Lijinsky & Shubick, 1964). Not long after, a revolutionary assay to quantify mutagenic activity was developed by Ames et al. (1975) based on Salmonella typhimurium strains (Ames et al., 1975). This assay helped Sugimura and co-workers to find high mutagenic activity in particles of smoke produced by cooking proteinaceous foodstuffs and immediately afterwards in charred parts of broiled fish and meat (Nagao et al., 1977). Mutagenic activity was also detected in meat

prepared under domestic conditions (Commoner et al., 1978). These findings initiated research into heterocyclic amines (HCAs) and since then several series of mutagenic HCAs have been identified. Some potential and new HCAs have been recently reported in thermally treated food (Busquets et al., 2007, 2008; Turessky et al., 2007). HCAs result from the reaction of natural components present in protein rich food at normal cooking conditions. In 2005, the U.S. National Toxicology Program listed four HCAs as reasonably anticipated human carcinogens, status that has been maintained in the latest report (RoC, 2011). Earlier, in 1993, the IARC already listed one HCA as probable human carcinogen (group 2A) and eight HCAs as possible human carcinogens (group 2B) and recommended a decrease in their intake (IARC, 1993). Furan, mainly found in coffee, baby food, beer and canned sauces and soups, was also classified as possibly carcinogenic to humans (Group 2B) (IARC, 1995). This compound is formed from three major routes beginning with sugars, ascorbic acid or unsaturated fatty acids (Al Taki et al., 2011; Maga, 1979). For a review, see Crews and Castle (Crews & Castle, 2007). Recently, acrylamide, listed within the group 2A (IARC, 1994) and formed from the reaction between asparagine and glucose (Mottram et al., 2002; Tareke et al., 2002;) has also been found in carbohydrate-rich foods. The major exposure to acrylamide mainly appears to come from the consumption of French fries, crisps, biscuits or cereals (Bermudo et al., 2006; Tareke et al., 2002). At present, additional naturally occurring substances such as 5-(hydroxymethyl)-2-furfural (HMF) and related compounds, which are formed from hexoses in acidic media, are being evaluated for their potential human genotoxicity. In particular, high levels of HMF have been quantified in honeys, caramel products, plum-derived products, coffee and balsamic vinegars (Glatt & Sommer, 2006; Teixidó et al., 2006). Some examples of relatively abundant cooking mutagens among the types listed above, are the nitrosamine NMDA (N-nitrosodimethylamine); the polycyclic aromatic hydrocarbon BPA (benzo[a]pyrene); the heterocyclic aromatic amine PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine); HMF; furan and acrylamide, shown in Fig. 1.

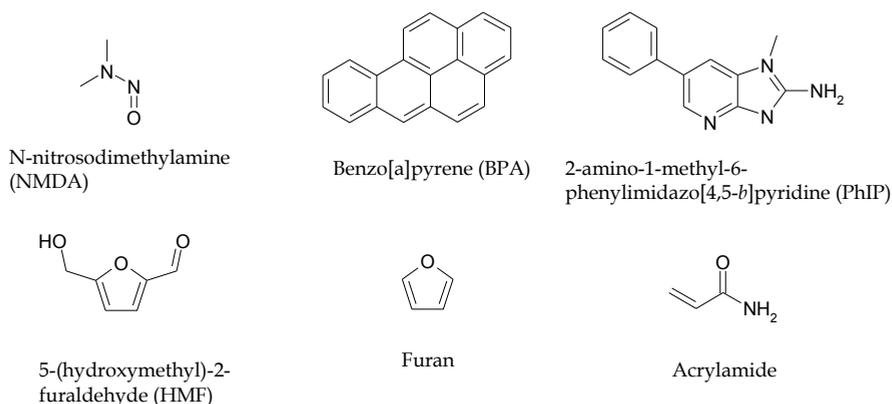


Fig. 1. Examples of food borne mutagens.

When somebody is informed about the generation of potential harmful compounds in common food items, whom asks who or what is responsible for that exposure. The answer to that is our eating preferences and habits, as it will be explained later in this book chapter. Some may recall previous information they had about it "I heard that the charred part of

food is not healthy". This is a good start, because it means that research has been disseminated and people are aware to some extent of the lack of safety in burnt food. However the information received is partly inaccurate as potential hazardous compounds can also be present in the non overcooked parts of the food. For instance, Fig. 2 shows chicken cooked using different methods and the corresponding concentration of mutagenic HCAs analysed in these food items. It can be seen that non charred meat can contain relatively high levels of cooking mutagens, HCAs in this case. Besides, very different levels of HCAs can be found in an item presenting similar degree of doneness and browning that has been processed using different cooking methods.

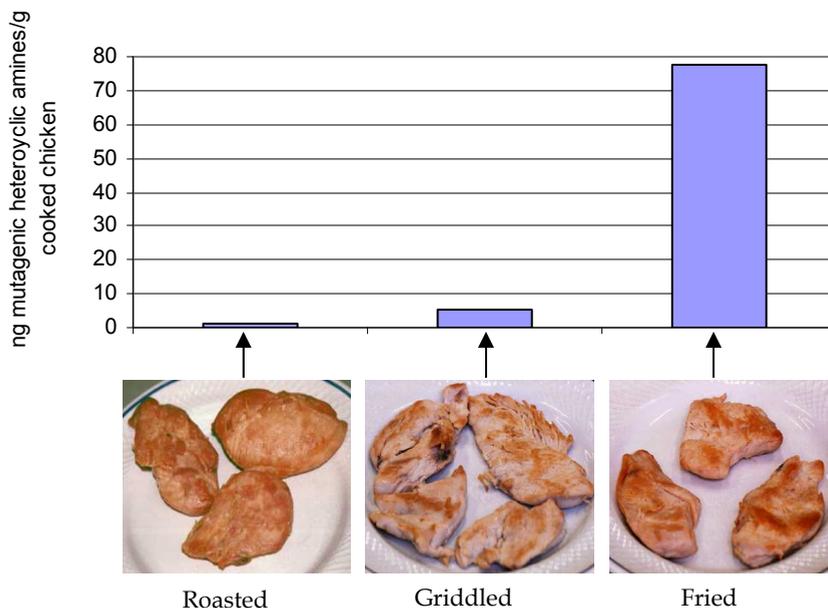


Fig. 2. Level of mutagenic HCAs in chicken cooked in different ways. Each bar corresponds to the concentration of HCAs quantified in the respective item displayed. The cooking and analysis conditions have been reported elsewhere (Busquets et al., 2004, 2008).

Finally, despite the effort of scientists to study food borne mutagens, human behaviour is complex and, in some occasions, the public reacts saying "I like barbecued meat and I love crisps and there is no way I will stop eating them". In summary, if in the best case people have been warned on the certain risks associated to some food items and they will not make an effort to reduce the exposure, who would care about them; are food borne carcinogens a dead end?

2. Exposure to food borne carcinogens. Heterocyclic amines (HCAs), a case study

The formation of HCAs results from the reaction of hexoses, creatine/creatinine and amino acids (Jägerstad et al, 1983a, 1983b; Murkovic et al., 1999, 2004) and is highly affected by the

chemical and physical parameters during the cooking process as well as the composition of the raw food. It is important to understand the effect of such parameters on exposure to HCAs, as an example of food borne mutagens, to understand, to some extent, the absence of legislation, and subsequently the low interest of the companies to monitor or reduce the level of HCAs in food items. The proposed route for the formation of HCAs (quinolines and quinoxalines) is shown in Fig 3 and the proposed mechanism for the formation of pyridinic HCAs is given in Fig. 4.

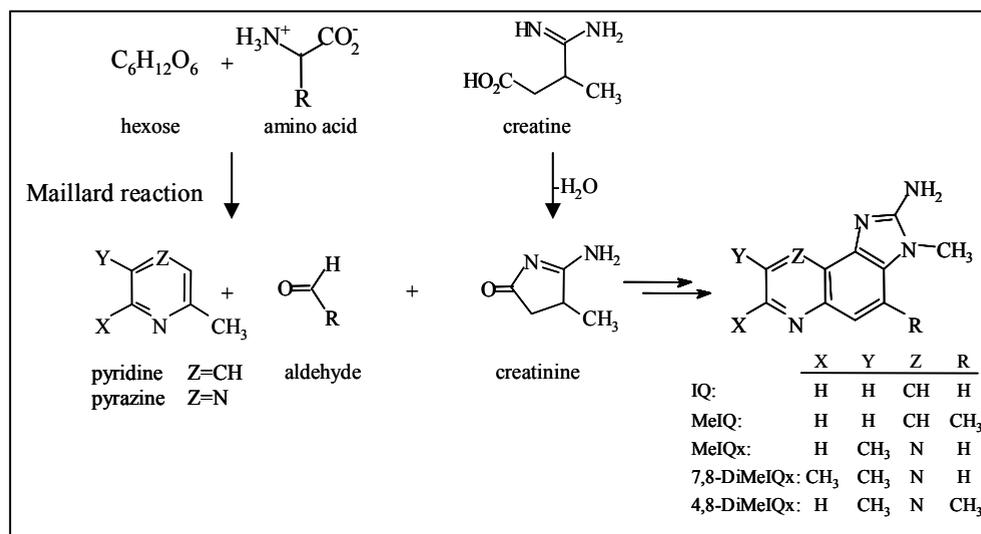


Fig. 3. Proposed pathway for the formation of quinoline (IQ, MeIQ) and quinoxaline type (MeIQx, 4,8-DiMeIQx and 7,8-DiMeIQx) of HCAs. Adapted from Jägerstad et al. (Jägerstad et al., 1983b).

