IQ (2-AMINO-3-METHYLIMIDAZO[4,5-*f*]QUINOLINE)

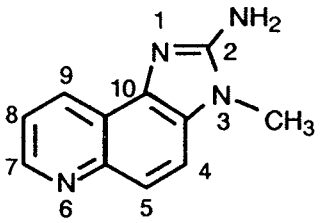
This substance was considered by a previous Working Group, in October 1985 (IARC, 1986a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Services Reg. No.: 76180–96–6
Chem. Abstr. Name: 3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine
IUPAC Systematic Name: 2-Amino-3-methyl-3*H*-imidazo[4,5-*f*]quinoline



$C_{11}H_{10}N_4$ Mol. wt: 198.23

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Crystalline solid (Kasai *et al.*, 1981)
(*b*) *Melting-point*: > 300 °C (Kasai *et al.*, 1981)
(*c*) *Spectroscopy data*: Ultraviolet (Sugimura *et al.*, 1981), proton nuclear magnetic resonance (Kasai *et al.*, 1980a), infrared absorbance (Kasai *et al.*, 1981) and mass spectral data (Spingarn *et al.*, 1980) have been reported.
(*d*) *Solubility*: Soluble in methanol, ethanol and dimethyl sulfoxide (Kasai *et al.*, 1980a, 1981; Lee *et al.*, 1982; Schunk *et al.*, 1984)
(*e*) *Stability*: Stable under moderately acidic and alkaline conditions and in cold dilute aqueous solutions protected from light (Sugimura *et al.*, 1983)
(*f*) *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*

The complex matrix of cooked foods makes analysis of IQ difficult. IQ was originally isolated from broiled, sun-dried sardines, extracted with methanol and purified by Diaion HP-20 column chromatography, chloroform–methanol–water partitioning and Sephadex LH-20 column chromatography, silica-gel column chromatography and, finally, 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 (Kasai *et al.*, 1980b, 1981).

IQ has been isolated from beef extract by dichloromethane extraction, column chromatography on Adsorbosil-5 and Sephadex LH-20 and HPLC, with analysis by mass spectrometry, ultraviolet spectrophotometry and/or mutagenesis assay (Hargraves & Pariza, 1983; Turesky *et al.*, 1983). IQ was detected in fried ground beef following dichloromethane extraction, chromatography on XAD-2 resin, three different HPLC separations and off-line mass spectrometry (Felton *et al.*, 1984).

IQ 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 (referred to as the 'blue cotton' adsorption technique). The adsorbed IQ is eluted with an ammonia–methanol solution and quantified by HPLC (Hayatsu *et al.*, 1983).

More sophisticated methods of detecting IQ in cooked foods using deuterium-labelled internal standards and HPLC-thermospray-mass spectrometry have been devised (Yamaizumi *et al.*, 1986; Turesky *et al.*, 1988). Although they differ in detail, these methods involve methanol extraction, acid–base partitioning and 'blue cotton' adsorption prior to analysis by HPLC–thermospray–mass spectrometry.

Monoclonal antibodies to IQ have been developed (Vanderlaan *et al.*, 1988), and Yanagisawa *et al.* (1990) showed that their antibodies bound to IQ and related heterocyclic amines with varying specificities. 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.

A practical, solid-phase extraction and HPLC (Kieselgur–Sephasorb) method for the analysis of IQ and other heterocyclic amines in foods and food extracts was devised by Gross *et al.* (1989). Improvements to the method (Gross, 1990; Gross & Grüter, 1992) allow determination of IQ and most of the other known heterocyclic amines at a level of 1 ng/g from only 10 g of food sample. 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 IQ were first reported by Kasai *et al.* (1980b). Its structure was confirmed by chemical synthesis, in which 5,6-diaminoquinoline was reacted

with cyanogen bromide and the resulting cyclic intermediate was converted to IQ by heating the tetramethylammonium salt under reduced pressure. Final purification was accomplished by sublimation, silica-gel column chromatography and crystallization from aqueous methanol (Kasai *et al.*, 1980a, 1981).

Improved synthetic routes were devised by Lee *et al.* (1982), Adolfsson and Olsson (1983) and Waterhouse and Rapoport (1985). Synthesis of ^{14}C-labelled IQ was reported by Adolfsson and Olsson (1983) and of tritium- and deuterium-labelled IQ by Waterhouse and Rapoport (1985).

