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MUTAGENS AND CARCINOGENS IN FOODS

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CONTENTS

INTRODUCTION

Epidemiological studies have shown that diets and life-styles are closely related to human cancer (12, 26). For instance, the incidences of stomach and colon cancers among Japanese immigrants in the second generation shifted away from the pattern in Japan to that in the country of residence (60); this reveals the importance of food habits in inducing cancers of the digestive tract. Foods contain both initiators and promoters (104) of carcinogenesis, and various types

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of mutagens and carcinogens in foods are known. These include (*a*) naturally occurring mutagens and carcinogens, especially in edible plants or spices, such as pyrrolidine alkaloids, flavonoids, and anthraquinones (2, 23); (*b*) the nitrosamines and nitrosamides that are produced from food components and nitrite by nitrosation reaction either during cooking and food processing or in the stomach (9, 70); (*c*) mycotoxins produced by fungi contaminating in foods (14, 129); (*d*) heterocyclic amines and polycyclic aromatic hydrocarbons produced by pyrolysis of amino acids, proteins, and food components; (*e*) mutagenic dicarbonyl compounds produced by heating carbohydrates or by fermentation; (*f*) mutagens produced by the browning reaction (aminocarbonyl reactions) (127); (*g*) food additives and contaminants (8); and (*h*) others.

This paper reviews the mutagenic and carcinogenic activities of the structurally defined mutagens and carcinogens that are produced by heating foods; namely compounds of types (*d*) and (*e*) listed above.

HETEROCYCLIC AMINES AND RELATED COMPOUNDS

Mutagens-Carcinogens Produced by Pyrolysis of Amino Acids and Proteins and in Cooked Foods

In 1976 Sugimura et al (84, 106) found that broiled dried fish had mutagenic activity detectable by Ames' test (79) with *Salmonella typhimurium*. Since then, mutagenic activities have been widely found in pyrolysates of amino acids (61), peptides (74), and proteins (83) and in cooked foods (10, 57, 97, 101–103, 125). Harman (Har) and norharman (NorHar), compounds that were not themselves mutagenic but had comutagenic activity, were also found in pyrolysates of amino acids (Table 1) (73, 86, 87, 124). Up to the present, 14 new chemical compounds have been isolated from pyrolysates of amino acids and proteins and from cooked foods, as shown in Table 1. Although Har and NorHar are already known as alkaloids, they are also included. Table 1 shows the names, abbreviations, chemical structures, and mutagenic activities on *S. typhimurium* TA98 of these chemicals and the original materials from which they were isolated. Har, NorHar, and Lys-P-1 are heterocyclic imino compounds, but all the other chemicals are heterocyclic amines. AαC, MeAαC, 3AH, 3AN, Trp-P-1, Trp-P-2, Glu-P-1, Glu-P-2, Phe-P-1, and Orn-P-1 have a common 2-amino-pyridine structure, and IQ, MeIQ, and MeIQx have a common 2-amino-imidazole structure.

Genotoxicity of Pyrolysis Products in Mammalian Cells in vitro

The in vitro effects on mammalian cells, including human cells, induced by pyrolysis products are summarized in Table 2. These pyrolysis products in-

duced diphtheria toxin resistance (88), ouabain resistance (117), chromosomal aberration (98), sister chromatid exchange (98), and in vitro transformation (7, 113, 114) in mammalian cells. They also induced 8-azaguanine resistance (64–66), chromosomal aberration (98), and sister chromatid exchange (98, 119, 120) in human cells.

Genotoxicity of Pyrolysis Products in vivo

Results were positive in somatic eye-color mutation (16) and the wing spot test (139) in *Drosophila melanogaster* and in the spot test in mice (54). Induction of ATPase-deficient foci in rat liver (50) was also reported (see Table 3).

Carcinogenicities

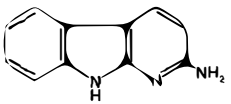
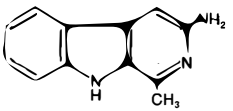
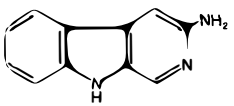
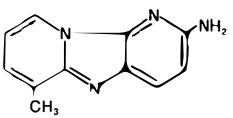
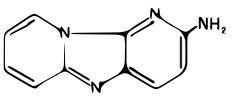
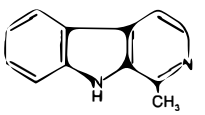
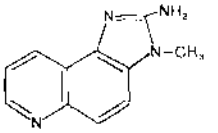
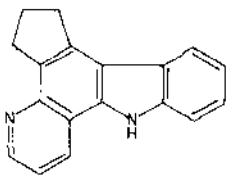
At present 7 of 16 pyrolysis products have been demonstrated to be strongly carcinogenic. These seven carcinogenic chemicals are AαC (95), Glu-P-1 (95, 115), Glu-P-2 (95, 115), IQ (94, 116), MeAαC (95), Trp-P-1 (72, 116a), and Trp-P-2 (27, 72). Experimental results are summarized in Table 4. Oral administration of these seven chemicals to rats or mice induced hepatocellular carcinomas and tumors in some other organs.