A study using precursors of PhIP (structure shown in Fig. 1) labelled with ^{13}C was key to clarify the reaction mechanism involved in the formation of this amine, which is the most abundant mutagenic HCA in cooked meat and fish. Phenylalanine labelled with ^{13}C at three non-aromatic positions (C-1, C-2 and C-3) (see Fig. 4) provided important information. When labelling the carbon atom of the carboxylic acid of phenylalanine (C-1), there was no incorporation of ^{13}C , probably due to fast decarboxylation. When labelling the C-2 of the amino acid, two different signals were detected in ^{13}C -NMR (C-5 and C-7 in PhIP); and when labelling at C-3, just one position of PhIP incorporated the ^{13}C (C-3 in PhIP). From these experiments, Murkovic et al. proposed the mechanism of formation of PhIP that is reproduced in Figure 4 (Murkovic et al., 1999). C-1 of phenylacetaldehyde (2), i.e. Strecker degradation product of phenylalanine (1), undergoes aldol condensation with creatine (3) to form (A), which suffers dehydration to form (B). A and B intermediates were isolated from model systems and from heated meat in Dr. Murkovic's research group (Zöchling et al., 2002). Experiments with ^{15}N -labelled phenylalanine, carried out to identify the origin of the nitrogen forming the pyridine moiety of PhIP, revealed that this amino acid was not the only source of this atom, and that creatine or even free ammonia could also provide it.

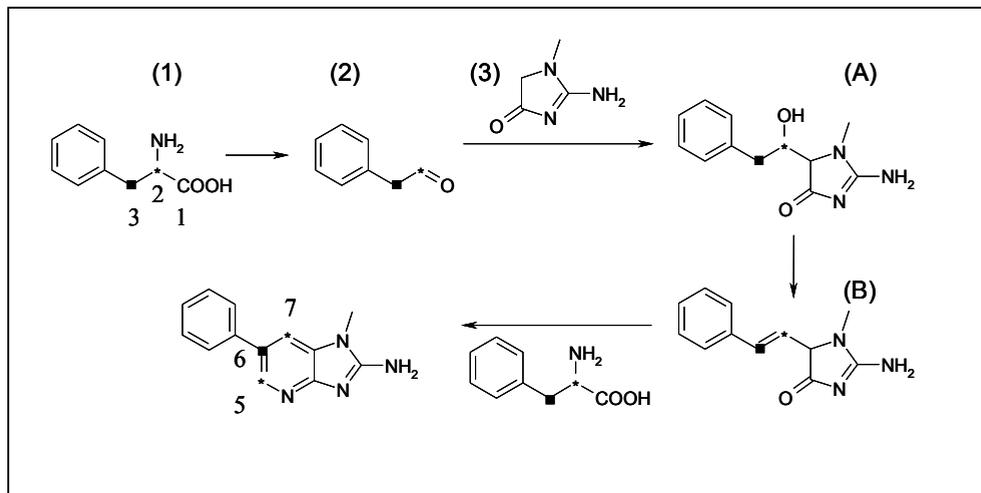


Fig. 4. Formation of PhIP. The marked carbon atoms correspond to the labelled positions in the experiments. Intermediate reaction products are signalled. Adapted from Murkovic et al. (Murkovic et al., 1999; Murkovic, 2004).

2.1 Parameters affecting the yield of HCAs

Among the different parameters affecting the formation of HCAs, temperature is the most important. The levels of HCAs are highly dependent on the temperature of the cooking process. In general, the amounts of HCAs increase at high temperature (Knize et al., 1994; Skog et al., 1995, 1997). Thus, HCAs form primarily in the crust of the cooked products and to a lesser extent in the inner part, which is where the temperature is lower (Skog et al., 1995).

Heat and mass transfer are variables that affect the formation of HCAs in cooking processes. Heating of meat produces protein denaturation, losses of fat and moisture and changes in the shrinkage and porosity of the meat or fish matrix. When heat is applied to the surface of the meat, it is transferred to the centre, creating a temperature gradient between the surface and the centre. As the temperature at the surface increases, the partial pressure of water increases at the surface, which causes a vapour flow towards the centre, where it condenses and releases heat. The increase of water content at the centre produces a flow of water towards the surface, even out of the meat (Persson et al., 2002). This water transport brings precursors of HCAs to the surface of the meat and to the drippings. In consequence, heat from the hot source favours the reaction between precursors of HCAs, and therefore HCAs can be found in drippings, even at higher amounts than in the food itself (Skog et al., 1997; Pais et al., 1999). Mechanisms controlling heat and mass transfer during thermal processing of beefburgers were studied by Bea. Kovácsné in a doctoral thesis at Lund University (B. Kovácsné, 2004). Cooking methods involve different heat and mass flows. Roasting entails transference of heat by convection through the air and radiation through the walls. In cooking methods where liquid surrounds the meat, such as stewing, boiling or deep-frying, heat is transferred by convection. Pan-frying produces heat transference to the meat by conduction and convection through a layer of fat and water. In contact frying, the temperature in the outermost part of the meat does

not rise above 100°C as long as water is present, and from the crust to a certain depth there is an evaporation zone. When crust is formed, heat flow towards the inside of the meat slows down because the crust insulates to some extent. Likewise, coating foods can reduce the formation of HCAs due to the insulating effect of the coating, and conductive heat transfer dominates inside the meat (Busquets et al., 2008; Persson et al., 2002; Skog et al., 2003). In general, roasting, boiling, stir-frying and stewing are the cooking methods in which lower amount of HCAs are formed; whereas griddling, pan-frying, barbecuing and deep-frying are the methods that lead to higher levels of HCAs, due to greater heat transfer (Busquets et al., 2004, 2008; Sinha et al., 1998a, 1998b; Skog et al., 1998). An example of the profile of temperatures when frying meat is shown in Fig. 5. Chicken breasts fillets, 1 cm in thickness, were fried in an aluminium frying pan, without adding fat, at 220 °C for 5 minutes each site. K-type thermocouples were inserted in different sites of the fillet; 2 in the centre of the fillet (T centre 1, 2); two were fixed at 1 mm below the upper and the lower surface (T surface 1,2), and one thermocouple was placed between the pan surface and the fillet to measure the temperature (Frying T), which was recorded every 10 seconds. The temperature profile measured was found highly reproducible when frying different fillets evidencing that the heat and mass transfer mechanisms taking place during the cooking process are reproducible. The temperature in the centre of the fillet did not go over 100 °C and the temperature at 1 mm below the surface never reached the frying temperature.

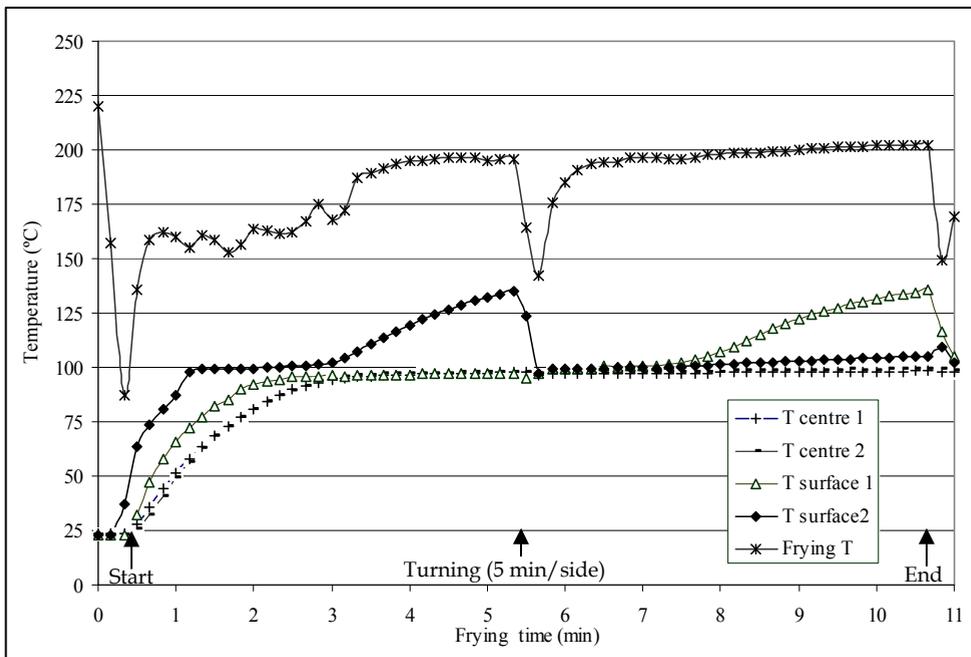


Fig. 5. Temperature profiles during pan-frying of a chicken fillet (1cm thick). Each side of the fillet was in contact with the hot surface for 5 minutes. The temperature of the pan was set at 220 °C.

Knowledge on the physical mechanisms affecting the formation of HCAs has led researchers to look for ways to decrease the formation of these mutagens. Changing cooking practices to minimize weight loss resulted in less formation of HCAs because of the alteration of the mass transfer of HCA precursors. The addition of NaCl, sodium tryphosphate or carbohydrates with water-holding capacity to meat prior to cooking was an efficient and simple way to reduce the subsequent formation of HCAs, explained by a reduction in the transport of water-soluble precursors towards the crust (Persson et al., 2003, 2004). Based on the same principle, microwaving beef patties before frying caused a reduction in mutagenicity possibly due to the loss of water and HCA precursors during the pre-treatment (Felton et al., 1994). Flipping the food frequently reduced the formation of HCAs because the meat has spent less time in contact with the hot surface (Salmon et al., 2000; Tran et al., 2002); and shortening cooking time or lowering cooking temperature also resulted in lower heat and mass transfer. As a result of the above-mentioned studies, easy-to-adopt cooking practices that reduce exposure to HCAs can be recommended.

