MeIQx (2-AMINO-3,8-DIMETHYLIMIDAZO[4,5-*f*]QUINOXALINE)

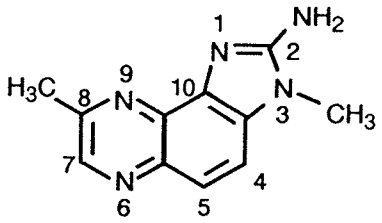
This substance was considered by a previous Working Group, in October 1985 (IARC, 1986). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Services Reg. No.: 77500-04-0
Chem. Abstr. Name: 3,8-Dimethyl-3*H*-imidazo[4,5-*f*]quinoxalin-2-amine
IUPAC Systematic Name: 2-Amino-3,8-dimethyl-3*H*-imidazo[4,5-*f*]quinoxaline



$C_{11}H_{11}N_5$ Mol. wt: 213.24

1.1.2 *Chemical and physical properties*

(*a*) *Melting-point*: 295–300 °C (with slight decomposition) (Grivas & Olsson, 1985)
(*b*) *Spectroscopy data*: Ultraviolet (Kasai *et al.*, 1981a,b), proton nuclear magnetic resonance (Kasai *et al.*, 1981b; Knize *et al.*, 1987) and mass spectral data (Kasai *et al.*, 1981b; Hargraves & Pariza, 1983; Felton *et al.*, 1984) have been reported.
(*c*) *Solubility*: Soluble in methanol (Kasai *et al.*, 1981a) and dimethyl sulfoxide (Dooley *et al.*, 1992)
(*d*) *Stability*: Stable under moderately acidic and alkaline conditions and in cold dilute aqueous solutions protected from light (Sugimura *et al.*, 1983)
(*e*) *Reactivity*: Rapidly degraded by dilute hypochlorite; not deaminated by weakly acidic nitrite solutions (Tsuda *et al.*, 1985)

1.1.3 *Trade names, technical products and impurities*

No data were available to the Working Group.

1.1.4 *Analysis*

MeIQx was initially isolated and purified by acid–base partitioning, Sephadex LH-20 column chromatography and reverse-phase high-performance liquid chromatography (HPLC). The structure was deduced mainly from data obtained by proton nuclear magnetic resonance and high-resolution mass spectral analysis and by comparison with synthetic MeIQx (Kasai *et al.*, 1981b).

MeIQx was isolated from beef extract by dichloromethane extraction, column chromatography on Adsorbosil-5 and Sephadex LH20 and HPLC, with analysis by mass spectrometry and ultraviolet spectrophotometry (Hargraves & Pariza, 1983; Turesky *et al.*, 1983). MeIQx was detected in fried ground beef at 1 ng/g by acid extraction, absorption on XAD-2 resin, preparative and analytical HPLC and off-line mass spectrometry (Felton *et al.*, 1984).

MeIQx can be adsorbed from aqueous solutions onto cellulose or cotton to which CI Reactive Blue 21, a trisulfo-copper phthalocyanine dye, has been bound covalently. The adsorbed MeIQx is eluted with an ammonia–methanol and quantified by assay for mutagenic activity (Hayatsu *et al.*, 1983). This 'blue cotton' adsorption technique has been used in several procedures for the detection of MeIQx.

MeIQx has also been quantified in cooked beef products using a deuterium-labelled internal standard and liquid chromatography–thermospray–mass spectrometry (Turesky *et al.*, 1988a). This method involves methanol extraction, acid–base partition and 'blue cotton' adsorption prior to analysis.

Turesky *et al.* (1989) used monoclonal antibodies immobilized on a support for selective immunoaffinity chromatography as a clean-up procedure in the analysis of beef extracts used for bacteriological media and of food-grade beef extracts. Vanderlaan *et al.* (1988) produced monoclonal antibodies which bound to MeIQx and related heterocyclic amines with varying specificities.

Derivatization and capillary gas chromatography–mass spectrometry analysis of fried beef with picogram sensitivity for MeIQx has been reported (Murray *et al.*, 1988). Cooked beef was analysed using only a 10-g sample, and isotope-labelled MeIQx internal standard was used to determine recovery accurately.