Metabolic Pathways

All these mutagens required metabolic activation by a liver microsomal fraction (S9 mix) in order to exert their mutagenic effects on *S. typhimurium* (109). Trp-P-2 was converted to the 2-hydroxyamino derivative (*N*-OH-Trp-P-2) in vitro (22, 135) by cytochrome P-448, which was purified from the liver of rats treated with polychlorinated biphenyls or 3-methylcholanthrene (49, 92, 128). Synthetic *N*-OH-Trp-P-2 with or without *O*-acetylation reacted with DNA, as shown in Figure 1 (22). Serine and seryl-tRNA synthetase from yeast (137), and proline and prolyl-tRNA synthetase from rat liver (136), enhanced the in vitro binding of *N*-OH-Trp-P-2 to DNA in a manner similar to the enhancement of activated 4-hydroxyaminoquinoline 1-oxide (112). IQ, MeIQ, AαC, MeAαC, Glu-P-1, Glu-P-2, Lys-P-1, Trp-P-1, and 3-acetyl-Trp-P-1 were also activated in vitro by cytochrome P-448 of rat liver microsomes induced by 3-methylcholanthrene, but not by cytochrome P-450 induced by phenobarbitone (128). Glu-P-1, AαC, and IQ are also activated to hydroxyamino derivatives (21, 92, 96). The hydroxyamino derivative of Glu-P-1 reacted with DNA only after *O*-acetylation and produced an adduct, 2-(C^8-guanyl)amino-6-methylpyrido[1,2-*a*:3',2'-*d*]imidazole (21), as shown in Figure 2. Recently the ultimate forms of Glu-P-1, Glu-P-2, IQ, MeIQ, and MeIQx (but not of Trp-P-1, Trp-P-2, MeAαC, and AαC) in *Salmonella* were suggested to be sulfate esters of the *N*-hydroxy derivatives of these amines (82).

All these heterocyclic amines were quickly degraded and they also lost mutagenic activity on treatment with hypochlorite, which is usually present in

Table 1 Pyrolysis products of amino acids and proteins and in cooked foods

Name (abbreviation)	Structure	Mutagenic activity on *S. typhimurium* TA98 + S9 mix (revertants/μg) (109)	Original source
1. 2-Amino-9*H*-pyrido[2,3-*b*]-indole (AαC)		300	Soybean globulin pyrolysate (140)
2. 3-Amino-1-methyl-9*H*-pyrido[3,4-*b*]-indole (3AH)		0[a,b]	L-Tryptophan pyrolysate (111)
3. 3-Amino-9*H*-pyrido[3,4,-*b*]-indole (3AN)		0.4[a]	L-Tryptophan pyrolysate (111)
4. 2-Amino-6-methyl-dipyrido-[1,2-*a*:3',2'-*d*]-imidazole (Glu-P-1)		49,000	L-Glutamic acid pyrolysate (134)
5. 2-Aminodipyrido-[1,2-*a*:3',2'-*d*]-imidazole (Glu-P-2)		1,900	L-Glutamic acid pyrolysate (134)
6. 1-Methyl-9*H*-pyrido[3,4-*b*]-indole (Har)		0 (comutagenic) (73)	L-Tryptophan pyrolysate (61)
7. 2-Amino-3-methylimidazo-[4,5-*f*]quinoline (IQ)		433,000	Broiled sardine (56,59)
8. 3,4-Cyclopenteno-pyrido[3,2-*a*]-carbazole (Lys-P-1)		86	L-Lysine pyrolysate (126)

[a]M. Nagao, personal communication.
[b]Positive in SCE induction (120).

Table 1 (continued)

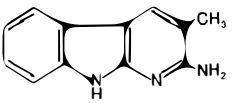
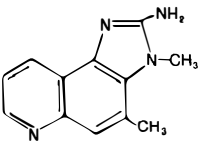
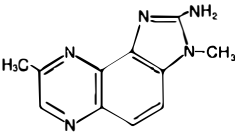
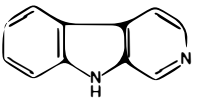
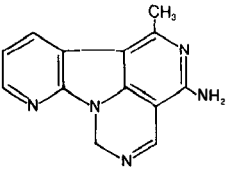
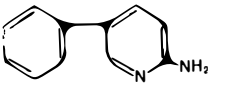
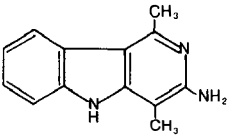
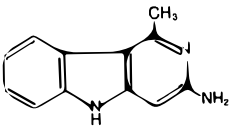
Name (abbreviation)	Structure	Mutagenic activity on *S. typhimurium* TA98 + S9 mix (revertants/μg) (109)	Original source
9. 2-Amino-3-methyl-9*H*-pyrido[2,3,-*b*]-indole (MeAαC)		200	Soybean globulin pyrolysate (140)
10. 2-Amino-3,4-dimethylimidazo-[4,5-*f*]quinoline (MeIQ)		611,000	Broiled sardine (58,59)
11. 2-Amino-3,8-dimethylimidazo-[4,5-*f*]quinoxaline (MeIQx)		145,000	Fried Beef (57)
12. 9*H*-Pyrido[3,4-*b*]-indole (NorHar)		0 (comutagenic) (87)	L-Tryptophan pyrolysate (61)
13. 4-Amino-6-methyl-1*H*-2,5,10,10*b*-tetraaza-fluoranthene (Orn-P-1)		56,800	L-Ornithine pyrolysate (138)
14. 2-Amino-5-phenyl-pyridine (Phe-P-1)		41	L-Phenyl-alanine pyrolysate (105)
15. 3-Amino-1,4-dimethyl-5*H*-pyrido[4,3,-*b*]-indole (Trp-P-1)		39,000	L-Tryptophan pyrolysate (105)
16. 3-Amino-1-methyl-5*H*-pyrido[4,3-*b*]-indole (Trp-P-2)		104,000	L-Tryptophan pyrolysate (105)