IQ is produced commercially in small quantities for research purposes.

1.2.2 *Use*

IQ is not used commercially.

1.3 Occurrence

As cooking terms such as broiling and grilling have different meanings in different parts of the world, the authors' terminology has been retained.

IQ is formed during the cooking of various meats and fish. It was originally isolated from broiled fish and has also been quantified in fried ground beef and beef extracts. The amounts found in these and other samples are listed in Table 1. IQ was also detected but not quantified in fried ground pork (Gry *et al.*, 1986), in beef extracts used for bacteriological media and in food-grade beef extracts (Hargraves & Pariza, 1983).

Table 1. Concentrations of IQ in foods

Sample	Concentration (ng/g)	No. of samples	Reference
Sardines, sun-dried, broiled	~ 20	1	Kasai *et al.* (1980b)
	158	1	Sugimura *et al.* (1981)
Ground beef, fried			
240 °C	0.5–20[a]	2	Barnes *et al.* (1983)
250 °C	0.02	1	Felton *et al.* (1984)
275 °C	0.3–1.9	3	Turesky *et al.* (1988)
Ground beef, broiled	0.5	1	Yamaizumi *et al.* (1986)
Beef, broiled	0.19	1	Wakabayashi *et al.* (1992)
Beef extract, food-grade	< 0.2	1	Takahashi *et al.* (1985)
	< 0.1–6.2	3	Turesky *et al.* (1989)
Salmon, broiled	0.3–1.8	2	Yamaizumi *et al.* (1986)
Fish, fried at 260 °C	0.16	1	Zhang *et al.* (1988)
Egg, fried at 325 °C	0.1	1	Grose *et al.* (1986)

[a]20 ng/g in a high-fat sample, 0.5 ng/g in a low-fat sample

IQ was found in a mixture of creatine and proline heated to 180 °C (Yoshida *et al.*, 1984), in a mixture of glycine, fructose and creatinine heated to 128 °C (Grivas *et al.*, 1986), in dry mixtures of creatinine and phenylalanine or of creatinine, phenylalanine and glucose heated

to 200 °C (Felton & Knize, 1990) and in a dry mixture of serine and creatinine heated to 200 °C (Knize *et al.*, 1988). Quantities of mixtures of heterocyclic amines found in different foods are listed in Table 2.

Table 2. Representative concentrations of heterocyclic amine (ng/g) in various food samples and in cigarette smoke condensate

Sample	PhIP (ng/g)	MeIQx (ng/g)	IQ (ng/g)	MeIQ (ng/g)	Reference
Beef, fried at 190 °C	48.5	8.3	ND[a]	ND[a]	Gross (1990)
Walleye pollack, fried at 260 °C	69.2	6.44	0.16	0.03	Zhang *et al.* (1988)
Ground beef, fried at 250 or 300 °C	15	1.0	< 0.1	Trace	Felton *et al.* (1986)
Chicken, broiled	38.1	2.33	NA	NA	Hayatsu *et al.* (1991)
Ground beef, fried at 250°C	NA	1.0	0.02	ND	Felton *et al.* (1984)
Salmon, baked at 200 °C for 30′	18	4.6	ND	ND	Gross & Grüter (1992)
Cigarette smoke condensate	NA	ND	0.26 ng per cigarette	ND	Yamashita *et al.* (1986)

ND, not detected by method used; NA, not analysed
[a]Limit of detection 1 and 2 ng/g according to the method used

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 IQ itself. Cancer risks associated with consumption of broiled and fried foods, which may contain IQ as well as other heterocyclic amines, have, however, been addressed in a number of case–control studies. Several of these are summarized below. IQ is also a component of tobacco smoke, which has been considered in a previous IARC monograph (IARC, 1986b).

A large number of studies on diet and cancer have been conducted, most of which addressed specific hypotheses (e.g., dietary fat intake and risk of colorectal cancer) (see Tomatis *et al.*, 1990). Many of the investigators, however, either failed to collect data on methods of food processing, or, if they collected such data, did not analyse the findings at all or reported only summary findings. Thus, it is possible that the studies reviewed below are only a small segment of the data potentially available on the effects in humans of heterocyclic amines formed in cooking, and a positive reporting bias cannot be ruled out.