A practical, solid-phase extraction and medium-pressure liquid chromatographic method for the analysis of MeIQx and other heterocyclic amines was devised by Gross *et al.* (1989) and used with food-grade and bacterial beef extracts as well as fried beef. Improvements to the method (Gross, 1990; Gross & Grüter, 1992) allow determination of MeIQx and most of the other known heterocyclic amines at a level of 1 ng/g from only 3 g of meat and 10 g of fish. Replicate samples and spiking allow accurate determination of extraction losses; chromatographic peak identities are confirmed using a diode array–ultraviolet detector.

1.2 Production and use

1.2.1 *Production*

The isolation and identification of MeIQx were first reported by Kasai *et al.* (1981b). Its structure was confirmed by chemical synthesis, in which 6-amino-3-methyl-5-nitroquinoxaline was methylated, reduced to the 5-amino derivative and cyclized with cyanogen

bromide to form MeIQx (Kasai *et al.*, 1981a; Sugimura *et al.*, 1983). Subsequent purification from fried beef confirmed the original structure (Knize *et al.*, 1987).

Improved synthetic routes have been reported from 4-fluoro-*ortho*-phenylenediamine (Grivas & Olsson, 1985), through benzoselenadiazole (Grivas, 1986) and through copper(I)-promoted quinoxaline formation (Knapp *et al.*, 1989).

Synthesis of isotopically-labelled [^{13}C, $^{15}N_2$] MeIQx was reported by Murray *et al.* (1988).

MeIQx is produced commercially in small quantities for research purposes.

1.2.2 *Use*

MeIQx is not used commercially.

1.3 Occurrence

MeIQx has been detected in cooked beef, fish, chicken and mutton in varying amounts (Table 1).

Table 1. Concentrations of MeIQx in foods

Sample	Concentration (ng/g)	No. of samples	Reference
Ground beef, uncooked	ND	1	Murray *et al.* (1988)
Ground beef, fried			
190 °C	0.45	1	Hargraves & Pariza (1983)
	5.1–8.3	2	Gross *et al.* (1990)
200 °C	1.3–2.4	2	Murray *et al.* (1988)
250 °C	0.5–1.5	2	Turesky *et al.* (1989)
	1.0	1	Felton *et al.* (1984)
	1.1–1.4[a]	1	Gross *et al.* (1989); Turesky *et al.* (1989)
275 °C	2.7–12.3	3	Turesky *et al.* (1988a)
300 °C	1.0	1	Felton *et al.* (1986)
No temperature given	0.64	1	Wakabayashi *et al.* (1992)
Beef, broiled	2.11	1	Wakabayashi *et al.* (1992)
Beef extract, food-grade	3.1	1	Takahashi *et al.* (1985)
	8.5–30	4	Gross *et al.* (1989)
	28	1	Hargraves & Pariza (1983)
Mutton, broiled	1.01	1	Wakabayashi *et al.* (1992)
Fish, fried	6.44	1	Zhang *et al.* (1988)
Salmon, pan-broiled, 200 °C	1.4–5	4	Gross & Grüter (1992)
Salmon, oven-cooked, 200 °C	< 1–4.6	3	Gross & Grüter (1992)
Salmon, barbecued, 270 °C	< 1	4	Gross & Grüter (1992)
Mackerel, smoked, dried	0.8	1	Kato *et al.* (1986)
Chicken, broiled	2.33	1	Wakabayashi *et al.* (1992)
Eel, roasted, tinned	1.1	1	Lee & Tsai (1991)

ND, not detected

[a]Depending on the method used

Amounts of MeIQx relative to the three other heterocyclic amines included in this volume are listed in the monograph on IQ (p. 168).

MeIQx has also been found in refluxing diethylene glycol mixtures of glycine, glucose and creatinine (Jägerstad *et al.*, 1984) and has been formed from mixtures of glycine, fructose and creatinine (Grivas *et al.*, 1986) and glycine, glucose and creatinine (Skog & Jägerstad, 1990). Dry mixtures, heated at 200 °C, of creatine and either serine, alanine or tyrosine formed MeIQx (Övervik *et al.*, 1989).