Alternatively, solutions can also be found interfering in the chemical reactions leading to the formation of HCAs. For instance, one of the most effective methods reported for the inhibition of the formation of PhIP has been marinating the meat with red wine previous to the cooking process involving heat, effect that was markedly different to control marinades containing water and ethanol (Busquets et al., 2006). An example of the reduction of PhIP in fried chicken with marinating time is shown in Fig. 6.

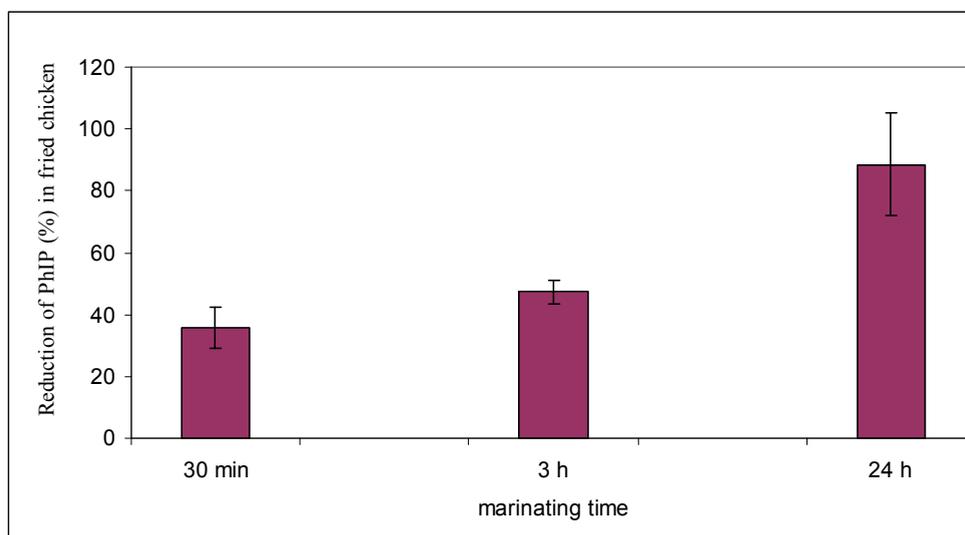


Fig. 6. Effect of marinating time on the reduction of PhIP in fried chicken. The marinating media was red wine. The wine characterisation and experimental conditions are as reported in Busquets et al. 2006.

One way to interfere in the formation of HCAs is using antioxidants, which may affect radical reactions involved in the formation of HCAs by scavenging free radicals (Kikugawa, 1999). Antioxidants have been shown to exert both anti- and pro-oxidative effects,

depending on their concentration and type. For instance, Johansson and Jägerstad studied the effect of several antioxidants, at different concentrations, on the formation of HCAs in model systems. The results showed that, surprisingly, most antioxidants increased the formation of HCAs and that the rate of the effect depended on the concentration. Likewise, a lack of correlation was found between the concentration of the antioxidant and the effect observed (Johansson & Jägerstad, 1996). In summary, the formation of the heterocyclic amines which mechanism of formation may involve radical reactions can be enhanced or reduced depending on the particular cooking conditions used. Therefore, the effect of antioxidants on the formation of HCAs is not clear yet (Balogh et al., 2000; Britt et al., 1998; Melo 2008; Murkovic et al., 1998; Oguri et al., 1998; Shin et al., 2002; Tai et al., 2001; Tsen et al., 2006).

2.2 Levels of HCAs in food

Nowadays it is accepted that the main source of exposure to HCAs is the intake of cooked meat and fish. In order to know the type and amounts of HCAs to which humans are exposed, the content of HCAs has been determined in a high number of food items and the reported amounts are compiled periodically (Felton et al. 2000; Layton et al., 1995; Skog et al., 1998). To date about 20 mutagenic HCAs have been identified in cooked proteinaceous food and new ones may be identified in the future; species which structure is close to HCAs, if not HCAs, have been detected recently (Busquets et al., 2008). The most commonly found HCAs in thermally treated proteinaceous food are shown in Fig. 7.

To have an overview on the amount of HCAs in commonly consumed food items, the concentration of HCAs in over 20 publications have been summarized in Fig. 8 (Ahn et al 2005; Bermudo et al., 2005 ; Borgen et al., 2004; Busquets et al., 2004, 2006, 2008; Casal et al., 2004; Cheng et al., 2007; Gerbl et al., 2004; Khan et al., 2008; Lan et al., 2004; Melo et al., 2008; Ni et al., 2008; Oz et al., 2007; Persson et al., 2004; Ristic et al. 2004; Salmon et al., 2006; Toribio et al., 2007; Tsen et al., 2006; Warzecha et al., 2004; Wong et al, 2005). The average concentrations of several HCAs in meats cooked using different methods shows that chicken presents the highest concentration of HCAs, and in particular of the amines called DMIP and PhIP, which are structurally related, and the comutagens and neurotoxic amines harman and norharman, which were also found at relative high concentrations in venison. For a review on the latter ones, see Pfau & Skog (2004). The higher abundance of PhIP and DMIP in chicken can be due to the higher amount of some free amino acids such as phenylalanine mainly but also tyrosine, leucine, isoleucine or threonine, whereas the lower content identified in other meats can be due to the lower content of sugars or creatine/creatinine (Bjeldanes et al., 1982; Jägerstad et al., 1983a, 1983b ; Khan et al., 2009). Cooking methods also play an important role in the formation of PhIP because low amounts of this usually abundant amine have also been quantified in fried chicken breast cooked in the Chinese style (Wong et al., 2005; Salmon et al., 2006). Interestingly, low content of PhIP, below 2 ng/g, was found in turkey cooked by a prolonged frying process (15 min/side at 190-200°C) (Warzecha et al., 2004). Pork showed the highest content of the HCAs named IQ, MeIQx, 4,8-DiMeIQx, Trp-P-2 and Trp-P-1, and any HCA stand out in beef samples in terms of concentration level. The median concentration of HCAs in beef was below 3 ng/g; and even lower amounts were quantified in fish. Compared with previous data (Layton et al., 1995; Skog et al., 1998; Felton et al., 2000), the amounts of HCAs determined in fish for the

studied period are low. The cause of this low occurrence may be the oriental recipes used, which use ingredients with antioxidant properties and cooking methods with low heat transfer (Wong et al., 2005; Salmon et al., 2006). The data in the papers included in Fig. 8 corroborates that the cooking methods involving higher heat transfer (barbecuing, frying, griddling and grilling) are related to higher levels of HCAs, whereas the processes with lower heat transfer (stewing, stir-frying, roasting, coated-frying and boiling) are related to lower amounts of HCAs.

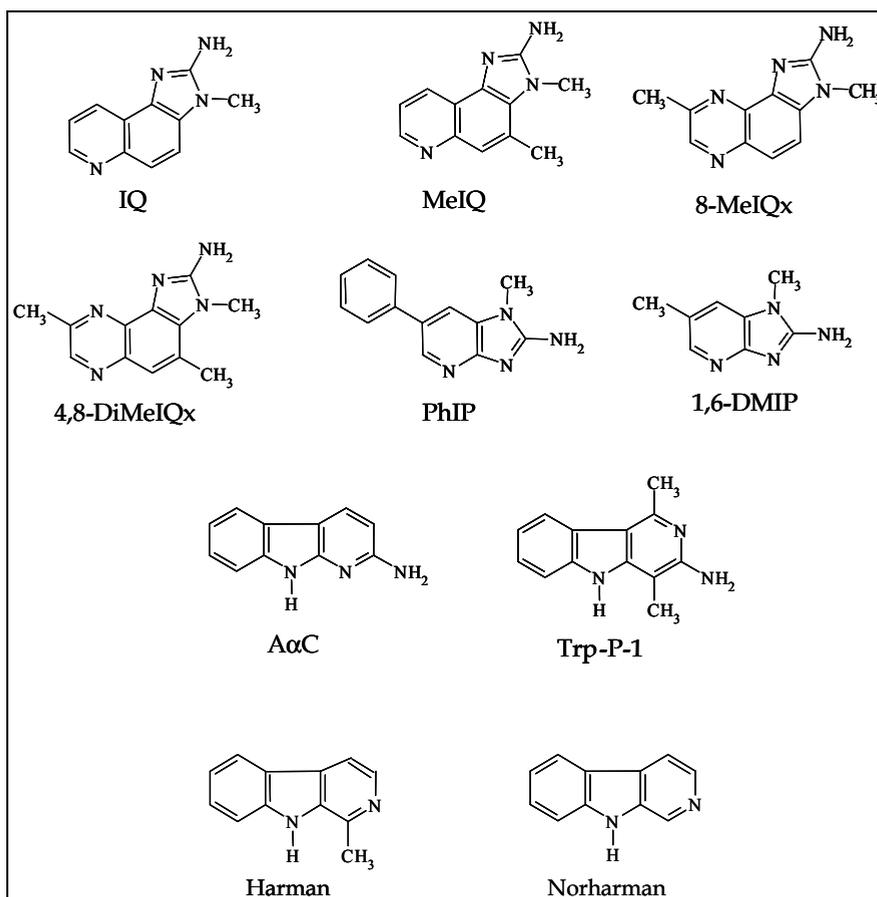


Fig. 7. Chemical structure of HCAs commonly found in cooked protein rich food.

2.3 Assessment of the exposure to HCAs

The toxicological effect of the habitual exposure of HCAs on humans is still unknown. There are two main approaches to quantifying exposure to HCAs; the first one evaluates the correlation between the intake of HCAs and increased risk of different types of human cancer; the second, searches for biomarkers of exposure to HCAs in biological fluids that correlate with the final molecule causing DNA damage. However analytical methodology

for the analysis of such biomarkers under a normal exposure to HCAs is at its initial stages (Busquets et al., 2009; Frandsen et al., 2002, 2007, 2008); a few biomarker of exposure have been proposed so far but their analysis and correlation with cancer incidence in large cohorts has not been carried out yet, to the best of our knowledge.