2.1 Cohort studies

A study by Ikeda *et al.* (1983) involved 11 203 subjects already enrolled in the Adult Health Study of the Radiation Effects Research Foundation in Hiroshima and Nagasaki

between 1968 and 1970. Complete personal histories and information on current dietary and other habits were available for 7553 of these subjects (1781 men and 3341 women in Hiroshima; 965 men and 1466 women in Nagasaki). After 11 years of follow-up, there were 244 deaths from cancer, 79 of which were from stomach cancer. Intake of five foods was assessed in a multivariate analysis: the relative risks associated with consumption of broiled fish were 1.7 for gastric cancer and 1.3 for cancers at all sites, after other food variables had been taken into account (both $p < 0.05$).

The report of a large prospective study of 88 751 nurses followed up from 1980, when they answered a mailed questionnaire, to 1986 mentions that no association was found between 150 incident cases of colon cancer and the degree of cooking of red meat, but no data were shown (Willett *et al.*, 1990).

2.2 Case–control studies

2.2.1 *Cancer of the colon and rectum*

A case–control study included 340 colon and rectum cancer patients and 1020 hospital controls enrolled during 1959 from seven hospitals in Kansas City, USA (Higginson, 1966). A food frequency questionnaire was used. Unadjusted proportions of subjects in different categories were presented. No difference was observed between cases and controls with respect to consumption of fried potatoes, fried meats, fried food for breakfast or method of cooking meats. [The Working Group noted that confounding by intake of other nutrients was not controlled.]

Wynder *et al.* (1969) carried out a hospital-based case–control study in two cancer hospitals in Tokyo, Japan, in which 157 cases of colonic or rectal cancer and 307 sex- and age-matched controls were interviewed concerning their usual adult intake of a number of foods, including fried foods and charcoal-broiled fish. No consistent difference was found. [The Working Group noted that confounding by intake of other nutrients and method of cooking was not controlled.]

Phillips (1975) interviewed 41 Seventh-day Adventists with colonic–rectal cancer and 77 with breast cancer discharged from two Adventist-operated hospitals in 1969–73, each matched by age, sex and race with three Adventist controls: two hospitalized for hernia or osteoarthritis and the third from the general population [details not given]. Consumption of beef, meat in general and several sources of saturated fat were positively associated with the incidence of colonic but not breast cancer. Fried foods were positively associated with cancers at each site; the association with fried potatoes was statistically significant at the 5% level (odds ratio (OR), 2.7 for colonic and 2.4 for breast cancer). [The Working Group noted that only a crude, unmatched analysis was presented and that confounding by intake of other nutrients and method of cooking was not controlled.]

Young and Wolf (1988) reported a case–control study of 353 cases of colonic cancer (152 proximal and 201 distal subsites) in people aged 50–89, drawn from the Wisconsin (USA) Cancer Reporting System, and 618 general population controls. The study was population-based, but 62.2% of the potential study subjects were alive and could be contacted and interviewed; 17.7% refused to participate, 13 patients were < 50 years old, thus leaving 353 cases for the study. Information on the frequency of consumption of foods in 27 groups and

replies to questions about eating habits and cooking styles were requested for three periods: before the age of 18, between 18 and 35 years of age and after the age of 35. Consumption of broiled foods increased markedly with age and was consistently lower among cases than controls; on the contrary, the frequency of consumption of pan-fried foods decreased with age but was higher among cases. Consumption of processed meat and pan-fried foods was consistently associated with increased risks for cancers at each site. A significant risk for the upper *versus* the lowest quartile of consumption of pan-fried foods was observed for cancer of the proximal colon in association with diet in young adults (18–35 years old) (OR, 1.79; 95% confidence interval [CI], 1.15–2.80, adjusted for age and sex). The overall association (for both proximal and distal subsites) was not, however, significant. [The Working Group noted that confounding by intake of other nutrients was not controlled.]

Peters *et al.* (1989) reported a study of 147 men with colorectal carcinomas among 232 eligible cases, all of whom were aged 24–44 years at diagnosis and were identified through the Los Angeles County (USA) Cancer Surveillance Program, and 147 neighbourhood controls who were compared in terms of occupational exposure, tobacco and alcohol use and usual consumption of foods grouped into a few broad categories. There was no significant difference between cases who were interviewed and those not interviewed with regard to marital status, religion, birth place, social class or subsite. Elevated risks for tumours located in the right (ascending) side of the colon were associated with heavy consumption (five or more times per week) of deep-fried foods (OR, 3.9; 95% CI, 1.4–10.7), fried bacon or ham (2.6; 0.9–7.9) and barbecued or smoked meats (2.9; 1.2–7.3). The only item associated with risk for rectal cancer was deep-fried food (4.3; 1.5–12.1). These findings did not change after control for physical activity, body mass and occupational exposure to dust or fumes in a multivariate analysis. [The Working Group noted that it was not clear whether each food was adjusted for the others.]