Since many foods in the human diet contain heterocyclic amines, methods have been developed to estimate the dietary dose from urinary excretion after food ingestion and metabolism. Murray *et al.* (1989) determined the recovery of MeIQx in urine to be 1.8–4.9% of the ingested amount after 12 h. The amount of MeIQx in the urine of 10 subjects on a normal diet was 11–47 ng/24 h. After adjustment for metabolic transformation, the daily dose of MeIQx was estimated to range from 0.2 to 2.6 μg for the individuals who participated in the study. MeIQx was not detected (< 1 ng/24-h urine sample) in the urine of three patients who were receiving parenteral nutrients (Ushiyama *et al.*, 1991). Total amounts in the diet thus appear to range from virtually none for people eating a diet contained few cooked foods (especially meat) to perhaps a few micrograms per day.

1.4 Regulations and guidelines

No data were available to the Working Group.

2. Studies of Cancer in Humans

No epidemiological study was available that addressed the carcinogenic risk to humans of MeIQx itself. Cancer risks associated with consumption of broiled and fried foods, which may contain MeIQx as well as other heterocyclic amines, have, however, been addressed in a number of case–control studies. Several of these are summarized in the monograph on IQ.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration[1]

3.1.1 *Mouse*

Groups of 40 male and 40 female CDF_1 [(BALB/cAnN × DBA/2N) F_1] mice, six weeks old, were fed a diet containing 0 or 600 mg/kg MeIQx [purity unspecified] for 84 weeks. Animals that became moribund were killed and autopsied. The first leukaemia, in a treated

[1]The Working Group was aware of a study in progress on MeIQx given in the diet of mice (Ghess *et al.*, 1992) and of a study by gavage to non-human primates carried out at the US National Cancer Institute, Division of Cancer Etiology.

male mouse, was detected in week 48, and the numbers of mice that survived after that time were taken as the effective numbers. The average survival times in weeks (mean ± SD) of treated males, treated females, control males and control females were 76 ± 11, 75 ± 7, 77 ± 11 and 82 ± 4, respectively. A significantly larger number of treated mice than controls had liver tumours (adenomas and carcinomas combined): males, 16/37 *versus* 6/36; females, 32/35 *versus* 0/39; 10 males and 25 females in the treated group developed hepatocellular carcinomas. The incidence of lung tumours (adenomas and adenocarcinomas) was significantly greater in treated female mice than in controls: 15/35 *versus* 4/39; adenocarcinoma of the lung was observed in 11 treated males, six treated females, seven control males and two control females. The incidence of lymphoma and leukaemia in treated male mice was significantly greater than in controls: 11/37 *versus* 2/36. In mice of each sex, the average time to appearance of lymphomas or leukaemias was significantly shorter among treated animals than controls: males, 69 *versus* 84 weeks; females, 70 *versus* 79 weeks (Ohgaki *et al.*, 1987).

3.1.2 *Rat*

Groups of 20 male and 20 female Fischer 344 rats, seven weeks old, were fed a diet containing 0 or 400 mg/kg of diet MeIQx (purity, > 99%) for 429 days. Animals that became moribund were killed and autopsied. The first tumour of the Zymbal gland was seen in a treated female on day 177, and the numbers of rats that lived after that time were taken as the effective numbers. The average survival times in days (mean ± SD) of treated males, treated females, control males and control females were 326 ± 36, 364 ± 61, 427 ± 8 and 429 ± 0, respectively. Treated animals had significantly more liver tumours than controls: males, 20/20 (19 hepatocellular carcinomas, 1 neoplastic nodule) *versus* 0/19; females, 10/19 (all neoplastic nodules) *versus* 0/20. In six of the treated males, hepatocellular carcinomas metastasized to the lung. A significant increase in the incidence of tumours of the Zymbal gland was found in treated animals over that in controls: males, 15/20 (13 squamous-cell carcinomas, 2 squamous-cell papillomas) *versus* 0/19; females, 10/19 (all squamous-cell carcinomas) *versus* 0/20. Clitoral gland tumours (squamous-cell carcinomas) were found in 12/19 treated females and in no control. Skin tumours were found in 7/20 treated males and in 1/19 treated females; the skin tumours in males were diagnosed as five squamous-cell carcinomas, one basal-cell carcinoma and one squamous-cell papilloma, and the tumour in the female as a squamous-cell carcinoma (Kato *et al.*, 1988).

