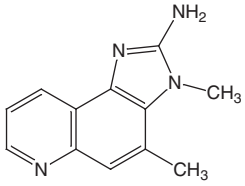
Selected Heterocyclic Amines

Introduction

Heterocyclic amines (HCAs) are formed during the cooking of meat, by condensation of creatinine with amino acids. Four individual HCAs are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* (in separate listings). 2-Amino-3-methylimidazo[4,5-*f*]quinoline (IQ) was first listed in the *Tenth Report on Carcinogens* (2002), and three other HCAs, 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ), 2-amino-3,8-dimethylimazo[4,5-*f*]quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), were listed for the first time in the *Eleventh Report on Carcinogens* (2004). The evidence for the carcinogenicity for each of the individual HCAs listed in this report is discussed separately. However, most of the information on additional information relevant to carcinogenicity, properties, use, production, exposure, and regulations is common to all four of the listed HCAs and therefore has been combined into one section following the carcinogenicity discussion of the individual HCAs.

2-Amino-3,4-Dimethylimidazo-[4,5-*f*]Quinoline (MeIQ) CAS No. 77094-11-2

Reasonably anticipated to be a human carcinogen
First Listed in the *Eleventh Report on Carcinogens* (2004)



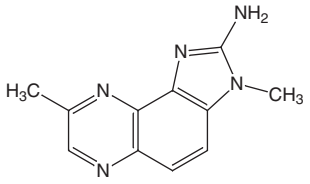
Carcinogenicity

MeIQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals and supporting genotoxicity data. MeIQ administered orally caused tumors at multiple tissue sites in both mice and rats, thus providing sufficient evidence of carcinogenicity in experimental animals. In mice, MeIQ caused forestomach tumors in both sexes and tumors of the cecum, colon, and liver in females. In rats, it caused tumors of the colon, oral cavity, and Zymbal gland in both sexes, mammary-gland tumors in females, and skin tumors in males. The carcinogenic effects of MeIQ may be inhibited or enhanced by many factors, including interactions of HCA mixtures (NTP 2002).

There is inadequate evidence to evaluate the carcinogenicity of MeIQ in humans. In one case-control study, the odds ratios for MeIQ intake were elevated for rectal and colon cancers but were null or close to null for bladder and kidney cancers (Augustsson *et al.* 1999). Although epidemiological evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans, the data are insufficient to support the conclusion that this risk is due specifically to MeIQ present in these foods.

2-Amino-3,8-Dimethylimidazo [4,5-*f*]Quinoxaline (MeIQx) CAS No. 77500-04-0

Reasonably anticipated to be a human carcinogen
First Listed in the *Eleventh Report on Carcinogens* (2004)



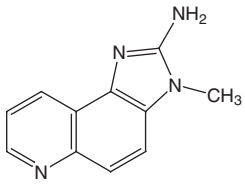
Carcinogenicity

MeIQx is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals and supporting genotoxicity data. MeIQx administered orally caused tumors in both mice and rats and at multiple tissue sites, thus providing sufficient evidence of carcinogenicity in experimental animals. In mice, MeIQx caused liver tumors in both sexes, lung tumors in females, and lymphoma and leukemia in males. In rats, MeIQx caused liver and Zymbal-gland tumors in both sexes, skin tumors in males, and clitoral-gland tumors in females. MeIQx also caused liver tumors in neonatal mice exposed by intraperitoneal (i.p.) injection. MeIQx did not cause cancer in cynomolgus monkeys given MeIQx by nasogastric intubation for 84 months. This finding was attributed to a low level of metabolic activation of MeIQx via *N*-hydroxylation in this species; however, the study period may not have been long enough to detect tumors. The carcinogenic effects of MeIQx may be inhibited or enhanced by many factors, including interactions of HCA mixtures. In rats injected i.p. with *N*-hydroxy-MeIQx (a metabolite of MeIQx), the incidence of soft-tissue tumors at the injection site was significantly increased (NTP 2002).