Lyon and Mahoney (1988) identified all histologically confirmed cases of adenocarcinoma of the colon occurring in the population covered by the Utah (USA) Cancer Registry from 1976 to 1978 and aged 40–74 at diagnosis. Out of 348 eligible cases, 246 (71%) were interviewed. Controls were chosen by random-digit dialling: 484 subjects were interviewed out of 560 eligible people identified through a census of all adult householders from 92% of all residential telephone numbers selected at random. The food frequency questionnaire, which focused on diet five years before the interview, included questions on the method of food preparation, from which a score was derived for the frequency of consumption of broiled (including barbecued) foods and deep-fat and/or pan-fried foods. A slight increase in risk was seen with increasing level of ingestion of fried meats, which, however, was present only in women and was no longer significant after adjustment for total caloric intake. The age- and calorie-adjusted ORs for the upper tertile *versus* the lower tertile of intake were 1.3 (95% CI, 0.8–2.1) for women and 1.2 (0.8–1.9) for men. No association was found with eating broiled meat.

In a population-based case–control study of colorectal adenocarcinoma conducted in Stockholm, Sweden, in 1986–88 (Gerhardsson de Verdier *et al.*, 1990a,b, 1991), fairly high participation rates were obtained for both cases (559 interviewed; 78% of incident cases) and controls (505 interviewed; 81% of an age- and sex-stratified random sample of the resident population). Diet was investigated by replies to a self-administered food frequency

questionnaire, supplemented, when necessary, by interview by a nurse's aide for cases and by telephone for controls. The usual portion size was estimated from a photograph to be small, moderate or large. The overall results of the study showed that protein, fat intake and body mass index increased risk, while dietary fibre and physical activity decreased risk—each factor having different effects on cancers at different colorectal subsites. The questions regarding meat (Gerhardsson de Verdier *et al.*, 1991) focused on bacon/smoked ham, beef/pork and sausages; for beef/pork and sausages, separate questions were asked for each of three cooking methods: fried, oven-roasted and boiled. A significantly increased risk, systematically higher for rectal than for colonic cancer, was observed for high consumption of each type of meat; the ORs were higher, however, for eating boiled meat than for fried or roasted meat. The risk associated with consumption of fried or roasted meat disappeared after adjustment for protein. Respondents who ever ate fried meat were also asked about browning of the meat surface during the previous five and previous 20 years, with three response alternatives: preference for meat with a light, moderately or heavily browned surface. They were also asked if they preferred fried meat to be prepared by high- or low-temperature frying. The risks for both colonic and rectal cancer were significantly higher for frequent consumption (more than once a week) of brown gravy (OR, 1.8 for colon and 2.1 for rectum), for preference for heavily browned meat surface, especially in the past five years (ORs, 2.3 and 3.7) and for high-temperature frying (ORs, 1.9 and 1.6). The association was slightly reduced when total fat was adjusted for and when browned meat was adjusted for high frying temperature and *vice versa*, indicating that these questions may partly reflect the same exposure. The adjusted risk estimates nevertheless remained elevated and statistically significant. Adjustment for other potential confounding factors, namely total energy, dietary fibre, body mass and physical activity, had little or no effect on the magnitude of the association. The authors stated that restriction of the analysis to patients without gastrointestinal symptoms at diagnosis or to patients who had not required help in filling in the questionnaire did not alter the overall findings. People with a preference for heavily browned meat surface and with high consumption of fried meat and brown gravy had higher risks than people with a preference for moderately browned meat and low consumption of fried meat and brown gravy. Fat intake but not protein was adjusted for in the analysis. [The Working Group noted that the finding of a higher risk with boiled than with other methods of cooking meat makes these results difficult to interpret with respect to the carcinogenicity of heterocyclic amines formed in cooking.]