3.2 Intraperitoneal administration

Mouse

Groups [initial numbers unspecified] of newborn male B6C3F$_1$ mice were injected intraperitoneally with MeIQx (> 98% pure) at total doses of 0, 0.625 or 1.25 μmol [133.3 or 266.5 μg] (maximal tolerated dose) dissolved in 5, 10 or 20 μl dimethyl sulfoxide and administered on days 1, 8 and 15 after birth, respectively. The incidence of hepatocellular adenomas was significantly higher in treated mice than in controls at 12 months: controls, 5/44; low-dose, 8/24; and high-dose, 17/20 (Dooley *et al.*, 1992).

3.3 Administration with known carcinogens

Rat

In a short-term assay for tumour-initiating activity in the liver, a group of 10 male Fischer 344 rats, five weeks of age, each received a single intragastric dose of 80 mg/kg bw MeIQx [source and purity unspecified] in corn oil, and, two weeks later, were fed a diet containing 0.05% phenobarbital for six weeks. The rats received a two-thirds partial hepatectomy three weeks after the MeIQx treatment. The number and total area of foci of phenotypically altered hepatocytes in the liver were scored using expression of placental-form glutathione *S*-transferase (GST-P) as the marker. The number of foci was not significantly increased over that in five vehicle-treated control rats, and, in the absence of subsequent phenobarbital treatment, MeIQx did not induce a significant increase in the number of foci in five rats. Another group of 10 rats received a two-thirds partial hepatectomy 12 h before MeIQx treatment, were placed on phenobarbital as above and one week after phenobarbital treatment received a single intraperitoneal injection of 300 mg/kg D-galactosamine. Administration of MeIQx significantly increased the number of foci by six fold and the area by five fold over that in five vehicle-treated control rats. MeIQx without subsequent phenobarbital treatment, but with galactosamine, produced a smaller increase in the number of foci in five rats. These results suggest that MeIQx has tumour-initiating activity in rat liver if combined with prior partial hepatectomy (Tsuda *et al.*, 1990).

As part of a medium-term carcinogenicity study on the synergistic effects of five heterocyclic amines, groups of 14–18 male Fischer 344 rats, six weeks of age, each received a single intraperitoneal injection of 200 mg/kg *N*-nitrosodiethylamine and, two weeks later, were fed a diet containing MeIQx at 16, 80 or 400 ppm (mg/kg diet). A two-thirds partial hepatectomy was performed in week 3 of the experiment; all animals were killed after eight weeks. Fifteen rats treated with the nitrosamine alone and groups of three rats given MeIQx at the three dose levels and saline instead of nitrosamine served as controls. The effects were assessed by counting the numbers of GST-P-positive foci in the liver. MeIQx at the high dose level significantly increased the area and the number of GST-P-positive foci (Ito *et al.*, 1991).

A group of 15 male Wistar rats, six weeks old, underwent a two-thirds partial hepatectomy, followed 17 h later by a single intraperitoneal injection of 50 mg/kg bw MeIQx (purity, > 99%) dissolved in acid water (pH 5.0); animals were then fed a diet containing 200 mg/kg 2-acetylaminofluorene during weeks 2 and 3 and received 2 ml[3.2 mg]/kg bw carbon tetrachloride by gavage at the beginning of week 3. All animals were killed at the end of week 6. Significantly more γ-glutamyl transpeptidase-positive liver-cell foci were found in the group treated with MeIQx (1.7 foci/cm^2) than in 17 controls given 0.9% saline instead of MeIQx (0.48 foci/cm^2) (Kleman *et al.*, 1989).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

The toxicology and metabolism of heterocyclic aromatic amines have been reviewed (Övervik & Gustafsson, 1990; Aeschbacher & Turesky, 1991).

4.1.1 *Humans*

Six male volunteers had a test meal of 320 g of ground beef fried at normal cooking temperature. In all six, MeIQx was detected in 12-h urine collected after the test meal, while no detectable amount was found before the meal. Two to five percent of the ingested amount of MeIQx was excreted unchanged in the urine (Murray *et al.*, 1989).

4.1.2 *Experimental systems*

After intravenous administration of ^{14}C-MeIQx to mice, radiolabel, measured by autoradiography, was distributed throughout the body after 10 min. The label persisted in the liver and in the gut contents four days after exposure (Gooderham *et al.*, 1991). In rats administered ^{14}C-MeIQx by gavage, radiolabel was widely distributed in the body after 1 h. Non-extractable radiolabel persisted in the liver and kidneys six days after administration (Tjøtta *et al.*, 1992).