Table 2 Genotoxicity of pyrolysis products in mammalian cells in vitro

Endpoint measured	Cells	Test compound	Exposure concentration	
8-Azaguanine resistance ($8AG^r$)	Human embryonic diploid cells	Trp-P-1	0.3	μg/ml
		Trp-P-2	1.0	μg/ml
		Glu-P-2	0.3–30	μg/ml
Diptheria toxin resistance (DT^r)	Chinese hamster lung cells (CHL)	AαC	25–100	μg/ml
		Glu-P-1	250–750	μg/ml
		Glu-P-2	500–1500	μg/ml
		IQ	5–40	μg/ml
		MeIQ	10–50	μg/ml
		MeIQx	10–100	μg/ml
		Trp-P-1	7–20	μg/ml
		Trp-P-2	1–5	μg/ml
Ouabain resistance (Oub^r)	Chinese hamster V79 cells	Lys-P-1	10–50	μg/ml
		Trp-P-2	1–5	μg/ml
Chromosomal aberration	PHA-stimulated human lymphocytes (HL)	Trp-P-1	0.2–0.5	μg/ml
		Trp-P-2	2–3	μg/ml
	Chinese hamster cells (Don-6)	Trp-P-1	0.5–2.0	μg/ml
		Trp-P-2	5–7.5	μg/ml
	Chinese hamster embryonic cells (B-131)	Trp-P-1	0.25–2.0	μg/ml
		Trp-P-2	2.5–10	μg/ml
Sister Chromatid exchange	Human lymphoblastoid cells (NL3)	AαC	1–100	μM
		3AH	100–500	μM
		3AN	100–1000	μM
		Glu-P-1	1–50	μM
		Trp-P-1	1–50	μM
		Trp-P-2	0.1–10	μM
	Human embryonic fibroblasts (He 2144)	Trp-P-1	0.2–0.3	μg/ml
	PHA-stimulated human lymphocytes (HL)	Trp-P-1	0.2–0.5	μg/ml
		Trp-P-2	1–3	μg/ml
	Chinese hamster cells (Don-6)	Trp-P-1	0.1–1	μg/ml
		Trp-P-2	0.1–7.5	μg/ml
	Chinese hamster embryonic cells (B-131)	Trp-P-1	0.25–1	μg/ml
		Trp-P-2	2.5–5	μg/ml
Morphological transformation	Syrian Golden hamster embryo cells	Glu-P-1	10, 20	μg/ml
		Trp-P-1	0.1, 0.5	μg/ml
		Trp-P-2	0.1, 0.5	μg/ml
	Golden hamster embryo cells	Trp-P-2	0.5	μg/ml
		Trp-P-2	X ray 50 rad +	
		Trp-P-2	0.5	μg/ml
			X ray 100 rad +	
		Trp-P-2	0.5	μg/ml

[a]t.c. = transformed colonies.

Table 2 *(continued)*

Exposure time	Results	References
4 hr	7.0 $8AG^r/10^5$ survivors	(64, 65)
4 hr	2.8 $8AG^r/10^5$ survivors	(66)
4 hr	0.9–2.7 $8AG^r/10^5$ survivors	(65)
3 hr	180–500 $DT^r/2.5\times10^5$ survivors	(88)
3 hr	100–170 $DT^r/2.5\times10^5$ survivors	
3 hr	50–120 $DT^r/2.5\times10^5$ survivors	
3 hr	75–120 $DT^r/2.5\times10^5$ survivors	
3 hr	80–150 $DT^r/2.5\times10^5$ survivors	
3 hr	80–150 $DT^r/2.5\times10^5$ survivors	
3 hr	70–130 $DT^r/2.5\times10^5$ survivors	
3 hr	50–260 $DT^r/2.5\times10^5$ survivors	
2 days	19.5–22.2 $Oub^r/10^6$ survivors	(117)
2 days	1.9–13.1 $Oub^r/10^6$ survivors	
48 hr	0.04–0.18 chromatid breaks/cell	(98)
48 hr	0.03–0.08 chromatid breaks/cell	
26–30 hr	0.07–1.17 chromatid breaks/cell	
26–30 hr	0.15–0.35 chromatid breaks/cell	
25–27 hr	0.10–0.31 chromatid breaks/cell	
25–27 hr	0.07–0.20 chromatid breaks/cell	
2 hr	1.6– 9.2 induced SCEs/cell	(119)
2 hr	1.1– 5.5 induced SCEs/cell	(120)
2 hr	3.5– 5.5 induced SCEs/cell	
2 hr	1.4– 9.0 induced SCEs/cell	(119)
2 hr	2.8–11.0 induced SCEs/cell	
2 hr	5.3–14.7 induced SCEs/cell	
44 hr	6.7– 7.9 induced SCEs/cell	(98)
48 hr	23.2–46.0 induced SCEs/cell	
48 hr	5.6–10.8 induced SCEs/cell	
26–30 hr	3.3–11.3 induced SCEs/cell	
26–30 hr	2.1– 9.3 induced SCEs/cell	
25–27 hr	28.8–33.1 induced SCEs/cell	
25–27 hr	3.8– 4.1 induced SCEs/cell	
8 days	2 t.c.[a]/ 730 or 811 survivors	(113)
8 days	2 t.c. / 412 and 3 t.c./223 survivors	(114)
8 days	3 t.c. / 505 and 7 t.c./459 survivors	
10 days	30 t.c. /2423 survivors	(7)
10 days	68 t.c. /4431 survivors	
10 days	95 t.c. /2220 survivors	