Schiffman *et al.* (1989) and Schiffman and Felton (1990) reported the results of a case-control study of adenocarcinoma of the colon and rectum, diet and faecal mutagenicity carried out in three hospitals in Washington DC, USA, which was based on 50 cases diagnosed in 1985–87 and 96 age- and sex-matched surgical controls. The response rates were about 30%. Virtually all subjects reported frequent consumption of cooked meats, but cases were more likely than controls to report that they usually ate their red meat well done (medium to medium-well done, OR, 0.9; 95% CI, 0.4–2.5; well done, OR, 3.5; 95% CI, 1.3–9.6; compared to rare to medium rare). [The Working Group noted that only a crude analysis was reported and that details on how information was collected was not provided.]

2.2.2 *Other sites*

In a population-based case–control study carried out in Stockholm, Sweden, in 1985–87 (Steineck *et al.*, 1990), information was collected from 323 patients (78% response rate) with urothelial cancer and/or squamous-cell carcinoma of the lower urinary tract (94% bladder cancers) and from 392 subjects (77% response rate) randomly sampled within strata of gender and year of birth. Diet was investigated on the basis of replies to a mailed food frequency questionnaire supplemented by a telephone interview. Usual portion size was estimated from a photograph to be small, moderate or large. Information on intake of fried meat was obtained by asking questions about consumption of fried and oven-cooked meat/pork/sausages, smoked ham and bacon. An increased OR was seen for eating fried eggs (1.8; 95% CI, 1.0–3.1, for weekly *versus* less often), gravy (1.6; 1.0–2.4) and fried potatoes (1.6; 1.1–2.6); increased ORs were also suggested to be associated with consumption of fried meat and grilled foods, but not fried fish. Collating the data on fried eggs, fried potatoes, fried meat and gravy in a single variable and adjusting for age, gender, smoking habits and average daily intake of fat gave an OR for moderate intake (exposed to two or three of the fried foods) of 1.7 (95% CI, 0.9–3.0) and an OR for high intake (exposed to all four fried foods) of 2.2 (1.2–4.1).

In the study from Kansas City, described in detail above, a series of 93 gastric cancer patients were also compared to 279 controls (Higginson, 1966). Cases reported slightly greater consumption of fried potatoes, fried meats and fried food for breakfast, but the difference was not significant. No difference was suggested according to the method of cooking meat.

Norell *et al.* (1986) carried out a case–control study in Sweden on dietary habits and tobacco smoking among 99 cases of pancreatic cancer (out of 120 eligible patients) and 138 population controls (out of 162 eligible subjects). As an additional control group, 163 patients hospitalized for inguinal hernia were interviewed, out of 179 eligible subjects. Cases were drawn from all patients diagnosed in 1982–84 at the three surgical departments in Stockholm and Uppsala where suspected pancreatic cancer cases are referred. Frequent consumption of a number of meat items was associated with an increased risk, whatever control group was used for comparison, but most of the effect was confined to fried/grilled meat. Subjects who ate meat at least twice a week and grilled/fried meat at least twice a week showed an OR of 2.5 (95% CI, 1.2–5.3; population controls) in comparison with subjects who ate meat less often. Eating meat at least twice a week but grilled/fried meat less often was not associated with increased risk. Controlling for tobacco smoking and a number of other food items associated with the risk of pancreatic cancer was stated to increase slightly the association with fried/grilled meat, but data were not shown. [The Working Group noted that adjustment for nutrients was not attempted.]

A case–control study from Ankara, Turkey, included 100 cases of adenocarcinoma of the stomach, enrolled during 1987–88 from seven hospitals, 61 controls from the same hospitals with no cancer and 39 healthy controls (Demirer *et al.*, 1990). Cases and controls did not differ in their consumption of fried potatoes, fried meat or fried fish.

Kono *et al.* (1988) conducted a study in a low-risk area for stomach cancer in rural northern Kyushu, Japan. Between 1979 and 1982, 139 newly diagnosed cases of gastric

cancer (85% histologically confirmed) were identified among 4729 subjects who had visited a referral centre in the area for the diagnosis of gastrointestinal diseases. Cases were compared with two sets of controls: 2574 hospital controls free of gastrointestinal disease and 278 general population controls who were similar to the cases by sex, year of birth and residence. Two different groups of people, using a standard questionnaire, interviewed patients before diagnostic procedures at the referral centre and the general population about dietary habits in the year preceding the interview or before a change in dietary habits. Consumption of broiled fish or grilled meat was not associated with an increased risk.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