After oral administration to mice of [2-^{14}C]-MeIQx, MeIQx was rapidly absorbed and metabolized, 20–25% of the radiolabel being excreted in the urine within 6 h. Radiolabel was found in all organs studied: stomach, small intestine, large intestine, blood, liver, spleen, lung, kidney (Alldrick & Rowland, 1988).

When male Sprague-Dawley rats were given [2-^{14}C]-MeIQx at 0.01, 0.2 or 20 mg/kg bw by gavage, the recovery of radiolabel was about 90% of the administered dose, and higher in faeces than in urine. Small amounts of radiolabel were found after 72 h, especially in liver and kidney. At the two higher doses, excretion occurred mainly *via* sulfamate formation, while at the low dose conjugation with glucuronic acid was the most important pathway. Induction of cytochrome P450 enzymes by polychlorinated biphenyls led to increased levels of glucuronic and sulfuric acid conjugates and a decreased level of sulfamate formation (Turesky *et al.*, 1991a).

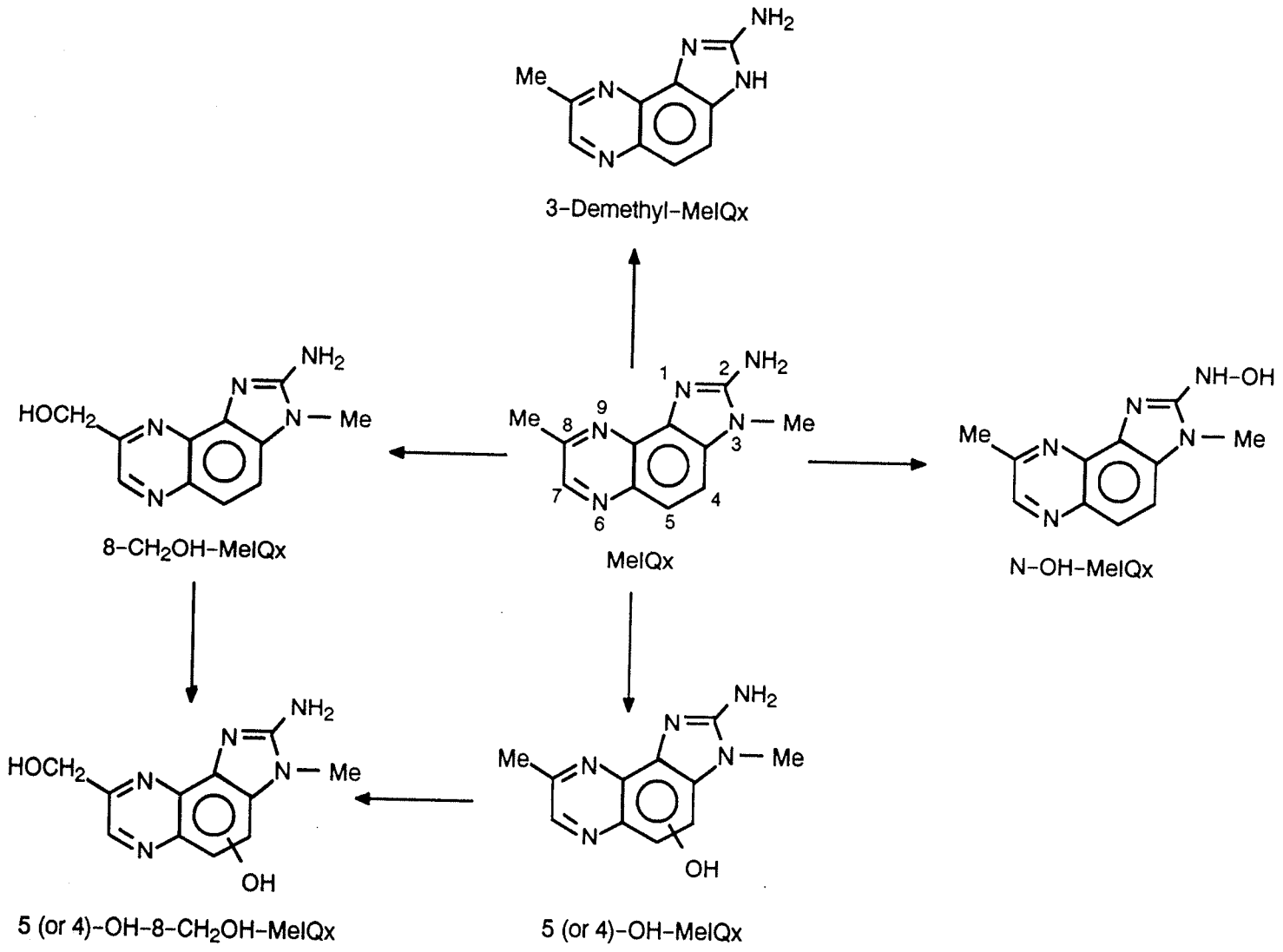
Human liver microsomes could activate MeIQx to a DNA-reactive species. The isozyme involved was tentatively identified as CYP IA2 (P450 IA2) (Shimada *et al.*, 1989). Human liver and colon cytosols contained *O*-acetyltransferase activity that metabolized *N*-hydroxy-MeIQx into a DNA-binding form (Turesky *et al.*, 1991b). (See Fig. 1, in the monograph on IQ, p. 178).

