Heterocyclic Amines (Selected)

Also known as HCAs

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-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ) was first listed in the *Eleventh Report on Carcinogens* (2004).
- 2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) was first listed in the *Eleventh Report on Carcinogens* (2004).
- 2-Amino-3-methylimidazo[4,5-*f*]quinoline (IQ) was first listed in the *Tenth Report on Carcinogens* (2002).
- 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) was first listed in the *Eleventh Report on Carcinogens* (2004).

The profiles for these four HCAs follow. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for each HCA. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to all four listed HCAs and therefore is combined into one section following the discussions of cancer studies.

Note on Cancer Studies of Selected HCAs in Humans

Epidemiological evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans. However, 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. Furthermore, the carcinogenic effects of these HCAs may be inhibited or enhanced by many factors, including interactions of HCA mixtures. It is therefore difficult for human epidemiological studies to establish associations between cancer risk and specific HCAs. For each of these four selected HCAs, the data from epidemiological studies are insufficient to evaluate whether the increased cancer risk is due specifically to consumption of that particular HCA in food (NTP 2002).

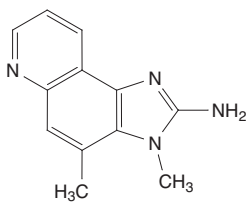
2-Amino-3,4-dimethylimidazo[4,5-*f*]-quinoline

CAS No. 77094-11-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as MeIQ



Carcinogenicity

MeIQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

Oral exposure to MeIQ caused tumors at several different tissue sites in mice and rats. In mice of both sexes, MeIQ increased the combined incidence of benign and malignant forestomach tumors (papilloma, squamous-cell carcinoma, and sarcoma). In female mice, it also caused cancer of the cecum and colon (adenocarcinoma) and increased the combined incidence of benign and malignant liver tumors (fibrosarcoma and hepatocellular adenoma and carcinoma). In rats of both sexes, MeIQ increased the combined incidence of benign and malignant colon tumors (adenoma and adenocarcinoma) and caused cancer of the oral cavity and Zymbal gland (squamous-cell carcinoma). In addition, MeIQ caused skin cancer (squamous-cell carcinoma) in male rats and cancer of the mammary gland (adenocarcinoma) in female rats (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to MeIQ. In one case-control study, MeIQ intake was associated with increased risks for rectal and colon cancer but not for urinary-bladder or kidney cancer (Augustsson *et al.* 1999).

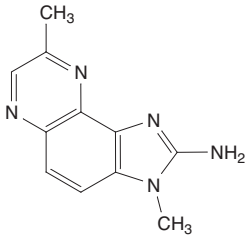
2-Amino-3,8-dimethylimidazo[4,5-*f*]-quinoxaline

CAS No. 77500-04-0

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as MeIQx



Carcinogenicity

MeIQx is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

MeIQx caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral exposure to MeIQx increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice and rats of both sexes and the combined incidence of benign and malignant lung tumors (adenoma and adenocarcinoma) in female mice. It also caused lymphoma and leukemia in male mice. In rats, orally administered MeIQx also increased the combined incidence of benign and malignant Zymbal-gland tumors (sebaceous-gland adenoma and squamous-cell papilloma and carcinoma) in both sexes, and it caused skin cancer in males and cancer of the clitoral gland in fe-

males (squamous-cell carcinoma in both cases). Newborn mice exposed to MeIQx by intraperitoneal injection developed benign liver tumors (hepatocellular adenoma). In cynomolgus monkeys, MeIQx administered by stomach tube for 84 months did not cause cancer. 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 for detection of tumors (NTP 2002).

In rats, administration of *N*-hydroxy-MeIQx (a metabolite of MeIQx) by intraperitoneal injection caused soft-tissue tumors at the injection site (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to MeIQx. Case-control studies (one study for each tissue site) suggested that MeIQx may increase the risk of benign colon tumors (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 urinary-bladder, kidney, or colon cancer (Augustsson *et al.* 1999). The results for breast cancer were conflicting, with two studies reporting increased risk (De Stefani *et al.* 1997, Sinha *et al.* 2000a) and one study reporting decreased risk (Delfino *et al.* 2000).

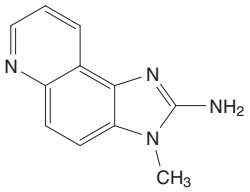
2-Amino-3-methylimidazo[4,5-*f*]quinoline

CAS No. 76180-96-6

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as IQ



Carcinogenicity

IQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

IQ caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. In rats of both sexes, oral exposure to IQ caused cancer of the liver (hepatocellular carcinoma), large intestine (adenocarcinoma), and Zymbal gland (squamous-cell carcinoma). It also caused cancer of the mammary gland (adenocarcinoma) and clitoral gland (squamous-cell carcinoma) in female rats and cancer of the small intestine (adenocarcinoma) and skin (squamous-cell carcinoma) in male rats. In mice of both sexes, oral exposure to IQ increased the combined incidences of benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma), forestomach (papilloma and squamous-cell carcinoma), and lung (adenoma and adenocarcinoma). Newborn mice administered IQ by intraperitoneal injection developed benign and malignant liver tumors (hepatocellular adenoma and carcinoma). Male rats adminstered IQ by intrarectal infusion developed cancer of the colon (carcinoma) and skin (squamous-cell carcinoma) and benign liver tumors (hepatocellular adenoma). In cynomolgus monkeys, IQ administered orally caused liver cancer (hepatocellular carcinoma) (NTP 1999).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to IQ. One case-control study suggested that IQ intake increased the risk of breast cancer (De Stefani *et al.* 1997), but another case-control study found no association between IQ and cancer of the colon, rectum, urinary bladder, or kidney (Augustsson *et al.* 1999).