A group of 40 male and 40 female CDF_1 mice [(BALB/cAnN × DBA/2N)F_1], seven weeks of age, were fed a pelleted diet containing 300 mg/kg IQ (purity, > 99.6%) for 675 days, at which time the experiment was terminated. A group of 40 males and 40 females fed basal diet alone served as controls. The numbers of survivors on day 394, when leukaemia was found in a female control, were similar in the four groups: 39/40 treated males, 36/40 treated females, 33/40 control males and 38/40 control females. The number of mice with liver tumours (hepatocellular adenomas and hepatocellular carcinomas) was significantly higher in treated groups than in controls: 16/39 *versus* 2/33 in males; 27/36 *versus* 0/38 in females; hepatocellular carcinomas occurred in eight treated males and 22 treated females. One male and three female controls developed haemangioendotheliomas. The incidences of tumours of the lung and forestomach were also significantly higher in treated mice than in controls: combined incidences of adenoma and adenocarcinoma of the lung, 27/39 *versus* 7/33 in males and 15/36 *versus* 7/38 in females; incidences of adenocarcinoma of the lung, 14/39 *versus* 3/33 in males and 8/36 *versus* 4/38 in females; combined incidences of papilloma and squamous-cell carcinoma of the forestomach, 16/39 *versus* 1/33 in males and 11/36 *versus* 0/38 in females; and incidences of squamous-cell carcinoma of the forestomach, 5/39 *versus* 0/33 in males and 3/36 *versus* 0/38 in females (Ohgaki *et al.*, 1984, 1986).

Groups of 10 or more female CDF1 mice, 27–31 days old, were treated with IQ (purity, > 98%; dissolved in 55% ethanol in 0.9% sodium chloride solution) at 200 or 400 mg/kg bw (one-half of the LD_{50}) by gavage twice at a four-day interval. The numbers of aberrant crypts in the colon scored 21 days after the first IQ treatment were dose-related. Crypts were found more frequently in the caecal end (Tudek *et al.*, 1989).

3.1.2 *Rat*

A group of 32 female Sprague-Dawley rats, six weeks of age, received IQ hydrochloride at 0.35 mmol [70 mg]/kg bw in 5% Emulphor by gavage three times per week during weeks 1–4, twice per week during weeks 5–8 and weekly during weeks 9–31 and were maintained without further treatment until sacrifice at week 52. A group of 27 rats received 0.25 ml 5% Emulphor according to the same schedule, and a further group of nine animals served as

untreated controls. Treated rats showed a 94% weight gain by the end of the experiment compared with controls. Twenty-one adenocarcinomas of the mammary gland were observed in 14/32 ($p < 0.05$) treated animals. No such tumour was observed in controls. Liver tumours were observed in 6/32 (three neoplastic nodules, two hepatocellular carcinomas and two haemangioendotheliomas) treated animals, but in none of the controls. Twelve squamous-cell carcinomas of the Zymbal gland were found in 11/32 treated animals, and no such tumour occurred in controls [$p = 0.002$; Fisher exact test]. The treated group also had altered liver-cell foci (17/32), atypical hyperplastic acinar-cell lesions in the pancreas (19/32) and altered proliferative foci in the adrenal cortex (5/32), none of which was present in the control group (Tanaka *et al.*, 1985).

Groups of 40 male and 40 female Fischer 344 rats, eight weeks of age, were fed a pelleted diet containing 300 mg/kg IQ (purity confirmed by HPLC [percentage not indicated]) for 104 weeks. Control groups of 50 males and 50 females were fed basal diet alone. The times of appearance of the first tumours in males were day 255 in the colon, day 239 in the small intestine and day 288 in the liver. Twenty males and four females from the treated group [but no control] were killed at 300 days, because the animals were moribund owing to the occurrence of tumours. Treated animals had a significantly increased incidence of tumours of the liver, Zymbal gland, colon and small intestine during the 104-week study (Table 3). No such tumour, except one hepatocellular carcinoma in a male, occurred in concurrent controls (Takayama *et al.*, 1984; Ohgaki *et al.*, 1986).