Table 3 Genotoxicity of pyrolysis products in vivo

Endpoint measured	Species	Strain	Sex	Organ	Test compound	Exposure concentration	Exposure time	Results	References
Somatic eye-color mutation	*Drosophila melanogaster*		M	Eye	Trp-P-1	200, 400 ppm	24 hr	19 red spots/7574 flies, 22 red spots/5059 flies	(16)
					Trp-P-2	400, 800 ppm	24 hr	11 red spots/6657 flies, 7 red spots/2304 flies	
Wing spot test	*Drosophila melanogaster*		M,F	Wing	AαC	400–1000 ppm	1 day	0.43–0.57 spot/wing	(139)
					Glu-P-1	100– 800 ppm	1 day	0.36–0.81 spot/wing	
					Glu-P-2	100– 800 ppm	1 day	0.50–0.67 spot/wing	
					IQ	100–1000 ppm	1 day	0.42–0.59 spot/wing	
					MeAαC	400 ppm	1 day	0.39 spot/wing	
					MeIQ	100 ppm	1 day	0.53 spot/wing	
					MeIQx	100– 200 ppm	1 day	0.44–0.51 spot/wing	
					Trp-P-1	200– 800 ppm	1 day	0.36–0.87 spot/wing	
					Trp-P-2	200– 800 ppm	1 day	0.55–0.89 spot/wing	
Spot test	Mouse	C57B1 /6J Han	F	Fur	Trp-P-1	4.2 mg/kg bw ip on days 8, 9, 10 of pregnancy		8 recessive spots/317 off spring	(54)
					Glu-P-1	18 mg/kg bw ip on days 8, 9, 10 of pregnancy		12 recessive spots/293 off spring	
ATPase-deficient foci	Rat	Sprague-Dawley	M	Liver	Trp-P-1	10 mg/kg bw/day × 6, ip + 0.05% phenobarbital diet 16 W		7.2 ATPase-deficient foci/10 cm^2	(50)
					Trp-P-1	10 mg/kg bw/day × 6, ip + 5 mg/kg bw × 2/day × 3, ip + partial hepatectomy + 0.05% phenobarbital diet 16 W		11.4 ATPase-deficient foci/10 cm^2	

Table 4 Carcinogenicity test of pyrolysis products on oral administration

Pyrolysis Product	Species	Strain	Sex and number of animals	Percentage in diet	Duration[a]	Tumor site	References
AαC	Mouse	CDF_1	M38 F34	0.08	685 d	Liver, interscapular brown-adipose tissue	(95)
Glu-P-1	Rat	Fischer F344	M42 F42	0.05	24 m	Liver, small intestine, colon, brain, zymbal gland, clitoral gland	(115)
	Mouse	CDF_1	M34 F38	0.05	685 d	Liver, interscapular brown-adipose tissue	(95)
Glu-P-2	Rat	Fischer F344	M42 F42	0.05	24 m	Liver, small intestine, colon, brain, zymbal gland, clitoral gland	(115)
	Mouse	CDF_1	M37 F36	0.05	685 d	Liver, interscapular brown-adipose tissue	(95)
IQ	Rat	Fischer F344	M20 F4	0.03	300 d	Liver, small intestine, colon, skin, oral cavity, zymbal gland, clitoral gland	(116)
	Mouse	CDF_1	M39 F36	0.03	675 d	Liver forestomach, lung	(94)
MeAαC	Mouse	CDF_1	M37 F33	0.08	685 d	Liver, interscapular brown-adipose tissue	(95)
Trp-P-1	Rat	Fischer F344	M40	0.015	365 d	Liver	(116a)
			F40	0.02	365 d	Liver	
	Mouse	CDF_1	M24 F26	0.02	621 d	Liver	(72)
Trp-P-2	Rat	ACI	M10 F9	0.01	870 d	Liver	(27)
	Mouse	CDF_1	M25 F24	0.02	621 d	Liver	(72)

[a]Day = d, month = m.

chlorinated tap water (122). Trp-P-1, Trp-P-2, Glu-P-1, Glu-P-2, AαC, and MeAαC (but not IQ, MeIQ, and MeIQx) were converted to their hydroxy derivatives (Figure 3) when treated with nitrite under acidic conditions and thereby lost their mutagenic activities (121). These differences in inactivations by hypochlorite and nitrite can be used to distinguish 2-amino-pyridine-type mutagens (Trp-P-1/2, Glu-P-1/2, AαC, and MeAαC) from 2-amino-imidazole-type mutagens (IQ, MeIQ, and MeIQx) in cooked foods (109). Trp-P-1, Glu-P-1, and AαC are broken down by peroxidases (myeloperoxidase, lactoperoxidase, and horseradish peroxidase) with H_2O_2 (130).

Fresh juices from vegetables and fruits, such as cabbage, broccoli, green pepper, eggplant, apple, burdock (*Arctium Lappa* L.), stone-leek (*Allium fistulosum* L.), ginger, mint leaf, and pineapple can inactivate the mutagenicities of tryptophan pyrolysis products (80). The factor inactivating Trp-P-1 and Trp-P-2 in extracts of leaves of cabbage (*Brassica oleracea*) was identified as a peroxidase. Its molecular weight was 43,000 and it contained a sugar moiety (28). Inhibitors and activators of the mutagenic activities of these heterocyclic amines against *S. typhimurium* TA98 were found. Biological pyrrole pigments such as hemin, biliverdin, chlorophyllin, and protoporphyrin (4) and fatty acids such as oleic acid and linoleic acid (24) are inhibitors, while cysteine and cysteamine are activators (91).