In the presence of liver microsomes from rats induced with 3-methylcholanthrene or polychlorinated biphenyls, MeIQx was metabolized to an *N*-hydroxylated derivative (Yamazoe *et al.*, 1988; Turesky *et al.*, 1991a). Metabolism occurred mainly by two forms of cytochrome P450, P448-H and P448-L (Yamazoe *et al.*, 1988). Formation of the 5-hydroxylated derivatives was strongly induced by polychlorinated biphenyls (Turesky *et al.*, 1991a).

In isolated rat liver cells, MeIQx was transformed into 10 metabolites, including *N*-hydroxy, 4- or 5-hydroxy, 8-hydroxymethyl and *N*3-demethylated derivatives, sulfate and glucuronide derivatives of these compounds, and sulfamate and glucuronide derivatives of MeIQx (Wallin *et al.*, 1989) (Fig. 1). After dietary administration of MeIQx to rats *in vivo*, *N*3-demethylated, *C*8-hydroxymethylated and *N*-acetylated derivatives of MeIQx were detected (Hayatsu *et al.*, 1987).

Similar metabolites were found in another study in rats. After intragastric administration of [2-^{14}C]-MeIQx, 40 and 49% of the radiolabel was recovered in the urine

Fig. 1. Oxidative metabolic pathways of MeIQx



From Wallin *et al.* (1989)

and faeces, respectively; 25–50% of the dose was recovered in the bile within 24 h. Five metabolites—two sulfamates, two glucuronides and an acetylated derivative—accounted for 96% of the radiolabel excreted in bile (Turesky *et al.*, 1988b,c). The importance of the acetylation reaction was also seen in bacterial mutagenicity studies in which inhibitors of *O*-acetyltransferase were applied (Negishi *et al.*, 1989).

Prior treatment of rats with MeIQx induced the metabolism of MeIQx administered subsequently (Degawa *et al.*, 1989).

In a study designed to provide information on the metabolic steps involved in the formation of the active mutagenic form, MeIQx was not mutagenic to *Salmonella typhimurium* TA98/1,8-DNP_6 (defective in esterifying activity) in the presence of an exogenous metabolic system (S9 mix), but it was strongly mutagenic to the original strain TA98 with S9 mix, suggesting that the ultimate mutagenic form of MeIQx is a reactive ester of its *N*-hydroxy derivative (Nagao *et al.*, 1983).

Covalent binding of MeIQx to albumin and DNA in microsomes and rat hepatocytes *in vitro* was dependent on cytochrome P450 enzymes. The efficiency of binding of MeIQx was similar to that of MeIQ and less than that of IQ (Wallin *et al.*, 1992).

4.2 Toxic effects

No data were available to the Working Group.

4.3 Reproductive and developmental toxicity

No data were available to the Working Group.

4.4 Genetic and related effects

The genetic effects of MeIQx have been reviewed (Sugimura, 1985; de Meester, 1989).

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 2 and Appendices 1 and 2)

MeIQx induced SOS repair and mutation in bacteria and somatic mutations in *Drosophila melanogaster*. It induced unscheduled DNA synthesis in primary cultures of hepatocytes from various species but, in hepatocytes from mice, only in cells derived from females. In mammalian cell lines, it induced chromosomal anomalies and diphtheria toxin-resistant mutants. MeIQx induced *hprt* locus mutations in a repair-deficient but not in a repair-proficient cell line. It induced sister chromatid exchange but not chromosomal aberrations in cultured human lymphocytes.