Although evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans, the data are insufficient to support the conclusion that this risk is due specifically to MeIQx present in these foods (NTP 2002). Case-control studies (one for each tissue site) suggest that MeIQx may increase the risk of colon adenoma (Sinha *et al.* 2001) and lung cancer (Sinha *et al.* 2000b). MeIQx intake was not associated with cancer risk in case-control studies of bladder, kidney, or colon cancer (Augustsson *et al.* 1999). The results for breast cancer were conflicting, with two studies reporting elevated odds ratios (De Stefani *et al.* 1997, Sinha *et al.* 2000a) and one study reporting decreased odds ratio (Delfino *et al.* 2000). The presence of an individual HCA in cooked meat is highly correlated with the presence of other HCAs and with many other constituents, including protein, animal fat, nitrosamines, and substances other than HCAs formed during cooking, such as polycyclic aromatic hydrocarbons. It is therefore difficult to establish associations between cancer risk and specific HCAs.

2-Amino-3-Methylimidazo [4,5-*f*]Quinoline (IQ) CAS No. 76180-96-6

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)



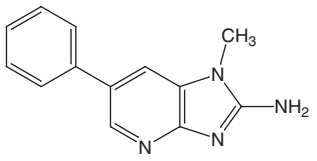
Carcinogenicity

IQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals. IQ administered orally caused benign and malignant tumors in multiple species (mice, rats, and monkeys) and at multiple tissue sites, thus providing sufficient evidence of carcinogenicity in experimental animals. In mice, IQ caused forestomach, liver, and lung tumors in both sexes. In rats, IQ caused tumors of the small intestine, liver, oral cavity, and Zymbal gland in both sexes; mammary- and clitoral-gland tumors in females; and colon and skin tumors in males. IQ administered orally to cynomolgus monkeys or by i.p. injection to mice caused liver tumors (NTP 1999).

No adequate epidemiology studies have been reported that would indicate a human cancer risk specifically associated with exposure to IQ or other HCAs. However, published epidemiology studies provide some indication that human cancer risk is related to consumption of broiled or fried foods that may contain IQ and/or other HCAs.

2-Amino-1-Methyl-6-Phenylimidazo[4,5-*b*]Pyridine (PhIP) CAS No. 105650-23-5

Reasonably anticipated to be a human carcinogen
First Listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

PhIP is *reasonably anticipated to be a human carcinogen based* on sufficient evidence of carcinogenicity in experimental animals and supporting genotoxicity data. PhIP administered orally caused tumors in both mice and rats at multiple tissue sites, thus providing sufficient evidence of carcinogenicity in experimental animals. In mice, PhIP caused lymphoma in both sexes and tumors of the small intestine in males. In rats, PhIP caused lymphoma and tumors of the small intestine, colon, and prostate in males and mammary-gland tumors in females. PhIP administered to neonatal male mice by i.p. injection caused liver tumors in two of three studies. The carcinogenic effects of PhIP may be inhibited or enhanced by many factors, including interactions of HCA mixtures. *N*-hydroxy-PhIP (a metabolite of PhIP) administered by i.p. injection increased the incidence of intestinal polyps in Apc knockout mice (which are unable to produce the tumor-suppressor protein APC) and increased, though not significantly, the incidences of colon and rare bladder tumors in ACI/Seg rats (a strain with high spontaneous incidence of prostate cancer) (NTP 2002).

Although evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans, the data are insufficient to support the conclusion that this risk is due specifically to PhIP present in these foods (NTP 2002). Case-control studies suggest that PhIP may increase the risk of breast or stomach cancer. However, the association with stomach cancer was based on only one study (De Stefani *et al.* 1998), and the association with breast cancer was found in two of three studies (De Stefani *et al.* 1997, Delfino *et al.* 2000, Sinha *et al.* 2000a). No association between PhIP intake and cancer risk was found in case-control studies of bladder, kidney, lung, colon, or prostate cancer (Augustsson *et al.* 1999, Norrish *et al.* 1999, Sinha *et al.* 2000b). An elevated risk was reported for PhIP intake and colon adenoma in one study but was no longer statistically significant when the analysis controlled for intake of other HCAs (Sinha *et al.* 2001). The presence of an individual HCA in cooked meat is highly correlated with the presence of other HCAs and with many other constituents, including protein, animal fat, nitrosamines, and substances other than HCAs formed during cooking, such as polycyclic aromatic hydrocarbons. It is therefore difficult to establish associations between cancer risk and specific HCAs.