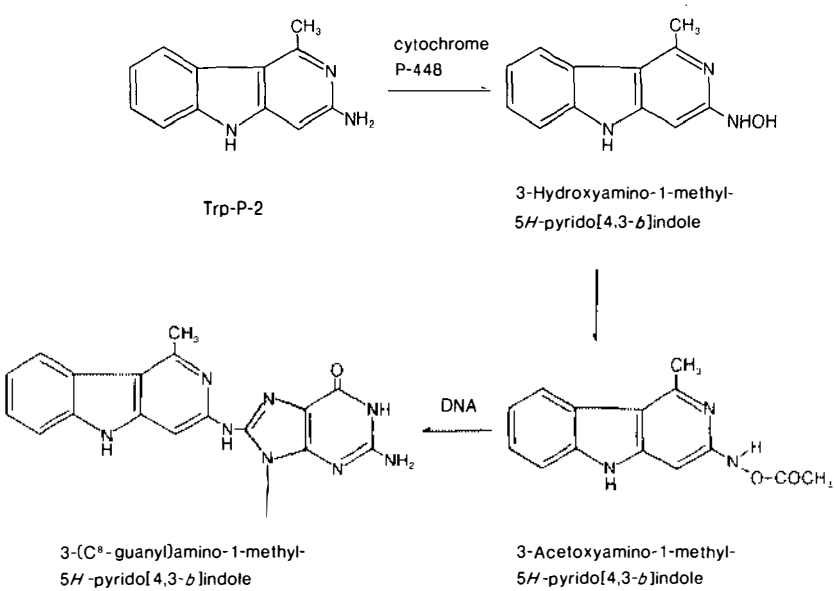
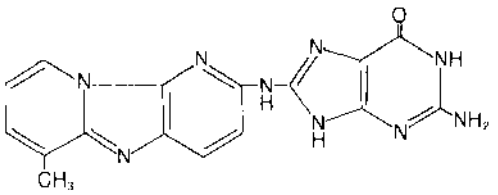


Figure 1 Adduct formation of Trp-P-2 with DNA.



2-(C^8-guanyl)amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole

Figure 2 Adduct of Glu-P-1 with guanine.

Amounts of Heterocyclic Amines in Cooked Foods

There have been few quantitative determinations of heterocyclic amines in normal cooked foods. These chemicals were partially purified by extraction with methanol or 1-N HCl, partitioning between alkaline water and dichloromethane, silica gel column chromatography, Sephadex LH-20 column, thin-layer chromatography, and high-performance liquid chromatography (HPLC). Finally, gas chromatography/mass spectrography with multiple ion detection was used to quantify these mutagens. Reported data on the contents of these chemicals in cooked foods are listed in Table 5 (75, 107, 131–133).

Organic Syntheses of Heterocyclic Amines and Heterocyclic Imino Compounds

Chemical syntheses of heterocyclic amines and heterocyclic imino compounds are shown in Figures 4*a* and 4*b*.

Formation of MeIQx and DiMeIQx from Creatinine, Amino Acids, and Saccharides

Precursors of quinoline and quinoxaline derivatives in fish and meat are intriguing (51, 52, 78, 141). MeIQx was detected in a model system in which creatinine, glucose, and glycine were heated together (53), and 7,8-DiMeIQx was formed on heating this same mixture (89). The presence of DiMeIQx in

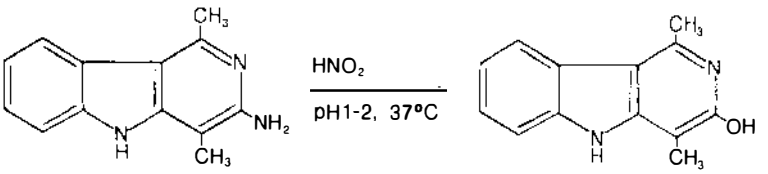


Figure 3 Degradation of Trp-P-1 with nitrite.

Table 5 Amounts of heterocyclic amines in cooked foods (μg/kg)[a]

	AαC	Glu-P-2	IQ	MeAαC	MeIQ	MeIQx	Trp-P-1	Trp-P-2
Broiled sun-dried sardine			158 (107)		72 (107)		13.3 (133)	13.1 (133)
Broiled or fried beef	651 (75)		0.02-0.6 (107)	63.5 (75)		1–2.4 (107)	53 (132)	
Grilled chicken	180 (75)			15.1 (75)				
Broiled sun-dried cuttlefish		280 (131)						
Grilled Chinese mushroom	47.2 (75)			5.4 (75)				
Grilled onion	1.5 (75)			ND[b] (75)				

[a]Numbers in parentheses are references.
[b]ND = not detected.