After administration *in vivo*, MeIQx formed DNA adducts in various rat and mouse organs. It did not induce mutation in the Dlb-1 locus (which determines the tissue-specific pattern of expression of the binding site for the lectin *Dolichos biflorus* agglutinin) in mouse

Table 2. Genetic and related effects of MeIQx

Test system	Result		Dose (LED/HID)[a]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS repair test, *Salmonella typhimurium* TA1535	0	+	0.0700	Nakamura *et al.* (1987)
PRB, *umu* expression, *Salmonella typhimurium* TA1535/psk 1002	0	+	2.0000	Shimada *et al.* (1989)
PRB, SOS repair, *Salmonella typhimurium* with human adult and fetal microsomes	0	+	2.0000	Kitada *et al.* (1990)
ERD, *Escherichia coli* K12, differential toxicity	-	+	0.2600	Knasmüller *et al.* (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	0.0100	Kasai *et al.* (1981b)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	0.0000	Grivas & Jägerstad (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SA2, *Salmonella typhimurium* TA102, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SA4, *Salmonella typhimurium* TA104, reverse mutation	0	-	0.0000	Felton & Knize (1990)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	+	0.0000	Felton *et al.* (1986)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	+	0.4000	Felton & Knize (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0050	Kasai *et al.* (1981a)
SA9, *Salmonella typhimurium* TA98, reverse mutation[b]	0	+	0.0000	Ishida *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	0.0025	Winton *et al.* (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.3125	Loprieno *et al.* (1991)
SA8, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	0	-	0.0250	Nagao *et al.* (1983)
SA8, *Salmonella typhimurium* TA96, reverse mutation	0	-	0.0000	Felton & Knize (1990)
SA8, *Salmonella typhimurium* TA97, reverse mutation	0	+	0.0000	Felton & Knize (1990)
DMM, *Drosophila melanogaster*, somatic mutation and recombination	+	0	25.0000	Yoo *et al.* (1985)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	0	1.0000	Yoshimi *et al.* (1988)
UIA, Unscheduled DNA synthesis, mouse primary hepatocytes (female) *in vitro*	+	0	10.0000	Yoshimi *et al.* (1988)
UIA, Unscheduled DNA synthesis, mouse primary hepatocytes (male) *in vitro*	-	0	10.0000	Yoshimi *et al.* (1988)
UIA, Unscheduled DNA synthesis, Syrian hamster primary hepatocytes *in vitro*	+	0	1.0600	Yoshimi *et al.* (1988)
GCL, Gene mutation, Chinese hamster lung cells DT^r *in vitro*	-	+	10.0000	Nakayasu *et al.* (1983)
GCL, Gene mutation, Chinese hamster lung cells *in vitro*	0	(+)	1.0000	Sugimura *et al.* (1989)

Table 2 (contd)