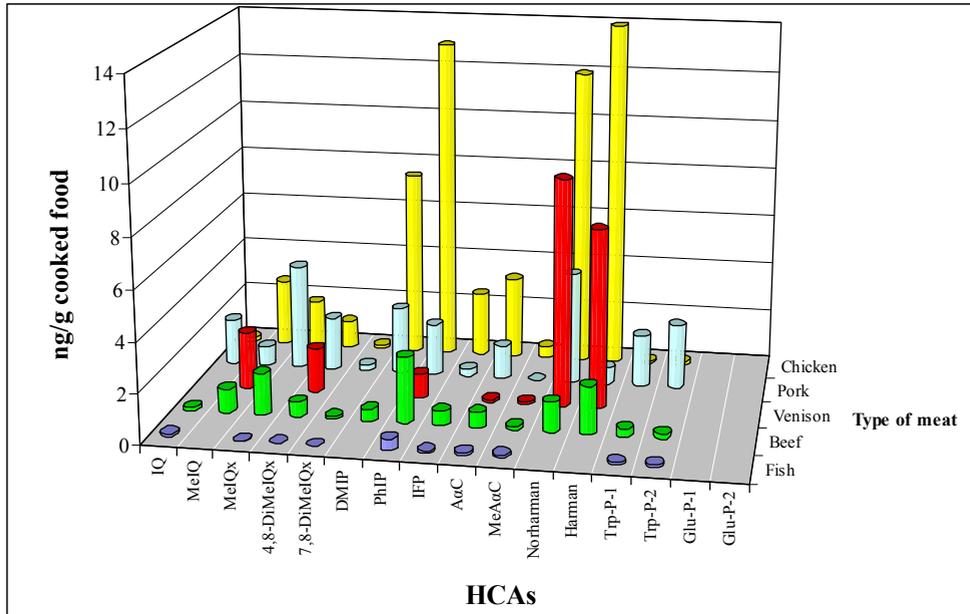


Fig. 8. Concentration of HCAs, identified by their acronym, reported in chicken, pork, venison, beef and fish items cooked in various ways.

Epidemiological studies relate the content of specific HCAs in food and the incidence of particular types of cancer. Several epidemiological studies have found a positive correlation between the intake of some HCAs and different types of human cancer (Butler et al., 2003; Cross A.J et al., 2011; Destefani et al., 1997, 1998; Martinez et al., 2007; Sinha et al., 2001) whereas other studies have found no such correlation (Augustsson et al., 1999; Gunter et al., 2005; Sonestedt et al., 2008). Numerous factors hinder reaching conclusions on the association of HCAs and human cancer by means of dietary calculations. Problems still to be surmounted are: the difficulty in getting accurate information on eating habits; bias, inconsistent reporting or misclassification; the fact that different cooking methods and degrees of doneness cause very different HCA content, as discussed earlier in this chapter; difficulty in quantifying cooking doneness using questionnaires; difficulty in considering variations in day-to-day diet; the existence of multiple HCAs and possibly some other factors that have not yet been identified. The representativity of the food analysed and the accuracy of HCA quantification must also be taken into account. For instance, several studies have related the occurrence of MeIQx or 4,8-DiMeIQx with cancer but these amines occur at low concentration, usually <2 ng/g cooked food, as it is shown in Figure 8, and their determination is difficult and possibly it is carried out with low accuracy. In addition, the whole amount of the HCAs ingested is not bioavailable, in part due to other components

of the meal, but epidemiologic studies can not take these unknown parameters into consideration. Furthermore, only a fraction of the bioavailable HCAs are activated to the ultimate electrophilic intermediate that causes the genetic damage and this activation can be more or less effective depending on the phenotypes of the enzymes involved in the activation pathways and on lifestyle factors (Le Marchand et al., 2001). Moreover, there are mechanisms in the human body that repair mutations and, in addition, the mutations that initiate cancer processes may be caused by environmental factors other than HCAs in diet. Another factor, not unique to HCAs, is that the delay between the evaluation of the exposure and disease outcome (Alexander et al., 2002). These factors show that there is a big gap between the estimation of HCA exposure and the identification of the origin of cancer processes by means of epidemiologic studies.

Regardless of all the existing limitations and approximations necessary to assess the exposure to HCAs, the individual daily exposure to HCAs has been quantified in several countries. For Asian populations: 50 ng in China (Wong et al., 2005) and 72 ng in Japan (Kobayashi et al., 2002) were estimated. In general, higher values have been found for European populations: 69 ng in Germany (Rohrmann et al., 2007); 160 ng (Augustsson et al., 1997), 690 ng (Ericson et al. 2007) and 520 ng (Sonestedt et al., 2008) in Sweden; 330 ng in Switzerland (Zimmerli et al., 2001); and 286 ng (Busquets et al., 2008) and 606 ng in Spain (Busquets et al., 2004). Several studies performed in the United States found high values: 1.690 ng (Layton et al., 1995), 455 ng (Keating & Bogen, 2001), 585 ng (Bogen & Keating, 2001) and 715-1.293 ng (Keating & Bogen, 2004). The quoted intakes were calculated for an average body mass of 65 Kg. The levels of exposure estimated from food frequency questionnaires and analysis of HCAs in food may be useful in toxicological studies to define the impact of HCAs on health and to make risk-based recommendations about reducing exposure to HCAs. However, the reported values have to be used in full awareness of the intrinsic limitations of exposure assessment by means of food frequency questionnaires and determination of HCAs in a limited number of cooked foods.

The intake of HCAs is not directly related with mutations in the DNA. Only a part of the total amount of HCAs present in heated proteinaceous food will be absorbed. To the best of our knowledge, few studies have focused on the bioavailable or effective dose of HCAs, although this is key to assessing the effective dose of the dietary intake of HCAs. To understand the influence of digestion parameters on the release of HCAs, Kulp and coworkers used a model system to test the effect of several enzymes (amylase, pepsin and pancreatin) on the digestion of well-done chicken (Kulp et al., 2003) and pancreatin was the only enzyme that favoured the bioavailability of HCAs. In addition, HCAs differed greatly from each other in ways that affected their bioavailability; PhIP, which is less polar than the other amines studied, was 50% present in each fraction, which implies that PhIP is less accessible than more polar HCAs. Very important also was the finding that the higher the degree of doneness, the lower the bioavailability of HCAs was (Kulp et al., 2003). Another factor that may affect the bioavailability of HCAs is the presence of fibre in the meal. Experiments carried out in rats revealed that dietary fibre, 95% of which is contributed by whole plant cell walls, may protect by adsorbing carcinogens, thus lowering their effective concentration in the alimentary tract, and by carrying the carcinogens out of the body in faeces (Ferguson & Harris, 1996). However, not all types of fibre had adsorptive abilities. The most hydrophobic plant cell wall preparations containing the polymer suberin, which occur in the diet, for example in potato skins, showed the highest adsorption capacity for

HCAs among the fibre examined and preparations with lignin showed intermediate adsorptive abilities. The adsorption of HCAs to the plant cell walls increased with increasing hydrophobicity of the HCA (Ferguson et al., 1995; Ferguson & Harris, 1996; Harris et al., 1996; Hayatsu et al., 1993b). Similarly, chlorophyllin, intestinal microflora and certain bacterial strains contained in fermented foods may decrease the bioavailability of HCAs by direct binding of HCAs to their structure (Hayatsu et al., 1993a; Kassie et al., 2001, 2004; Knasmüller et al., 2001; Orrhage et al., 1994; 2002).

Once the HCAs are bioavailable, they require metabolic activation to damage DNA. Most HCAs are oxidized in the body and just a small portion is excreted unchanged. The first step to activate HCAs is catalyzed by cytochrome P450 enzymes (CYP). 57 CYP genes have been identified in human genome, half of which are involved in xenobiotic metabolism (Glatt, 2006). Among the different CYPs, those of family 1 have been found to participate in the metabolism of HCAs. CYP1A2 shows the highest activity for N-hydroxylation or activation of the HCAs to the ultimate mutagenic specie (Boobis et al., 1994; Glatt, 2006; Rich et al., 1992; Zhao et al., 1994). CYP1A2 activity may vary from person to person and can be activated by lifestyle factors such as smoking or eating habits (Lang et al., 1994). N-hydroxylated HCAs undergo O-acetylation and O-sulphatation catalyzed by N-acetyltransferases and sulphotransferases, respectively. These esters are hydrolyzed to produce highly electrophilic arylnitrenium ions, considered to be the final genotoxicants, which react with some sites of the DNA. The reactive nitrenium ion also reacts with proteins (Buonarati et al., 1990; Turesky et al., 1992; Turesky et al., 2004). Detoxification involves converting the toxicants to polar molecules that can be excreted or transported to extrahepatic tissues. Various detoxification pathways, such as ring hydroxylation, catalyzed by CYPs, or glucuronidation, catalyzed by UDP-glucuronosyltransferases, compete with the activation routes. Understanding the metabolic pathways of HCAs and developing analytical methodology capable of determining metabolites from HCAs in biological fluids with high accuracy, despite their low concentration and complexity of the matrices, is providing the tools to identify species that could be proved to be biomarkers of exposure. The analysis of species proved to be biomarkers of exposure to HCAs in large cohorts and its relation with cancer incidence will be ultimate evidence to relate HCAs with human cancer.