Table 3. Tumour incidence in Fischer rats fed a diet containing IQ at 300 mg/kg for 104 weeks

Tumour type	Males	Females
Squamous-cell carcinoma, Zymbal gland	36/40	27/40
Adenocarcinoma, colon	25/40	9/40
Adenocarcinoma, small intestine	12/40	1/40
Hepatocellular carcinoma	27/40	18/40
Carcinoma, skin	17/40	3/40
Squamous-cell carcinoma, oral cavity	2/40	1/40
Squamous-cell carcinoma, clitoral gland	–	20/40

From Ohgaki *et al.* (1986)

Groups of 10 or more female Sprague-Dawley rats, 21 days old, were treated with IQ (purity, > 98%; dissolved in 55% ethanol in 0.9% sodium chloride solution) at 200 or 400 mg/kg bw (one-half of the LD_{50}) by gavage twice at a four-day interval. The numbers of aberrant crypts in the colon scored 21 days after the first IQ treatment were dose-related. Crypts were found more frequently in the caecal end (Tudek *et al.*, 1989).

3.1.3 *Monkey*

Twenty cynomolgus monkeys (*Macaca fascicularis*) (14 males, 6 females), about one year old, were administered 10 mg/kg bw IQ (purity, > 99.9%) suspended in hydroxypropyl cellulose by gavage five times a week for up to 60 months. Another 20 monkeys (8 males,

12 females) were administered IQ by gavage five times a week at a dose of 20 mg/kg bw. Hepatocellular carcinomas were found in 13 monkeys which were necropsied; 10 had received 20 mg/kg (average latent period, 37 months) and three, 10 mg/kg (first tumour seen after 30 months; average latent period, 45 months). Metastases to the lung occurred in several monkeys. No such tumour occurred in colony controls (Adamson *et al.*, 1990, 1991).

3.2 Intraperitoneal administration

Mouse

Groups [initial number unspecified] of newborn male B6C3F$_1$ mice were injected intraperitoneally with IQ (> 98% pure) at total doses of 0, 0.625 or 1.25 μmol [125–250 μg] (maximal tolerated dose) dissolved in 5, 10 or 20 μl dimethyl sulfoxide and administered on days 1, 8 and 15 after birth, respectively. Animals were sacrificed at 8 and 12 months. The incidence of hepatocellular adenomas was significantly higher in treated mice than in controls: at eight months, 1/44 in controls, 5/24 at the low dose and 5/16 at the high dose; at 12 months, 5/44 in controls, 7/19 at the low dose and 14/20 at the high dose. Two hepatocellular carcinomas were found in the high-dose group at 12 months (Dooley *et al.*, 1992).

3.3 Administration with known carcinogens

3.2.1 *Mouse*

In a two-stage skin carcinogenesis study, a group of 20 female CD-1 mice, seven weeks of age, received topical applications on the dorsal skin of 0.75 mg IQ in 0.1 ml dimethyl sulfoxide twice weekly for five weeks, followed one week later by topical applications of 2.5 μg 12-*O*-tetradecanoylphorbol 13-acetate (TPA) twice weekly for 47 weeks. A positive control group received applications of 7,12-dimethylbenz[*a*]anthracene (DMBA; total dose, 100 μg) plus TPA. Skin tumours were found in 0/20 mice treated with IQ, 1/20 mice treated with IQ and TPA, 4/19 mice treated with DMBA, 17/18 treated with DMBA and TPA and 0/20 solvent controls (Sato *et al.*, 1987).

3.2.2 *Rat*

Groups of 40 male Wistar rats, six weeks old, were given IQ at 10 mg/kg bw or solvent (water, acidified to pH 3.5 with citric acid) by gavage every day for two weeks. One week later, the rats were divided into two groups and received either no additional treatment or 500 ppm [mg/l] phenobarbital sodium in the drinking-water for the remainder of the study. Ten animals from each group were sacrificed at week 42, and the study was terminated after 58 weeks. Zymbal gland carcinomas were found in 2/40 rats that received IQ only and in 2/40 that received IQ plus phenobarbital but not in the untreated group or in the group that received phenobarbital only. A hepatocellular adenoma was found in one rat given IQ alone, and a hepatocellular adenoma and a tumour diagnosed as a cystic cholangiocarcinoma occurred in one rat in the group treated with IQ plus phenobarbital. Treatment with IQ and phenobarbital significantly increased ($p < 0.01$) the number of γ-glutamyl transpeptidase-

positive foci of altered hepatocytes in comparison with the respective controls; some such foci were also found after administration of phenobarbital alone (Kristiansen *et al.*, 1989).