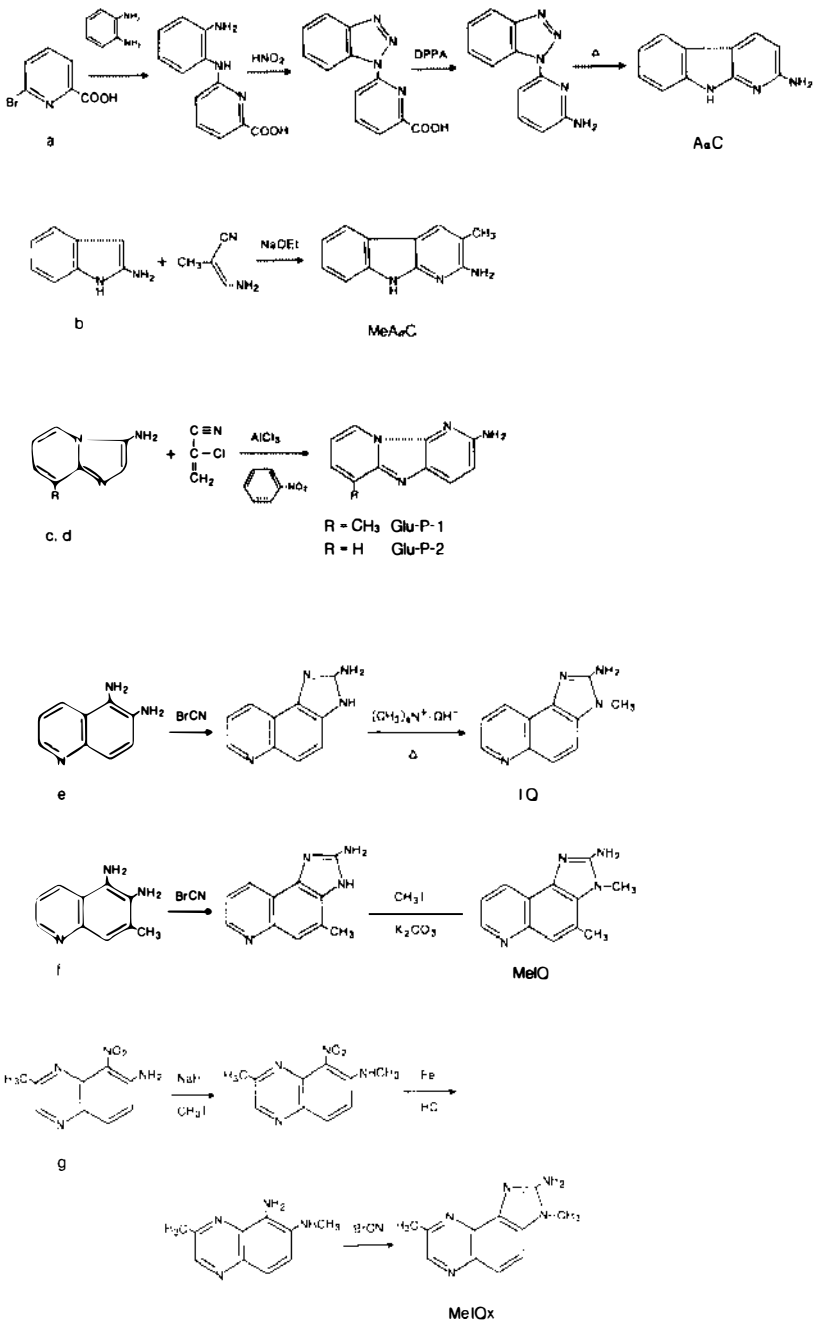


Figure 4a Organic syntheses of heterocyclic amines and heterocyclic imino compounds: (*a*) 6-Bromo-2-picolinic acid (77). (*b*) 2-Aminoindole (76). (*c*) 3-Amino-8-methylimidazo[1,2-α]pyridine (118). (*d*) 3-Aminoimidazo[1,2-α]pyridine (118). (*e*) 5,6-Diaminoquinoline (56). (*f*) 5,6-Diamino-7-methylquinoline (58). (*g*) 6-Amino-3-methyl-5-nitroquinoxaline (57).

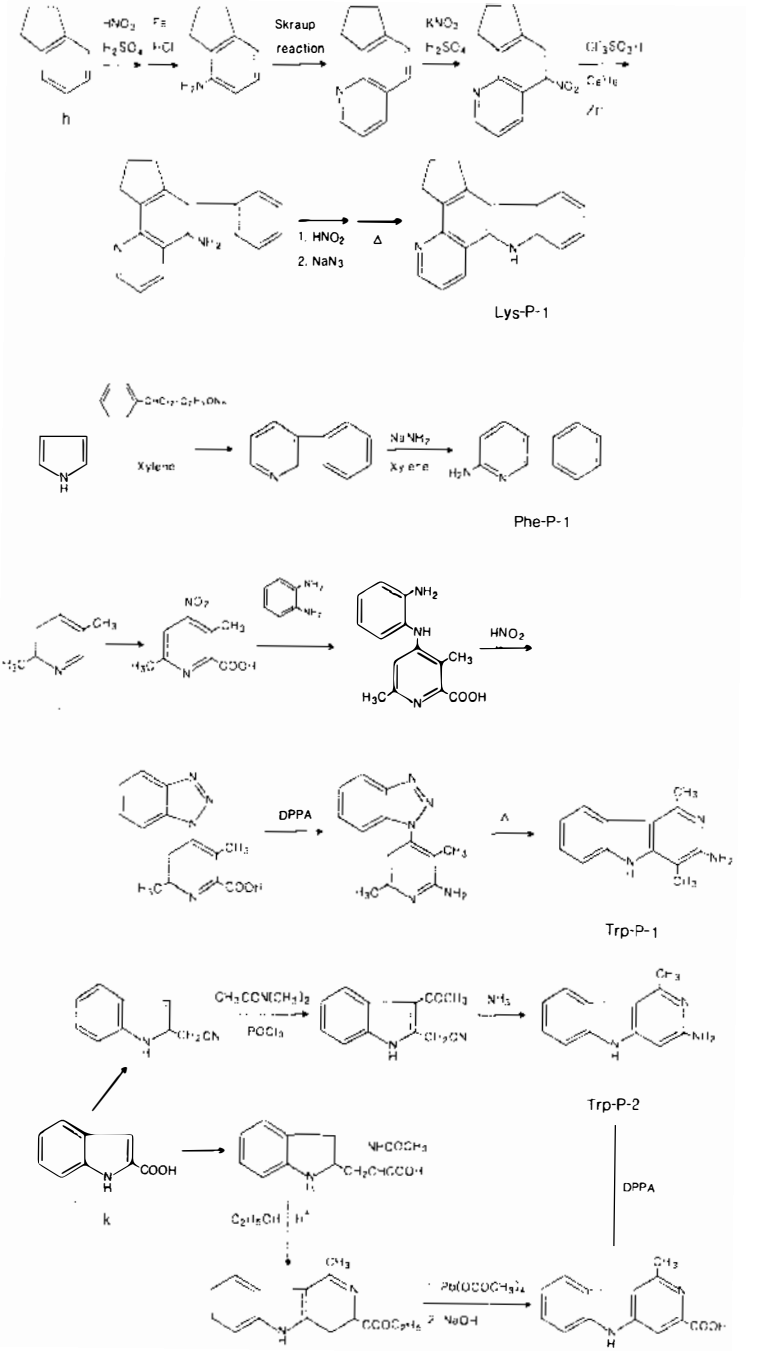


Figure 4b As in Figure 4*a*: (*h*) Indan (126). (*i*) Imidazole (123). (*j*) 2,5-Lutidine (1). (*k*) Indole-2-carboxylic acid (1).

cooked beef was suggested previously (15, 57). Formation of 4,8-DiMeIQx was demonstrated by heating a mixture of creatinine, glucose or ribose, and alanine or lysine (81) and a mixture of creatinine, glucose, and threonine (90). These mutagens were probably produced from creatinine, aldehydes, and Maillard reaction products. Formation of IQ in the heated product of a mixture of creatine and proline was also reported (142).