3. Conclusion

Heat treatments applied during cooking processes cause the formation of mutagenic compounds from the reaction of natural precursors present in raw food. Although the exposure to such toxicants seems unavoidable, it can be highly reduced by just applying minor changes in cooking and eating habits. The exposure to HCAs is currently being estimated with methods comprising many approximations. Different types and levels of food borne mutagens are present in frequently eaten food items. The bioavailability of these cooking mutagens, their metabolic activation and DNA repair mechanism are also variable. The pathogenesis can also be caused by other factors, and it appears with a delay on time with respect to the causes that induced the genetic damage. For these reasons, the link between food borne mutagens and cancer has not been well established in humans although the effect of high concentrations of the mutagens in animals has shown to cause tumours. The mortality rate of cancer, the economical burden that the disease represents, and the evidences on the exposure to food borne mutagens discussed in this chapter, claim major

attention from the legislative bodies, which should establish maximum concentration limits for these species in commercial food products and recommend guidelines for "good cooking practices". Legislation on this topic would encourage the food industry to monitor, control and ultimately reduce the exposure food borne mutagens. Besides, the public health institutions and scientist should inform the population about the existence of the food borne mutagens and ways to minimise their formation. A change towards healthier eating/cooking habits in terms of exposure to cooking toxicants may be fomented with the approach used when disseminating the information. If the exposure is presented as something unavoidable, the consumers will resign themselves and do nothing. However, the attitude from the public may be more active if they receive information in a positive way; there is exposure to hazardous compounds but it can be reduced easily by using certain practices such as cooking methods with low heat transfer (boiling, stewing, coating, flipping the food frequently); lowering cooking time and temperature or using ingredients that interfere in the Maillard reaction. Once individuals are aware of the problem and willing to solve it, these generate a commercial opportunity, and for the first time companies would invest in products for a diet with low in food borne toxicants without being pushed to it. In summary, food borne carcinogens are not a dead end; individuals, food companies and public bodies have health or business interest in them.

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5. References

- Ahn, J. & Gruen, I.U. (2005). Heterocyclic amines: 2. Inhibitory effects of natural extracts on the formation of polar and nonpolar heterocyclic amines in cooked beef. *J.Food Sci.*, 70, C263-C268.
- Alexander, J.; Reistad, R.; Hegstad, S.; Frandsen, H.; Ingebrigtsen, K.; Paulsen, J.E. & Becher, G. (2002). Biomarkers of exposure to heterocyclic amines: approaches to improve the exposure assessment. *Food Chem. Toxicol.*, 40, pp. 1131-1137.
- Altaki, M.S; Santos, F.J. & Galceran, M.T. (2011). Occurrence of furan in coffee from Spanish market: contribution of brewing and roasting. *Food Chem.*, Vol. 126, pp. 1527-1532.
- Ames, B.N.; McCann, J. & Yamasaki, E. (1975). Methods for detecting carcinogens and mutagens with the salmonella/mammalian-microsome mutagenicity test. *Mutat. Res.*, 31, pp. 347-363.
- Arnoldi, A.; Corain, E.A.; Scaglioni, L. & Ames, J.M. (1997). New Colored Compounds from the Maillard Reaction between xylose and lysine. *J. Agric. Food Chem.*, Vol. 45, pp. 650-655.
- Augustsson, K.; Skog, K; Jägerstad, M. & Steineck, G. (1997). Assessment of the Human Exposure to Heterocyclic Amines. *Carcinogenesis*, Vol. 18, pp. 1931-1935.

- Augustsson, K.; Skog, K.; Jägerstad, M.; Dickman, P.W. & Steineck, G. (1999). Dietary Heterocyclic Amines and Cancer of the Colon, Rectum, Bladder, and Kidney - A Population-Based Study. *Lancet*, Vol. 353, pp. 703-707.
- Balogh, Z.; Gray, J.I.; Gomaa, E.A. & Booren, A.M. (2000). Formation and Inhibition of Has in fried Ground Beef Patties. *Food Chem.Toxicol.*, Vol. 38, pp. 395-401.
- Bermudo, E.; Ruiz-Calero, V.; Puignou, L. & Galceran, M.T. (2005). Analysis of heterocyclic amines in chicken by liquid chromatography with electrochemical detection. *Anal. Chim. Acta*, Vol. 536, pp. 83-90.
- Bermudo, E.; Moyano, E.; Puignou, L. & Galceran, M.T. (2006). Determination of acrylamide in foodstuffs by liquid chromatography ion-trap tandem mass-spectrometry using an improved clean-up procedure. *Anal.Chim.Acta* Vol. 559, pp. 207-214.
- Bjeldanes, L.F.; Morris, M.M.; Felton, J.S.; Healy, S.; Stuermer, D.; Berry, P.; Timourian, H. & Hatch, F.T. (1982). Mutagens from the cooking of food. III. Survey by Ames/Salmonella test of mutagen formation in secondary sources of cooked dietary protein. *Food Chem Toxicol.*, 20, pp. 365-369.
- Boobis, A.R.; Lynch, A.M.; Murray, S.; Delatorre, R.; Solans, A.; Farre, M.; Segura, J.; Gooderham, N.J. & Davies, D.S. (1994). CYP1A2-catalyzed conversion of dietary heterocyclic amines to their proximate carcinogens is their major route of metabolism in humans. *Cancer Res.*, Vol. 54, pp. 89-94.
- Borgen, E. & Skog, K. (2004). Heterocyclic amines in some Swedish cooked foods industrially prepared or from fast food outlets and restaurants. *Mol.Nutr.Food Res.*, Vol. 48, pp. 292-298.
- Britt, C.; Gomaa, E.A.; Gray, J.I. & Booren, A.M. (1998). Influence of cherry tissue on lipid oxidation and heterocyclic aromatic amine formation in ground beef patties. *J. Agric. Food Chem.*, Vol. 46, pp. 4891-4897.
- Buonarati, M.H.; Turteltaub, K.W.; Shen, N.H. & Felton, J.S. (1990). Role of sulfation and acetylation in the activation of 2-hydroxyamino-1-methyl-6-phenylimidazo[4,5-b]pyridine to intermediates which bind DNA. *Mutat.Res.*, Vol. 245, pp. 185-190.
- Busquets, R.; Bordas, M.; Toribio, F.; Puignou, L. & Galceran, M.T. (2004). Occurrence of heterocyclic amines in several home-cooked meat dishes of the Spanish diet. *J. Chromatogr. B*, Vol. 802, pp. 79-86.
- Busquets, R.; Puignou, L.; Galceran, M.T. & Skog, K. (2006). Effect of red wine marinades on the formation of heterocyclic amines in fried chicken breast. *J. Agric. Food Chem.*, 54, pp. 8376-8384.
- Busquets, R.; Puignou, L.; Galceran, M.T.; Wakabayashi, K. & Skog, K. (2007). Liquid Chromatography tandem mass spectrometry analysis of 2-amino-1-methyl-6-(4-hydroxyphenyl)imidazo[4,5- b]pyridine in cooked meats. *J. Agric. Food Chem.*, Vol. 55, pp. 9318-9324.
- Busquets, R.; Mitjans, D.; Puignou, L. & Galceran, M.T. (2008). Quantification of heterocyclic amines from thermally processed meats selected from a small-scale population-based study. *Mol.Nutr. Food Res.*, Vol. 52, pp. 1408-1420.
- Busquets, R.; Jönsson, J. Å.; Frandsen, H.; Puignou, L.; Galceran, M.T. & Skog, K. (2009). Hollow-fibre supported liquid membrane extraction and LC-MS/MS detection for the analysis of heterocyclic amines in urine samples. *Mol. Nutr. Food Res.*, Vol. 53, pp. 1496-1504.

- Butler, L.M.; Sinha, R.; Millikan, R.C.; Martin, C.F.; Newman, B.; Gammon, M.D.; Ammerman, A.S. & Sandler, R.S.(2003). Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. *Amer.J.Epidemiol.*, Vol. 157, pp. 434-445.
- Casal, S.; Mendes, E.; Fernandes, J.O.; Oliveira, M.B.P.P.; & Ferreira, M.A. (2004). Analysis of heterocyclic aromatic amines in foods by gas chromatography-mass spectrometry as their tert.- butyldimethylsilyl derivatives. *J. Chromatogr. A*, Vol. 1040, 105-114.
- Cheng, K.W.; Wu, Q.; Zheng, Z.P.; Peng, X.; Simon, J.E.; Chen, F.; & Wang, M. (2007). Inhibitory Effect of Fruit Extracts on the Formation of Heterocyclic Amines. *J. Agric. Food Chem.*, Vol. 55, pp. 10359-10365.
- Commoner, B.; Vithayathil, A.J.; Dolara, P.; Nair, S.; Madyastha, P. & Cuca, G.C. (1978). Formation of mutagens in beef and beef extract during cooking. *Science*, Vol. 201, pp. 913-916.
- Chung, S.Y.; Yettella, R.R.; Kim, J.S.; Kwon, K.; Kim, M.C.; & Min D.B. (2011). Effects of grilling and roasting on the levels of polycyclic aromatic hydrocarbons in beef and pork. *Food Chem.*, Vol. 129, pp. 1420-1426.
- Cross, A.J., Freedman, N.I., Ren, J., Ward, M. H., Hollenbeck, A. R., Schatzkin, A., Sinha, R., & Abnet, C.C. (2011). Meat consumption and risk of esophageal and gastric cancer in a large prospective study. *Am.J.Gastroenterol.*, Vol. 106, pp. 432-442.
- Destefani, E.; Ronco, A.; Mendilaharsu, M.; Guidobono, M. & Deneopellegrini, H. (1997). Meat Intake, Heterocyclic Amines, and Risk of Breast-Cancer - A Case-Control Study in Uruguay. *Cancer Epidem.Biomarker.Prev.*, Vol. 6, pp. 573-581.
- Destefani, E.; Ronco, A.; Mendilaharsu, M. & Deneopellegrini, H. (1998). Case-Control Study on the Role of Heterocyclic Amines in the Etiology of Upper Aerodigestive Cancers in Uruguay. *Nutr.Cancer*, Vol. 32, pp. 43-48.
- Drabik-Markiewicz, G.; Dejaegher, B.; De Mey, E.; Kowalska, T.; Paelinck, H.; & Heyden Vander Y. (2011). Influence of putrescine, cadaverine, spermidine or spermine on the formation of N-nitrosamine in heated cured pork meat. *Food Chem.*, Vol. 126, pp. 1539-1545.
- Druckrey, H. & Preussmann, R. (1962). The formation of carcinogenic nitrosamines, for example, in tobacco smoke. *Naturwissenschaften.*, Vol. 49, pp. 498-499.
- Ericson, U.; Wirfält, E.; Mattisson, I.; Gullberg, B. & Skog, K. (2007). Dietary intake of heterocyclic amines in relation to socio-economic, lifestyle and other dietary factors: estimates in a Swedish population. *Public Health Nutr.*, Vol. 10, pp. 616-627.
- Felton, J.S.; Fultz, E.; Dolbeare, F.A. and Knize, M.G. (1994). Effect of microwave pretreatment on heterocyclic aromatic amine mutagens/carcinogens in fried beef patties. *Food Chem.Toxicol.* , Vol. 32, pp. 897-903.
- Felton, J.S.; Jägerstad, M.; Knize, M.G.; Skog, K.; & Wakabayashi, K. (2000). Content in Foods, Beverages and Tobacco. In: *Food Borne Carcinogens*, Nagao M, Sugimura T (Eds), pp. 31-71, JohnWiley & Sons Ltd.-VCH, ISBN 9780471983996, Weinheim.
- Ferguson, L.R.; Robertson, A.M.; Watson, M.E.; Triggs, C.M. & Harris, P.J. (1995). The Effects of a Soluble-Fiber Polysaccharide on the Adsorption of Carcinogens to Insoluble Dietary-Fibers. *Chem.Biol.Inter.*, Vol. 95, pp. 245-255.
- Ferguson, L.R. & Harris, P.J. Studies on the Role of Specific Dietary-Fibers in Protection Against Colorectal-Cancer. *Mutat.Res.Fundam.Mol.Mech.Mut.* 1996, 350, 173-184.