Selected Heterocyclic Amines
Additional Information Relevant to Carcinogenicity

Studies have consistently shown that MeIQ, MeIQx, IQ, and PhIP cause mutations in most test systems, including bacteria, rodents exposed *in vivo*, and cultured rodent and human cells. Moreover, in comparison to other well-known mutagens, such as benzo[*a*]pyrene, MeIQ, MeIQx, IQ, and PhIP show a high degree of potency. MeIQ, MeIQx, IQ, and PhIP also caused sister chromatid exchange, micronucleus formation (a sign of chromosome damage or loss), and unscheduled DNA synthesis (a DNA repair response), and most of them induced DNA damage and chromosomal aberrations (changes in chromosome structure or number) in *in vivo* studies in rodents and in *in vitro* human and rodent cell studies (IARC 1993, NTP 2002).

When ingested by humans or administered orally to experimental animals, HCAs are readily absorbed and rapidly distributed. They are metabolized by both phase I (activation) and phase II (conjugation) enzymes. The major phase I activation pathway is *N*-hydroxylation by the enzyme CYP1A2 (a member of the cytochrome P-450 family). Further activation by phase II enzymes, in the liver or in other tissues, is necessary for formation of the arylnitrenium ion, which ultimately binds to DNA (NTP 2002).

HCA-induced DNA adducts have been characterized and detected in humans and other mammalian species both *in vitro* and *in vivo*, and the major adduct for each HCA is similar in all species examined. In humans, DNA adducts form at dietarily relevant levels of HCA exposure and are usually present at higher frequencies than in rodents administered an equivalent dose. HCA-induced adducts have been identified in human colon tissue, breast tissue, and prostate tumors. The DNA adduct data indicate that metabolic activation of HCAs is more efficient in humans than in experimental animals and that rapid acetylators (individuals who produce an efficient version of the enzyme *N*-acetyltransferase) may be at higher risk of cancer than slow acetylators (individuals who produce less-efficient versions of this enzyme). In studies with experimental animals, HCA-induced DNA adducts are formed in a dose-dependent manner and are associated with carcinogenesis (NTP 2002).

Mutations involving guanine (such as G:C to T:A transversions) have been detected in proto-oncogenes (genes potentially associated with cancer) and tumor-suppressor genes, including Ki-*ras*, Ha-*ras*, *Apc*, *p53*, and β-catenin, suggesting that HCA-induced adducts are involved. The observed mutation patterns provide evidence for a mutational profile or "fingerprint" for PhIP-induced colon tumors and MeIQ-induced forestomach and Zymbal-gland tumors in mice (NTP 2002).

Properties

MeIQ, MeIQx, IQ, and PhIP are heterocyclic amines formed by condensation of creatinine with amino acids during the cooking of meat. (Creatinine is a breakdown product of creatine, an important constituent of muscle.) All of these HCAs share a common imidazole-ring structure with an exocyclic amino group and, therefore, are known chemically as amino-imidazoazaarenes. Most HCAs, including MeIQ, MeIQx, and IQ, are fully planar aromatic structures with no bulky out-of-plane functionalities; however, PhIP possesses a phenyl moiety that is not necessarily coplanar with the main bicyclic imidazopyridine.

All four of these selected HCAs occur as crystalline solids and are soluble in dimethylsulfoxide or methanol. Other physical and chemical properties are listed in the table below.

Physical and chemical properties of MeIQ, MeIQx, IQ, and PhIP

Property	MeIQ	MeIQx	IQ	PhIP
Molecular weight	212.2	213.2	198.2	224.1
Color	pale orange to brown	yellow-green	light tan	gray-white
Melting point (°C)	296–298	295–300	>300	327–328
Extinction coefficient	48,000 at 265 nm	41,000 at 273 nm	51,500 at 264 nm	19,400 at 316 nm

Source: (IARC 1993, Knize *et al.* 1995)

Use

MeIQ, MeIQx, IQ, and PhIP have no known commercial uses (IARC 1993).