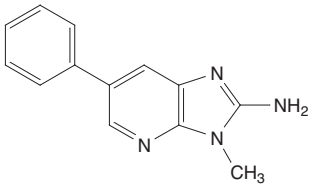
2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]-pyridine

CAS No. 105650-23-5

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as PhIP



Carcinogenicity

PhIP is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

PhIP caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral exposure to PhIP caused lymphoma in mice of both sexes and in male rats. In rats, it also caused prostate cancer (carcinoma) and cancer of the small intestine and colon (adenocarcinoma) and in males and mammary-gland cancer (adenocarcinoma) in females. In a short-term study using mice with a mutation that made them susceptible to intestinal and mammary-gland tumors, oral administration of PhIP increased the combined incidence of benign and malignant tumors of the small intestine (adenoma and adenocarcinoma) in males. PhIP administered to newborn male mice by intraperitoneal injection caused benign liver tumors (hepatocellular adenoma) (NTP 2002).

N-hydroxy-PhIP (a metabolite of PhIP) administered by intraperitoneal injection caused intestinal polyps in *Apc* knockout mice (which are unable to produce the tumor-suppressor protein APC). In ACI/Seg rats (a strain with high spontaneous incidence of prostate cancer) administered *N*-hydroxy-PhIP by intraperitoneal injection, the incidences of colon tumors and rare urinary-bladder tumors were increased, though not significantly (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to PhIP. 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 urinary-bladder, kidney, lung, colon, or prostate cancer (Augustsson *et al.* 1999, Norrish *et al.* 1999, Sinha *et al.* 2000b). PhIP intake was associated with increased risk of benign colon tumors (adenoma) in one study, but the risk was not significantly increased when the statistical analysis controlled for intake of other HCAs (Sinha *et al.* 2001).

Heterocyclic Amines (Selected)

Studies on Mechanisms of Carcinogenesis

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, compared with other well-known mutagens, such as benzo[a]pyrene, these HCAs show a high degree of potency. MeIQ, MeIQx, IQ, and PhIP also caused sister chromatid exchange, micronucleus formation, and unscheduled DNA synthesis, and most of these HCAs induced DNA damage and chromosomal aberrations in in vivo studies in rodents and in in vitro studies with human and rodent cell cultures (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 P450 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 usually are 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 were formed in a dose-dependent manner and were associated with carcinogenesis (NTP 2002).

Mutations involving guanine (such as G:C to T:A transversions) have been detected in proto-oncogenes 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 of these HCAs occur as crystalline solids and are soluble in dimethylsulfoxide or methanol. Physical and chemical properties of MeIQ, MeIQx, IQ, and PhIP are listed in the following table.

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 to 298	295 to 300	> 300	327 to 328
Log K_{ow}	1.822			
Extinction coefficient	48,000 at 265 nm	41,000 at 273 nm	51,500 at 264 nm	19,400 at 316 nm

Sources: 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 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 have also 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 ppm) but usually are less than 100 ng/g (Layton *et al.* 1995, Sinha *et al.* 1995, 1998a, 1998b, Knize *et al.* 1998, 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 is therefore 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 barbecue sauce (Nerurkar *et al.* 1999).

Occupational exposure to HCAs may occur by inhalation of aerosolized particles formed during the cooking process. PhIP and MeIQx were detected in smoke condensate formed during frying of beef patties and bacon (Thiébaud *et al.* 1995), and MeIQx was detected in aerosol from cooking of stir-fried fish (Yang *et al.* 1998). 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 these 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 was found at low levels or was not detectable in cooked beef, pork, or chicken; various studies 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 was also 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 barbecued 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.* 1998b). Another study found that fish contained about 1.2 ng/g (Johansson and Jägerstad 1994). Pork, other than 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/g of food consumed (Byrne *et al.* 1998). Daily MeIQx intake was estimated to be 2.61 ng/kg of body mass (Layton *et al.* 1995). 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*. (1998b) 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. Daily IQ intake from meat and fish was estimated to be 0.28 ng/kg of body mass (Layton *et al.* 1995).

PhIP

Evidence that the U.S. general population is exposed to PhIp comes from the 2013–2014 National Health and Nutrition Examination Survey, which found that the 95th-percentile concentration of PhIP in urine was 15.8 ng/L, based on a sample of 2,569 individuals of all ages, both genders, and all race and ethnicity groups (CDC 2018). The primary source of exposure is ingestion of food. 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 various 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 was found at lower concentrations in pork (0.1 to 2.3 ng/g). It was also 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 ng/day (Byrne *et al.* 1998). Daily PhIP intake was estimated to be 17 ng/kg of body mass (Layton *et al.* 1995). PhIP has also been found in air and surface water.

Regulations

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

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