- Frandsen, H.; Frederiksen, H. & Alexander, J. (2002). 2-amino-1-methyl-6-(5-hydroxy-)phenylimidazo[4,5-*b*]pyridine (5-OH-PhIP), a biomarker for the genotoxic dose of the heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP). *Food Chem. Toxicol.*, Vol. 40, pp. 1125-1130.
- Frandsen, H. Deconjugation of N-gluconide conjugated metabolites with hydrazine hydrate-Biomarkers for exposure to the food-borne carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine(PhIP). (2007).*Food Chem. Toxicol.*, Vol. 45, pp. 863-870.
- Frandsen, H. (2008). Biomonitoring of urinary metabolites of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) following human consumption of cooked chicken. *Food Chem. Toxicol.*, Vol. 46, pp. 3200-3205.
- Frandsen, H.; Frederiksen, H. & Alexander J. (2002). 2-amino-1-methyl-6-(5-hydroxy-)phenylimidazo[4,5-*b*]pyridine (5-OH-PhIP), a biomarker for the genotoxic dose of the heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP). *Food Chem. Toxicol.*, 40, pp. 1125-1130.
- Gerbl, U.; Cichna, M.; Zsivkovits, M.; Knasmüller, S. & Sontag, G. (2004). Determination of heterocyclic aromatic amines in beef extract, cooked meat and rat urine by liquid chromatography with coulometric electrode array detection. *J.Chromatogr.B*, 802, pp. 107-113.
- Glatt, H. & Sommer, Y. (2006). Health risks of 5-hydroxy-methyl-furfural (HMF) and related compounds, In: *Acrylamide and Other Hazardous Compounds in Heat-Treated Foods*, Skog, K., Alexander J. (Eds.), pp. 328-357, Woodhead Publishing Limited and CRC Press LLC, ISBN 1-84569-01107, Cambridge and Boca Raton.
- Gunter, M.J.; Probst-Hensch, N.M.; Cortessis, V.K.; Kulldorff, M.; Haile, R.W. & Sinha, R. (2005). Meat intake, cooking-related mutagens and risk of colorectal adenoma in a sigmoidoscopy-based case-control study. *Carcinogenesis*, Vol. 26, pp. 637-642.
- Harris, P.J.; Triggs, C.M.; Robertson, A.M.; Watson, M.E. & Ferguson, L.R. (1996). The Adsorption of Heterocyclic Aromatic-Amines by Model Dietary- Fibers with Contrasting Compositions. *Chem.Biol.Inter.*, Vol. 100, pp. 13-25.
- Hayatsu, H. & Hayatsu, T. (1993a) Suppressing Effect of Lactobacillus-Casei Administration on the Urinary Mutagenicity Arising from Ingestion of Fried Ground- Beef in the Human. *Cancer Lett.*, Vol. 73, pp. 173-179.
- Hayatsu, H.; Negishi, T.; Arimoto, S. & Hayatsu, T. (1993b). Porphyrins as Potential Inhibitors Against Exposure to Carcinogens and Mutagens. *Mutat.Res.*, Vol. 290, pp. 79-85.
- IARC Monographs on the evaluation of carcinogenic risks to humans. Some natural occurring substances: food items and constituents. Heterocyclic amines and mycotoxins. (1993). International Agency for Research on Cancer, Vol. 56, pp. 163-242, Lyon.
- IARC Acrylamide. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. (1994). International Agency for Research on Cancer, pp. 389, Lyon.
- IARC IARC Monographs on the evaluation of carcinogenic risks to humans. Dry cleaning, some chlorinated solvents, and other industrial chemicals. (1995). International Agency for Research on Cancer, Lyon 63, 393.
- IARC- World Health Organization. IARC classifies radiofrequency electromagnetic fields as possibly carcinogenic to humans. Press release 208. 31 May 2011.

- Jägerstad, M.; Reuterswärd, A.L.; Öeste, R.; Dahlqvist, A.; Grivas, S.; Olsson, K. & Nyhammar, T. (1983a). Creatinine and Maillard reaction products as precursors of mutagenic compounds formed in fried beef. *ACS Symp. Ser.*, 215, pp. 507-519.
- Jägerstad, M., Laser Reuterswärd, A., Olsson, R., Grivas, S., Nyhammar, T., Olsson, K., & Dahlqvist, A. (1983b). Creatin(in)e and Maillard reaction products as precursors of mutagenic compounds: effects of various amino acids. *Food Chem.*, Vol. 12, pp. 255-264.
- Johansson, M.A.E. & Jägerstad, M. (1996). Influence of pro-oxidants and antioxidants on the formation of mutagenic-carcinogenic heterocyclic amines in a model system. *Food Chem.*, Vol. 56, pp. 69-75.
- Kassie, F.; Lhoste, E.F.; Bruneau, A.; Zsivkovits, M.; Ferk, F.; Uhl, M.; Zidek, T.; & Knasmüller, S. (2004). Effect of intestinal microfloras from vegetarians and meat eaters on the genotoxicity of 2-amino-3-methylimidazo[4,5-f]quinoline, a carcinogenic heterocyclic amine. *J.Chromatogr.B*, Vol. 802, pp. 211-215.
- Kassie, F.; Rabot, S.; Kundi, M.; Chabicovsky, M.; Qin, H.M.; & Knasmüller, S. (2001). Intestinal microflora plays a crucial role in the genotoxicity of the cooked food mutagen 2-amino-3-methylimidazo[4,5-f]quinoline (IQ). *Carcinogenesis*, Vol. 22, pp. 1721-1725.
- Keating, G.A. & Bogen, K.T. (2001). Methods for estimating heterocyclic amine concentrations in cooked meats in the US diet. *Food Chem.Toxicol.*, Vol. 39, pp. 29-43.
- Keating, G.A. & Bogen, K.T. (2004). Estimates of heterocyclic amine intake in the US population. *J.Chromatogr.B*, Vol. 802, pp. 127-133.
- Kulp, K.S.; Fortson, S.L.; Knize, M.G. & Felton, J.S.(2003).An in vitro model system to predict the bioaccessibility of heterocyclic amines from a cooked meat matrix. *Food Chem.Toxicol.*, Vol. 41, pp. 1701-1710.
- Khan, M.R.; Busquets, R.; Santos, F.J. & Puignou, L.(2008).New method for the analysis of heterocyclic amines in meat extracts using pressurised liquid extraction and liquid chromatography-tandem mass spectrometry. *J. Chromatogr. A*, Vol. 1194, pp. 155-160.
- Khan, M.R.; Bertus, L.M.; Busquets, R.; & Puignou, L. (2009). Mutagenic heterocyclic amine content in thermally processed offal products. *Food Chem.*, Vol. 112, pp. 838-843.
- Kikugawa, K. (1999). Involvement of Free-Radicals in the Formation of Heterocyclic Amines and Prevention by Antioxidants. *Cancer Lett.*, Vol. 143, pp. 123-126.
- Kovácsné, B. (2004). The mechanisms controlling heat and mass transfer on frying of beefburgers, Lund University. *Doctoral thesis*.
- Knasmüller, S.; Steinkellner, H.; Hirschl, A.M.; Rabot, S.; Nobis, E.C. & Kassie, F. (2001). Impact of Bacteria in Dairy-Products and of the Intestinal Microflora on the Genotoxic and Carcinogenic Effects of Heterocyclic Aromatic-Amines. *Mutat.Res.Fundam.Mol.Mech.Mut.*, Vol. 480, pp. 129-138.
- Knize, M.G.; Dolbear, F.A.; Carroll, K.L.; Moore, D.H. & Felton, J.S. (1994). Effect of Cooking Time and Temperature on the Heterocyclic Amine Content of Fried Beef Patties. *Food Chem.Toxicol.*, Vol. 32, pp. 595-603.
- Kobayashi, M.; Hanaoka, T.; Nishioka, S.; Kataoka, H. & Tsugane, S. (2002). Estimation of dietary HCA intakes in a large-scale population-based prospective study in Japan. *Mutat.Res.*, Vol. 506-507, pp. 233-241.