Production

MeIQ, MeIQx, IQ, and PhIP are produced in small quantities for research purposes (IARC 1993). They all are formed naturally during the cooking of muscle-derived foods (meat and fish) as by-products of the Maillard (or browning) reaction (Robbana-Barnat *et al.* 1996, Felton *et al.* 2000). It is postulated that the amino-imidazo part of HCAs is formed from creatine, while the remaining parts of the compound are likely formed from Strecker degradation products, such as pyridines or pyrazines, which are formed in the Maillard reaction between hexose sugars and amino acids (Jagerstad *et al.* 1984, Skog *et al.* 1998). Formation of HCAs in food reportedly is affected by temperature, processing time, acidity, precursor concentrations, and types of amino acid present (Keating *et al.* 1999). In general, higher temperatures and longer cooking times increase the amount of HCAs produced (Knize *et al.* 1994, Skog *et al.* 1995). HCA formation also increases with cooking methods that use direct or efficient transfer of heat from the source to the food; frying or grilling of muscle meats produces more HCAs than do indirect-heat methods such as stewing, steaming, or poaching (Layton *et al.* 1995).

Exposure

Exposure to MeIQ, MeIQx, IQ, or PhIP occurs primarily through the consumption of cooked meats; however, HCAs also have been detected in processed food flavorings, beer, wine, and cigarette smoke. Dietary exposure to total HCAs has been estimated to range from less than 1 to 17 ng/kg of body weight per day (Layton *et al.* 1995).

Total HCA concentrations in cooked meat generally range from less than 1 to about 500 ng/g (0.001 to 0.5 parts per million) but usually are less than 100 ng/g (Layton *et al.* 1995, Sinha *et al.* 1995, Knize *et al.* 1998, Sinha *et al.* 1998a, Sinha *et al.* 1998b, Salmon *et al.* 2000). Pan residues usually contain higher HCA concentrations than the meat itself; therefore, gravy made from meat drippings and grease may have relatively high concentrations of HCAs. In four studies (reviewed by Keating *et al.* 1999), total daily HCA intakes (including MeIQx, IQ, and PhIP, but not MeIQ) ranged from 160 to 1,800 ng per person. In general, the dietary intake of these four HCAs is greatest for PhIP, followed by MeIQx, IQ, and MeIQ.

As discussed above (under "Production"), the concentration of HCAs in food is a function of cooking method; dietary intake therefore is a function of cooking method, doneness preference, and consumption frequency (Keating *et al.* 1999). Several studies have reported on possible methods for reducing dietary HCA (Skog *et al.* 1997, Knize *et al.* 1999, Salmon *et al.* 2000). Effective methods include using cooking temperatures below 200°C (392°F), turning meat more frequently during cooking, precooking meat in a microwave oven for at least two minutes and draining off the liquid before conventional cooking, and applying marinades before grilling. However, some marinades are more effective than others; PhIP and MeIQx concentrations were reduced by teriyaki sauce or turmeric-garlic sauce, but increased by a honey barbeque sauce (Nerurkar *et al.* 1999).

Occupational exposure to HCAs may occur by inhalation of aerosolized particles formed during the cooking process. Thiébaud *et al.* (1995) detected PhIP and MeIQx in smoke condensate formed during frying of beef patties and bacon, and Yang *et al.* (1998) detected MeIQx in aerosol from cooking of stir-fried fish. PhIP was detected in airborne particles, diesel-exhaust particles, and incineration ash from garbage-burning plants (Manabe *et al.* 1993).

Specific exposure information for each of the four HCAs follows.