POLYNUCLEAR AROMATIC HYDROCARBONS

Mutagens-Carcinogens in Cooked Foods

That carcinogenic polycyclic aromatic hydrocarbons are present in cooked foods has been known since the late 1950s (5, 13, 20, 63, 69). At present, at least 18 mutagenic and/or carcinogenic polycyclic aromatic hydrocarbons (shown in Table 6) are known. These chemicals have also been found in uncooked vegetables, fruit, cereals, and vegetable oils. There are many reports on the amounts of polycyclic hydrocarbons in various foods (see Refs. 34, 47). The amount of polycyclic hydrocarbons present in cooked foods depends on the time of cooking, the distance of materials from the heat source, whether the melted fat is allowed to drop into the heat source, etc. In vegetables, fruits, and cereals, the amounts of these chemicals depend on the degrees of industrial and traffic pollutants in the areas in which they are grown. The amounts of carcinogenic polycyclic aromatic hydrocarbons in foods vary from 0 to 400 μg/kg, as shown in Table 6.

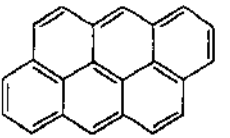
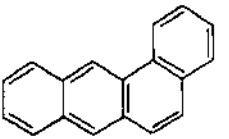
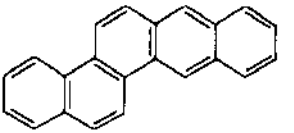
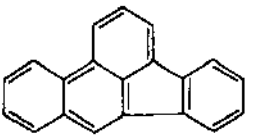
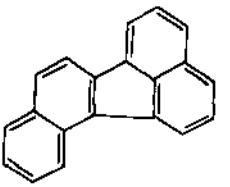
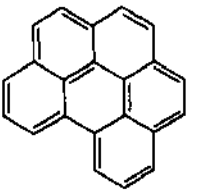
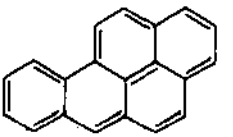
Mutagenicities

The mutagenic activities of polycyclic aromatic hydrocarbons found in cooked foods are also shown in Table 6. The mutagenic activities against *S. typhimurium* TA98 or TA100 in the presence of S9 mix vary from 0.8 to 121 revertants per nmole, and these values are lower than those of heterocyclic amines found in cooked foods, as shown in Table 1.

Carcinogenicities

Of the 18 polycyclic aromatic hydrocarbons that were detected in broiled meat (69) or smoked fish (71), at least 12 are known to be carcinogens, as shown in Table 6. Benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, dibenz[*a,h*]anthracene, 2-methylchrysene, and 3-methylchrysene are strong carcinogens; benzo[*e*]pyrene, chrysene, and indeno[1,2,3-*cd*]pyrene are moderate carcinogens; and anthanthrene and benzo[*b*]chrysene are weak carcinogens. Available data are inadequate to determine the carcinogenicities of benzo[*ghi*]perylene, coronene, perylene, and phenanthrene. The available data provide no evidence that fluoranthene and pyrene per se are carcinogenic to experimental animals.

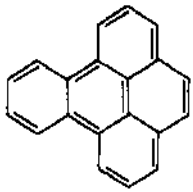
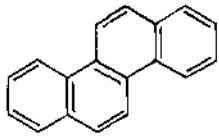
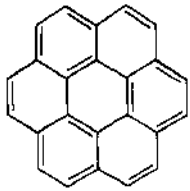
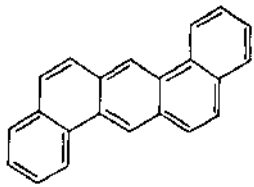
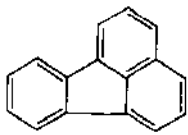
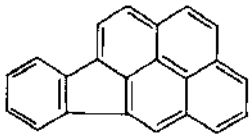
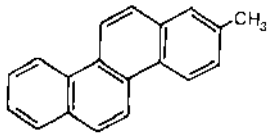
Table 6 Polynuclear aromatic hydrocarbons

Name	Structure	Mutagenic activity on *S. typhimurium* + S9 mix (revertants/nmole)
1. Anthanthrene		62 (TA98) (25)
2. Benz[*a*]anthracene		11 (TA100) (79)
3. Benzo[*b*]chrysene		——
4. Benzo[*b*]fluoranthene		15 (TA98) (25)
5. Benzo[*j*]fluoranthene		3 (TA98) (68)
6. Benzo[*ghi*]perylene		1.6 (TA100) (3)
7. Benzo[*a*]pyrene		121 (TA100) (79)