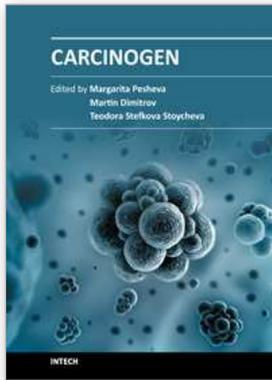
- Lan, C.M.; Kao, T.H. & Chen, B.H. (2004). Effects of heating time and antioxidants on the formation of heterocyclic amines in marinated foods. *J.Chromatogr.B*, Vol. 802, pp. 27-37.
- Lang, N.P.; Butler, M.A.; Massengill, J.; Lawson, M.; Stotts, R.C.; Hauerjensen, M. & Kadlubar, F.F. (1994). Rapid Metabolic Phenotypes for Acetyltransferase and Cytochrome P4501A2 and Putative Exposure to Food-Borne Heterocyclic Amines Increase the Risk for Colorectal-Cancer or Polyps. *Cancer Epidem.Biomarker.Prev.*, Vol. 3, pp. 675-682.
- Layton, D.W.; Bogen, K.T.; Knize, M.G.; Hatch, F.T.; Johnson, V.M. & Felton, J.S. (1995). Cancer Risk of Heterocyclic Amines in Cooked Foods - An Analysis and Implications for Research. *Carcinogenesis*, Vol. 16, pp. 39-52.
- Lezamiz, J.; Barri, T.; Jönsson, J.Å. & Skog, K. (2008). A simplified hollow-fibre supported liquid membrane extraction method for quantification of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) in urine and plasma samples. *Anal. Bioanal. Chem.*, Vol. 390, pp. 689-696.
- Lijinsky, W. & Shubik, B. (1964). Benzo[*a*]pyrene and other polynuclear hydrocarbons in charcoal-broiled meat. *Science (Washington, DC, United States)*. Vol. 145, pp. 53-55.
- Maga, J.A. (1979). Furans in foods. *Critical Reviews in Food Science and Nutrition*, Vol. 11, pp. 355-400.
- Martinez, M.E.; Jacobs, E.T.; Ashbeck, E.L.; Sinha, R.; Lance, P.; Alberts, D.S. and Thompson, P.A. (2007). Meat intake, preparation methods, mutagens and colorectal adenoma recurrence. *Carcinogenesis*, 28, pp. 2019-2027.
- Melo, A.; Viegas, O.; Eca, R.; Petisca, C.; Pinho, O.; & Ferreira, I.M.P.L. Extraction, Detection, and Quantification of Heterocyclic Aromatic Amines in Portuguese Meat Dishes by HPLC/Diode Array. (2008). *J.Liq.Chromatogr.Relat.Techno.*, Vol. 31, pp. 772-787.
- Mottram, D.S.; Wedzicha, B.L. & Dodson A.T. (2002). Acrylamide is formed in the Maillard reaction. *Nature*, Vol. 419, 448-449.
- Murkovic, M., Steinberger, D., & Pfannhauser, W. (1998). Antioxidant Spices Reduce the Formation of Heterocyclic Amines in Fried Meat. *Z.Lebensm.Unters.Forsch.A Foo.*, Vol. 207, pp. 477-480.
- Murkovic, M.; Weber, H.J.; Geiszler, S.; Frohlich, K. & Pfannhauser, W. (1999). Formation of the food associated carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]Pyridine (PhIP) in model systems. *Food Chem.*, Vol. 65, pp. 233-237.
- Murkovic, M. (2004). Formation of heterocyclic aromatic amines in model systems. *J. Chromatogr. B*, 802, pp. 3-10.
- Nagao, M.; Honda, M.; Seino, Y.; Yahagi, T. & Sugimura, T. (1977). Mutagenicities of smoke condensates and the charred surface of fish and meat. *Cancer Lett.*, Vol. 2, pp. 221-226.
- Ni, W.; McNaughton, L.; LeMaster, D.M.; Sinha, R.; & Turesky, R.J. (2008). Quantitation of 13 Heterocyclic Aromatic Amines in Cooked Beef, Pork, and Chicken by Liquid Chromatography-Electrospray Ionization/Tandem Mass Spectrometry. *J.Agric.Food Chem.*, Vol. 56, pp. 68-78.
- Oguri, A.; Suda, M.; Totsuka, Y.; Sugimura, T. & Wakabayashi, K. (1998). Inhibitory Effects of Antioxidants on Formation of Heterocyclic Amines. *Mutat. Res. Fundam. Mol. Mech. Mut.*, Vol. 402, pp. 237-245.

- Orrhage, K.; Sillerstrom, E.; Gustafsson, J.A.; Nord, C.E. & Rafter, J. (1994). Binding of Mutagenic Heterocyclic Amines by Intestinal and Lactic-Acid Bacteria. *Mutat.Res.Fundam.Mol.Mech.Mut.*, Vol. 311, pp. 239-248.
- Orrhage, K.M.; Annas, A.; Nord, C.E.; Brittebo, E.B. & Rafter, J.J. (2002). Effects of Lactic-Acid Bacteria on the Uptake and Distribution of the Food Mutagen Trp-P-2 in Mice. *Scand.J.Gastroenterol*, Vol. 37, pp. 215-221.
- Oz, F.; Kaban, G. & Kaya, M. (2007). Effects of cooking methods on the formation of heterocyclic aromatic amines of two different species trout. *Food Chem.*, 104, pp. 67-72.
- Pais, P.; Salmon, C.P.; Knize, M.G. & Felton, J.S. (1999) Formation of mutagenic/carcinogenic heterocyclic amines in dry- heated model systems, meats, and meat drippings. *J. Agric. Food Chem.* Vol. 47, pp. 1098-1108.
- Persson, E.; Sjöholm, I. & Skog, K. (2002). Heat and mass transfer in chicken breasts: Effect on PhIP formation. *Eur.Food Res.Techmol.*, Vol. 214, pp. 455-459.
- Persson, E.; Sjöholm, I. & Skog, K. (2003). Effect of High Water-Holding Capacity on the Formation of Heterocyclic Amines in Fried Beefburgers. *J.Agric.Food Chem.*, Vol. 51, pp. 4472-4477.
- Persson, E.; Sjöholm, I.; Nyman, M. & Skog, K. (2004). Addition of Various Carbohydrates to Beef Burgers Affects the Formation of Heterocyclic Amines during Frying. *J.Agric.Food Chem.*, Vol. 52, pp. 7561-7566.
- Pfau, W. & Skog, K. (2004). Exposure to β -carbolines norharman and harman. *J Chromatogr. B*, Vol. 802, pp. 115-126.
- Report on Carcinogens. National Toxicology Program. (2011). 12th ed. US Department of Health and Human Services, Public Health Services, Washington DC.
- Rich, K.J.; Murray, B.P.; Lewis, I.; Rendell, N.B.; Davies, D.S.; Gooderham, N.J.; & Boobis, A.R. N-Hydroxy-MeIQx is the major microsomal oxidation product of the dietary carcinogen MeIQx with human liver. (1992). *Carcinogenesis*, Vol. 13, pp. 2221-2226.
- Ristic, A.; Cichna, M. & Sontag, G. Determination of less polar heterocyclic aromatic amines in standardised beef extracts and cooked meat consumed in Austria by liquid chromatography and fluorescence detection. (2004). *J.Chromatogr.B*, Vol. 802, pp. 87-94.
- Rohrmann, S.; Linseisen, J.; Becker, N.; Norat, T.; Sinha, R.; Skeie, G.; Lund, E.; Martinez, C.; Barricarte, A.; Mattisson, I.; Berglund, G.; Welch, A.; Davey, G.; Overvad, K.; Tjonneland, A.; Clavel-Chapelon, F.; Kesse, E.; Lotze, G.; Klipstein-Grobusch, K.; Vasilopoulou, E.; Polychronopoulos, E.; Pala, V.; Celentano, E., Bueno-de-Mesquita, H.B.; Peeters, P.H.M.; Riboli, E. & Slimani, N. (2002). Cooking of meat and fish in Europe--results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Eur J Clin Nutr*, Vol. 56, pp. 1216-1230.
- Salmon, C.P.; Knize, M.G.; Panteleakos, F.N.; Wu, R.W.; Nelson, D.O. & Felton, J.S. (2000). Minimization of heterocyclic amines and thermal inactivation of Escherichia coli in fried ground beef. *J Natl Cancer Inst*, Vol. 92, pp. 1773-1778.
- Salmon, C.P.; Knize, M.G.; Felton, J.S.; Zhao, B. & Seow, A. (2006). Heterocyclic aromatic amines in domestically prepared chicken and fish from Singapore Chinese households. *Food Chem. Toxicol.*, Vol. 44, pp. 484-492.
- Shah, F. U.; Barri, T.; Jönsson, J. Å. & Skog, K. (2008). Determination of heterocyclic aromatic amines in human urine by hollow-fibre supported liquid membrane extraction and