MeIQ

MeIQ is found less frequently in food and generally at lower concentrations than are other HCAs, including MeIQx, PhIP, and IQ. The highest concentrations were detected in cooked fish, ranging from 0.03 to 72 ng/g; the concentrations were highest in grilled sun-dried sardines and lower in fried or broiled fish (IARC 1993, Lynch *et al.* 1995). MeIQ has been found to be present at low levels or nondetectable in cooked beef, pork, or chicken; various studies have reported concentrations ranging from 0.02 ng/g (in pork) to 1.7 ng/g (in well-done bacon) (Johansson and Jagerstad 1994, Lynch *et al.* 1995). It also has been detected in gravy, coffee beans, and cigarette smoke. In a Swiss population, daily MeIQ intake was estimated to be 0.6 ng/kg of body mass (Zimmerli *et al.* 2001).

MeIQx

MeIQx has been detected in beef, pork, chicken, and fish. The highest concentrations were found in well-done grilled chicken, beef (hamburger or steak), and bacon. Very-well-done grilled or barbequed chicken contained 9 ng/g, and very-well-done oven-broiled or pan-fried skinless, boneless chicken breasts contained 3 ng/g (Sinha *et al.* 1995). In one study, MeIQx concentrations in beef ranged from nondetectable to 8.2 ng/g in steak and from nondetectable to 4.6 ng/g in hamburger patties, depending on the cooking method and degree of doneness (Sinha *et al.* 1998a). Another study found that fish contained about 1.2 ng/g (Johansson and Jägerstad 1994). Pork, with the exception of bacon, contains very little MeIQx; MeIQx was detected at 0.9 to 18 ng/g in bacon and 1.4 to 27 ng/g in bacon fat (Gross *et al.* 1993). MeIQx also occurs in processed food flavors (bouillon and gravy concentrates) and wine. In three large U.S. cohort studies (two Nurses' Health Studies and the Health Professionals Follow-Up Study), estimated mean daily intake of MeIQx ranged from 33 to 44.8 ng/day (Byrne *et al.* 1998). Layton *et al.* (1995) estimated daily MeIQx intake to be 2.61 ng/kg of body mass. MeIQx also has been found in air and surface water.

IQ

IQ was originally isolated from broiled fish, fried ground beef, and beef extracts. It has since been detected in fried chicken, fried eggs, fried fish, broiled ground beef, minute steaks, meatballs, pork chops,

and cigarette smoke condensate. Reported concentrations in foods range from less than 0.1 to more than 150 ng/g, with most less than 1 ng/g (IARC 1993, Skog *et al.* 1995, Chiu *et al.* 1998). However, Sinha *et al.* (1998a) did not detect IQ in hamburgers, steaks, or roast beef cooked by varying methods to three levels of doneness. The highest reported IQ concentration occurred in broiled sun-dried sardines. The estimated daily IQ intake in the United States from meat and fish was 0.28 ng/kg of body mass (Layton *et al.* 1995).

PhIP

PhIP is the most abundant HCA detected in foods and has been found in beef, pork, chicken, lamb, and fish. The highest concentrations were detected in very-well-done grilled chicken; however, concentrations varied considerably from study to study. High concentrations (over 100 ng/g) were found in well-done steak and hamburgers. Concentrations of PhIP in fish varied greatly according to the type of fish and method of cooking; one study reported levels ranging from 1.7 to 73 ng/g in salmon cooked at 200°C by various methods (pan-broiled, oven-cooked, or barbecued) for different lengths of time (Gross and Grüter 1992), but another study (Skog *et al.* 1997) reported substantially lower levels (0.02 to 2.2 ng/g) for cod and Baltic herring fillets pan fried at temperatures ranging from 150°C to 225°C. PhIP occurs at lower concentrations in pork (0.1 to 2.3 ng/g). It also has been detected in processed food flavors, beer, and wine at concentrations ranging from 0.01 to 480 ng/g, and in cigarette smoke. In the same three large U.S. cohort studies cited above for MeIQx, mean daily PhIP intake ranged from 285.5 to 457.9 ng/day (Byrne *et al.* 1998). Layton *et al.* (1995) estimated daily PhIP intake to be 17 ng/kg of body mass. PhIP also has been found in air and surface water.

Regulations and Guidelines

No regulations or guidelines relevant to reduction of exposure to heterocyclic amines were identified

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