Test system	Result		Dose (LED/HID)[a]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
GCO, Gene mutation, Chinese hamster ovary cells (*uv5*) *hprt* locus *in vitro*	0	+	300.0000	Thompson *et al.* (1987)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	0	-	51.2000	Loprieno *et al.* (1991)
SIC, Sister chromatid exchange, Chinese hamster ovary (*uv5*) cells *in vitro*	0	(+)	200.0000	Thompson *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary (*uv5*) cells *in vitro*	0	(+)	600.0000	Thompson *et al.* (1987)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	0	-	80.0000	Loprieno *et al.* (1991)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	(+)	+	0.1000	Aeschbacher & Ruch (1989)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	-	-	130.0000	Loprieno *et al.* (1991)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	-	-	1000.0000	Aesbacher & Ruch (1989)
HMM, Host-mediated assay, *Escherichia coli* in intrasanguinous mice	+		2.30 × 1 ip, po	Knasmüller *et al.* (1992)
GVA, Gene mutation, mouse small intestinal cells, *Dlb*-1 expression *in vivo* (females)	-		20.00 × 10 po	Winton *et al.* (1990)
SVA, Sister chromatid exchange, rat hepatocytes *in vivo*	+		200.00 × 1 ip	Sawada *et al.* (1991)
SVA, Sister chromatid exchange, mouse (PCB-treated) bone-marrow cells *in vivo* (males)	-		50.00 × 1 ip	Tucker *et al.* (1989)
MVM, Micronucleus test, mouse bone-marrow cells *in vivo* (males)	-		40.00 × 1 po	Loprieno *et al.* (1991)
CVA, Chromosomal aberrations, rat hepatocytes *in vivo*	+		200.00 × 1 ip	Sawada *et al.* (1991)
BID, Binding (covalent) to DNA, rat hepatocytes *in vitro*	+	0	10.0000	Wallin *et al.* (1992)
BVD, Binding (covalent) to DNA, rat liver *in vivo*[c]	+		50.00 × 1 ip	Yamashita *et al.* (1988)
BVD, Binding (covalent) to DNA, mouse (various tissues) *in vivo*[d]	+		0.01065 × 1 po	Alldrick & Lutz (1989)
BVD, Binding (covalent) to DNA, rat liver *in vivo*[c]	+		0.48 diet × 1 wk	Yamashita *et al.* (1990)
BVD, Binding (covalent) to DNA, rat heart and liver *in vivo*[c]	+		48 diet × 4 wk	Övervik *et al.* (1991)
BVP, Binding (covalent) to DNA, mouse bone marrow *in vivo* (males)[d]	+		40.00 × 1 po	Loprieno *et al.* (1991)

+, positive; (+), weakly positive; -, negative; 0, not tested

[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; 0.0000, dose not given

[b]Rhesus liver S9

[c]^{32}P-Postlabel

[d]^{14}C-Label

small intestinal cells. Sister chromatid exchange was induced in rat hepatocytes, but not in mouse bone-marrow cells, following intraperitoneal administration of MeIQx.

N-Hydroxy-MeIQx binds nonenzymatically to DNA *in vitro* (Negishi *et al.*, 1989).

4.4.3 *Genetic changes in animal tumours*

Two of six Zymbal gland tumours induced in rats by MeIQx carried mutated c-Ha-*ras* genes, one being a G to T transversion at the second base of codon 13 and the other an A to T transversion at the second base of codon 61 (Kudo *et al.*, 1991).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

MeIQx (2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline) has been found in cooked meat and fish at concentrations of up to 12 ng/g. A few determinations indicated that the levels of MeIQx were lower than those of PhIP and higher than those of IQ and MeIQ.

5.2 Human carcinogenicity data

No data directly relevant to an evaluation of the carcinogenicity to humans of MeIQx were available. Studies on the consumption of cooked meat and fish are summarized in the monograph on IQ.

5.3 Animal carcinogenicity data

MeIQx was tested for carcinogenicity by oral administration in the diet in one experiment in mice and in one experiment in rats. In mice, it produced hepatocellular carcinomas in animals of each sex, lymphomas and leukaemias in males and lung tumours in females. In rats, it produced hepatocellular carcinomas in males, squamous-cell carcinomas of the Zymbal gland in animals of each sex, squamous-cell carcinomas of the skin in males and squamous-cell carcinomas of the clitoral gland in females.

Intraperitoneal injection of MeIQx to newborn male mice increased the incidence of hepatic adenomas.

A single oral treatment of rats with MeIQx followed by phenobarbital, combined with further modulating procedures, stimulated development of foci of altered hepatocytes. Sequential administration of MeIQx after *N*-nitrosodiethylamine enhanced the appearance of foci of altered hepatocytes in rats.

5.4 Other relevant data

No data were available on the genetic and related effects of MeIQx in humans.

MeIQx bound to DNA in several tissues of rodents dosed *in vivo*, and, in single studies, it induced chromosomal anomalies. It induced sister chromatid exchange in human cells *in*

vitro and DNA damage, gene mutation and sister chromatid exchange in rodent cells *in vitro*. It induced gene mutation in insects and gene mutation and DNA damage in bacteria.

MeIQx can be metabolized by human microsomes to a species that damages bacterial DNA.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of MeIQx.

There is *sufficient evidence* in experimental animals for the carcinogenicity of MeIQx.

Overall evaluation

MeIQx (2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline) *is possibly carcinogenic to humans (Group 2B).*

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[1]For definition of the italicized terms, see Preamble, pp. 26–29.

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