- liquid chromatography-ultraviolet detection system. *J. Chromatogr. B.*, Vol. 870, pp. 203-208.
- Shin, H.S.; Rodgers, W.J.; Goma, E.A.; Strasburg, G.M. & Gray, J.I. (2002). Inhibition of heterocyclic aromatic amine formation in fried ground beef patties by garlic and selected garlic-related sulfur compounds. *J. Food Protect.*, Vol. 65, pp. 1766-1770.
- Sinha, R.; Knize, M.G.; Salmon, C.P.; Brown, E.D.; Rhodes, D.; Felton, J.S.; Levander, O.A. and Rothman, N. (1998a). Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness. *Food Chem. Toxicol.*, Vol. 36, pp. 289-297.
- Sinha, R.; Rothman, N.; Salmon, C.P.; Knize, M.G.; Brown, E.D.; Swanson, C.A.; Rhodes, D.; Rossi, S.; Felton, J.S. & Levander, O.A. (1998b). Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings. *Food Chem. Toxicol.*, Vol. 36, pp. 279-287.
- Sinha, R.; Kulldorff, M.; Chow, W.H.; Denobile, J. & Rothman, N. (2001) Dietary-Intake of Heterocyclic Amines, Meat-Derived Mutagenic Activity, and Risk of Colorectal Adenomas. *Cancer Epidem. Biomarker. Prev.* Vol. 10, 559-562.
- Skog, K.; Steineck, G.; Augustsson, K. & Jägerstad, M. (1995). Effect of Cooking Temperature on the Formation of Heterocyclic Amines in Fried Meat-Products and Pan Residues. *Carcinogenesis* Vol. 16, pp. 861-867.
- Skog, K.; Augustsson, K.; Steineck, G.; Stenberg, M.; & Jägerstad, M. (1997). Polar and Nonpolar Heterocyclic Amines in Cooked Fish and Meat- Products and Their Corresponding Pan Residues. *Food Chem. Toxicol.*, Vol. 35, pp. 555-565.
- Skog, K.; Johansson, M.A.E.; & Jägerstad, M.I. (1998). Carcinogenic Heterocyclic Amines in Model Systems and Cooked Foods - A Review on Formation, Occurrence and Intake. *Food Chem. Toxicol.*, Vol. 36, pp. 879-896.
- Skog, K.; Eneroth, A.; and Svanberg, M. (2003). Effects of different cooking methods on the formation of food mutagens in meat. *Int. J. Food Sci. Technol.*, Vol. 38, pp. 313-323.
- Skog, K. & Jägerstad, M. (2006). Minimising the formation of hazardous compounds in foods during heat treatment, In: *Acrylamide and Other Hazardous Compounds in Heat-Treated Foods* Skog, K., Alexander J. (Eds.), pp. 407-424, Woodhead Publishing Limited and CRC Press LLC, ISBN 1-84569-01107, Cambridge and Boca Raton.
- Sonestedt, E., Ericson, U., Gullberg, B., Skog, K., Olsson, H., & Wirfält, E. (2008). Do both heterocyclic amines and omega-6 polyunsaturated fatty acids contribute to the incidence of breast cancer in postmenopausal women of the Malmö diet and cancer cohort? *Int. J. Cancer*, Vol. 123, pp. 1637-1643.
- Sugimura, T. (2002). Food and cancer. *Toxicology*, Vol. 181-182, pp. 17-21.
- Sullivan, R.; Peppercorn, J.; Sikora, K.; Zalberg, J.; Meropol, N. J.; Amir, E.; Khayat, D.; Boyle, P.; Autier, P.; Tannock, I.F.; Fojo, T.; Siderov J., Williamson, S.; Camporesi, S.; Gordon McVie J.; Purushotham, A. D.; Naredi, P.; Eggermont, A.; Brennan, M.F.; Steinberg, M. L.; De Ridder, M.; McCloskey, S. A.; Verellen, D.; Roberts, T.; Storme, G.; Hicks R. J; J Ell P.; Hirsch, B. R.; Carbone, D. P.; Schulman, K. A.; Catchpole, P.; Taylor, D.; Geissler, J.; Brinker, N. G., Meltzer, Da.; Kerr, D.; & Aapro, M. (2011). Delivering affordable cancer care in high-income countries *Lancet Oncol.*, Vol. 12, pp. 933-980.
- Tai, C.Y.; Lee, K.H. & Chen, B.H. (2001). Effects of various additives on the formation of heterocyclic amines in fried fish fibre. *Food Chem.*, Vol. 75, pp. 309-316.

- Tareke E.; Rydberg P.; Karlsson, P.; Eriksson, S & Tornqvist, M. (2002). Analysis of acrylamide, a carcinogen formed in heated foodstuffs. *J Agric Food Chem*; Vol. 50, pp. 4998-5006.
- Tehrani, K.A.; Kersiene, M.; Adams, A.; Venskutonis, R. & De Kimpe, N. (2002). Thermal degradation studies of glucose/glycine melanoidins. *J. Agric. Food Chem.*, Vol. 50, pp. 4062-4068.
- Teixidó E.; Santos F.J.; Puignou, L. & Galceran M.T. (2006). Analysis of 5-hydroxymethylfurfural in foods by gas chromatography-mass spectrometry. *J. Chromatogr A*, Vol. 1135, pp. 85-90.
- Toribio, F.; Puignou, L.; & Galceran, M.T. (1999). Evaluation of different cleanup procedures for the analysis of heterocyclic aromatic-amines in a lyophilized meat extract. *J.Chromatogr.A*, Vol. 836, 223-233.
- Toribio, F.; Busquets, R.; Puignou, L. & Galceran, M.T. (2007). Heterocyclic amines in griddled beef steak analysed using a single extract clean-up procedure. *Food Chem.Toxicol.*, Vol. 45, pp. 667-675.
- Tran, N.L., Salmon, C.P., Knize, M.G., & Colvin, M.E. (2002). Experimental and simulation studies of heat flow and heterocyclic amine mutagen/carcinogen formation in pan-fried meat patties. *Food Chem.Toxicol.*, Vol. 40, pp. 673-684.
- Tricker, A.R.; Kumar, R.; Siddiqi, M.; Khuroo, M.S.; & Preussmann, R. (1991). Endogenous formation of N-nitrosamines from piperazine and their urinary excretion following anthelmintic treatment with piperazine citrate. *Carcinogenesis*, Vol. 12, pp. 1595-1599.
- Tsen, S.Y.; Ameri, F.; & Smith, J.S. (2006). Effects of rosemary extracts on the reduction of heterocyclic amines in beef patties. *J.Food Sci.*, Vol. 71, C469-C473.
- Turesky, R.J.; Rossi, S.C.; Welti, D.H.; Lay, J.O.; Jr. & Kadlubar, F.F.(1992). Characterization of DNA adducts formed in vitro by reaction of N-hydroxy-2-amino-3-methylimidazo[4,5-f]quinoline and N-hydroxy-2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline at the C-8 and N2 atoms of guanine. *Chem Res Toxicol*, 5, pp. 479-490.
- Turesky, R.J. & Vouros, P. (2004). Formation and analysis of heterocyclic aromatic amine-DNA adducts in vitro and in vivo. *J.Chromatogr.B*, Vol. 802, pp. 155-166.
- Turesky, R.J. (2006). Mechanisms of carcinogenicity of heterocyclic amines In: Skog, K., Alexander J. (Eds.), pp. 247-274, Woodhead Publishing Limited and CRC Press LLC, ISBN 1-84569-01107, Cambridge and Boca Raton .
- Turesky, R.J.; Goodenough, A.K.; Ni, W.; McNaughton, L.; LeMaster, D.M.; Holland, R.D.; Wu, R.W. & Felton, J.S. (2007). Identification of 2-amino-1,7-dimethylimidazo[4,5-g]quinoxaline: an abundant mutagenic heterocyclic aromatic amine formed in cooked beef. *Chem. Res. Toxicol.*, Vol. 20, pp. 520-530.
- Warzecha, L.; Janoszka, B.; Blaszczyk, U.; Strozyk, M.; Bodzek, D. & Dobosz, C. (2004). Determination of heterocyclic aromatic amines (HAs) content in samples of household-prepared meat dishes. *J.Chromatogr.B*, Vol. 802, pp. 95-106.
- Widmark, E.M.P. (1939). Presence of cancer-producing substances in roasted food. *Nature*, Vol. 143, pp. 984.
- Wong, K.Y.; Su, J.; Knize, M.G.; Koh, W.P. & Seow, A. (2005). Dietary exposure to heterocyclic amines in a Chinese population. *Nutr. Cancer*, Vol. 52, pp. 147-155.
- World Health Organization. (2004). The 10 leading causes of death by broad income group. Fact sheet. N° 310, November 2008.

- Zhao, K.; Murray, S.; Davies, D.S.; Boobis, A.R. & Gooderham, N.J. (1994). Metabolism of the food-derived mutagen and carcinogen 2-amino-1- methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) by human liver- microsomes. *Carcinogenesis*, Vol. 15, pp. 1285-1288.
- Zimmerli, B.; Rhyn, P.; Zöller, O.; & Schlatter, J. (2001). Occurrence of Heterocyclic Aromatic-Amines in the Swiss Diet - Analytical Method, Exposure Estimation and Risk Assessment. *Food Addit.Contam.*, Vol. 18, pp. 533-551.
- Zöchling, S. & Murkovic, M. (2002).Formation of the heterocyclic amine PhIP: identification of precursors and intermediates. *Food Chem.*, Vol. 79, pp125-134.



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During the last decades, cancer diseases have increased all over the world. The low quality of food and strong pollution of environment are the main prerequisites for carcinogenesis. The main problem for scientists is to find strategy for prevention of cancer diseases. Therefore, the information about the models for studying carcinogenesis and mutagens which appear during cooking, environmental pollutants, and tests for specific detection of carcinogens is particularly important. The book "Carcinogen" is intended for biologists, researchers, students in medical sciences and professionals interested in associated areas.

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