Tumorigencity and carcinogenicity	Major source in foods (μg/kg)
skin, lung (37)	charcoal-broiled steak 2 (69)
lung adenoma, hepatoma, local sarcoma, skin papilloma, bladder carcinoma, forestomach papilloma, pulmonary adenocarcinoma (29)	broiled or smoked meat 0.2–31 (29, 69) smoked fish 0.02–189 (71) vegetables 0.3–230 (29) vegetable oils 0.5–125 (29)
initiating activity (skin papilloma) (99)	broiled meat 0.5 (69)
skin (papilloma & carcinoma), local sarcoma (31)	broiled or smoked fish 0.1–37 (71) smoked meat 0.4–15 (31)
skin (papilloma & carcinoma), lung carcinoma (39)	smoked fish 0.5–23 (71) grilled sausages 0.2–15 (33) margarine 2.3–10.5 (33)
inadequate experiments (38)	charcoal-broiled steak 4.5 (38, 69) edible oils 0–18 (38)
forestomach (papilloma & carcinoma), skin (papilloma & carcinoma) local sarcomas, mammary carcinomas, leukemias, esophageal papilloma (30)	smoked meat 0.02–107 (5, 30) vegetables 0.2–8 (30) vegetable oils 0.9–62 (30)

(continued)

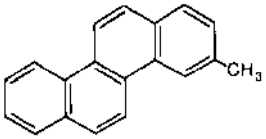
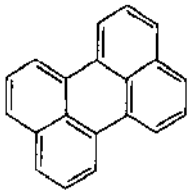
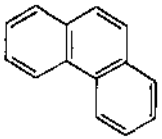
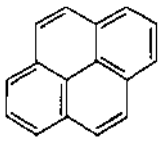
Table 6 *(continued)*

Name	Structure	Mutagenic activity on *S. typhimurium* + S9 mix (revertants/nmole)
8. Benzo[*e*]pyrene		15 (TA98) (25)
9. Chrysene		38 (TA100) (79)
10. Coronene		60 (TA98) (25)
11. Dibenz[*a*, *h*]anthracene		11(TA100) (79)
12. Fluoranthene		3 (TA98) (25)
13. Indeno[1,2,3-*cd*]pyrene		2.21 (TA98) (67)
14. 2-Methylchrysene		3.7 (TA100) (11)

Tumorigenicity and carcinogenicity	Major source in foods (μg/kg)
skin (papilloma & carcinoma) (32)	smoked fish 1.9–29 (5, 71) broiled or smoked meat 0.1–27 (32) vegetable oils 0.6–32 (32)
skin (papilloma & carcinoma), local sarcoma, hepatic tumor (40)	broiled meat 0.6–25 (35) smoked fish 0.3–173 (71) vegetables 5.7–395 (35)
inadequate experiments (41)	charcoal-broiled steak 2.3 (41, 69) edible oils 0–2.8 (41, 69)
forestomach (papilloma & carcinoma) (36)	broiled meat 0.2 (36, 69) vegetable oils & fats 0–4 (36)
not carcinogenic (42)	charcoal-broiled steak 20 (69)
skin, local sarcoma (43)	broiled sausages 0.3–9 (43) margarine 0.2–5.5 (43)
skin (44)	vegetables 0.9–6.2 (44)

(continued)

Table 6 *(continued)*

Name	Structure	Mutagenic activity on *S. typhimurium* + S9 mix (revertants/nmole)
15. 3-Methylchrysene		4.1 (TA100) (11)
16. Perylene		31 (TA98) (25)
17. Phenanthrene		2 (TA100) (93)
18. Pyrene		0.77 (TA 98) (85)

DICARBONYL COMPOUNDS

Methylglyoxal, Glyoxal, and Diacetyl

Methylglyoxal (Figure 5), found in coffee and various heated foods, is a direct acting mutagen toward *S. typhimurium* TA 100 (100,000 revertants/mg) (55). Methylglyoxal (MG) forms an adduct with guanine base in nucleic acid in vitro (62, 100). However, this adduct is unstable after isolation by HPLC and easily reverts to guanine base (C. Furihata et al, unpublished data). Administration of MG by gastric tube to male F344 rats at doses of 100 to 600 mg per kg body weight induced a 100-fold increase in ornithine decarboxylase (ODC) activity within 7 hr, a 26-fold increase in DNA synthesis within 16 hr, a 16-fold increase in the labeling index of S-phase cells within 16 hr, and an apparent unscheduled DNA synthesis within 2 hr in the glandular stomach mucosa.

Tumorigenicity and carcinogenicity	Major source in foods (μg/kg)
skin (44)	vegetables 1.7–20.2 (44)
inadequate experiment (45)	charcoal-broiled steak 2 (69)
inadequate experiment (46)	broiled meat 11 (69)
not carcinogenic (48)	broiled meat 18 (69)

These results suggest that methylglyoxal has potential promoter activity and may also have initiating activity in glandular stomach carcinogenesis (18).

Repeated subcutaneous injections of methylglyoxal in saline at a concentration of 10 mg/ml into male and female F344 rats for 10 weeks induced subcutaneous tumors in 4 of 18 rats within 17 months (17). The mutagenicity of methylglyoxal was inactivated by bisulfite at a physiologically feasible concentration (110). Methylglyoxal (1 μg) induced four diphtheria-toxin-resistant mutants per 10^6 CHL cells (108).

Glyoxal and diacetyl (Figure 5) were also found in coffee and were weakly mutagenic (6). The mutagenic activities of glyoxal and diacetyl against *S. typhimurium* TA100 without S9 mix are 9000 and 360 revertants/mg, respectively. Glyoxal at doses of 150 to 400 mg/kg body weight and diacetyl at doses of 300 to 1500 mg/kg body weight also induced ODC activity and DNA

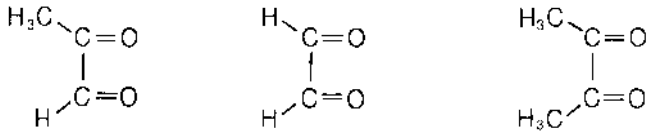


Figure 5 Chemical structures of methylglyoxal, glyoxal, and diacetyl.

synthesis and apparent unscheduled DNA synthesis in rat stomach mucosa after a single administration via gastric tube (19).

ACKNOWLEDGMENTS

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