In a short-term assay for tumour-initiating activity in the liver, groups of 20 male Fischer 344 rats, five weeks of age, each received a two-week dietary treatment with IQ at doses of 0.025, 0.05 and 0.1% (250, 500 and 1000 mg/kg of diet) and were then maintained on a diet supplemented with either 500 mg/kg phenobarbital or 24 mg/kg 3′-methyl-4-dimethylaminoazobenzene (3′-Me-DAB) from week 3 until final sacrifice at week 86. One group received only 0.1% IQ (1000 mg/kg of diet). All animals underwent a two-thirds partial hepatectomy at week 1. There were 14–19 effective animals per group, including both animals that survived to the end of the experiment and those that died with tumours after week 52. Administration of IQ alone or IQ at 0.025–0.1% with either phenobarbital or 3′-Me-DAB caused hyperplastic liver nodules in all animals; and subsequent administration of phenobarbital or 3′-Me-DAB caused a significant increase in the incidence of hepatocellular carcinomas: IQ alone, 0/19; 3′-Me-DAB with 0, 0.025, 0.05 and 0.1% IQ, 0/18, 1/17, 3/18 and 5/16; phenobarbital with 0, 0.025, 0.05 and 0.1% IQ, 0/18, 6/17, 7/18 and 7/14. Administration of IQ plus phenobarbital increased the incidence of thyroid adenomas and carcinomas: IQ alone, 1/19; phenobarbital plus 0, 0.025, 0.5 and 0.1% IQ, 2/18, 8/17, 8/18 and 9/14. IQ alone caused squamous-cell carcinomas or keratoacanthomas of the Zymbal gland (5/19; 26%), but the only effect of subsequent treatment with phenobarbital or 3′-Me-DAB was with 0.1% IQ plus phenobarbital (6/14; 43%). Animals that received IQ, phenobarbital or 3′-Me-DAB alone or in combination had preputial gland tumours at incidences ranging from 22 to 50%, but there did not appear to be a dose–response relationship (Tsuda *et al.*, 1988).

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 IQ and, two weeks later, were fed a diet containing 0.05% phenobarbital for six weeks. Rats received a two-thirds partial hepatectomy three weeks after the IQ 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. Treated rats had a significant, two-fold greater number of foci than five vehicle-treated control rats; IQ without subsequent phenobarbital treatment 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 IQ treatment, two weeks later was fed the diet containing phenobarbital as above, and then received a single intraperitoneal injection of 300 mg/kg D-galactosamine one week after the phenobarbital treatment. Administration of IQ increased the number and area of foci more than 10 fold over that in five vehicle-treated control rats. IQ without subsequent phenobarbital treatment, but with galactosamine, produced a smaller, nonsignificant increase in the number and area of foci. These results suggest that IQ has tumour-initiating activity in rat liver, especially if combined with partial hepatectomy (Tsuda *et al.*, 1990).

As part of a medium-term carcinogenicity study on the synergistic effects of five heterocyclic amines, groups of 13–15 male Fischer 344 rats, six weeks of age, each received a single intraperitoneal injection of 200 mg/kg bw *N*-nitrosodiethylamine and, two weeks later, were fed a diet containing IQ at 12, 60 or 300 ppm (mg/kg). A two-thirds partial hepatectomy was performed in week 3 of the experiment; all animals were killed after eight weeks. Fifteen rats

treated only with the nitrosamine served as controls. The effects were assessed by counting the numbers of GST-P-positive foci in the liver. IQ alone at the mid- and high-dose levels significantly increased the area of GST-P-positive foci (Ito *et al.*, 1991).

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*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The absorption and excretion of ^{14}C- and ^{3}H-IQ have been studied by fluorescence in rats and mice following gavage (Sjödin & Jägerstad, 1984; Alldrick & Rowland, 1988; Inamasu *et al.*, 1989) and that of IQ after intraperitoneal administration (Størmer *et al.*, 1987). IQ was absorbed rapidly, mainly from the small intestine (Alldrick & Rowland, 1988), metabolized and excreted almost quantitatively within three days; in rats, 36–49% and 46–68% of the administered dose was recovered in the urine and faeces, respectively (Sjödin & Jägerstad, 1984). The excretion pathways were essentially similar following dietary exposure (Inamasu *et al.*, 1989).

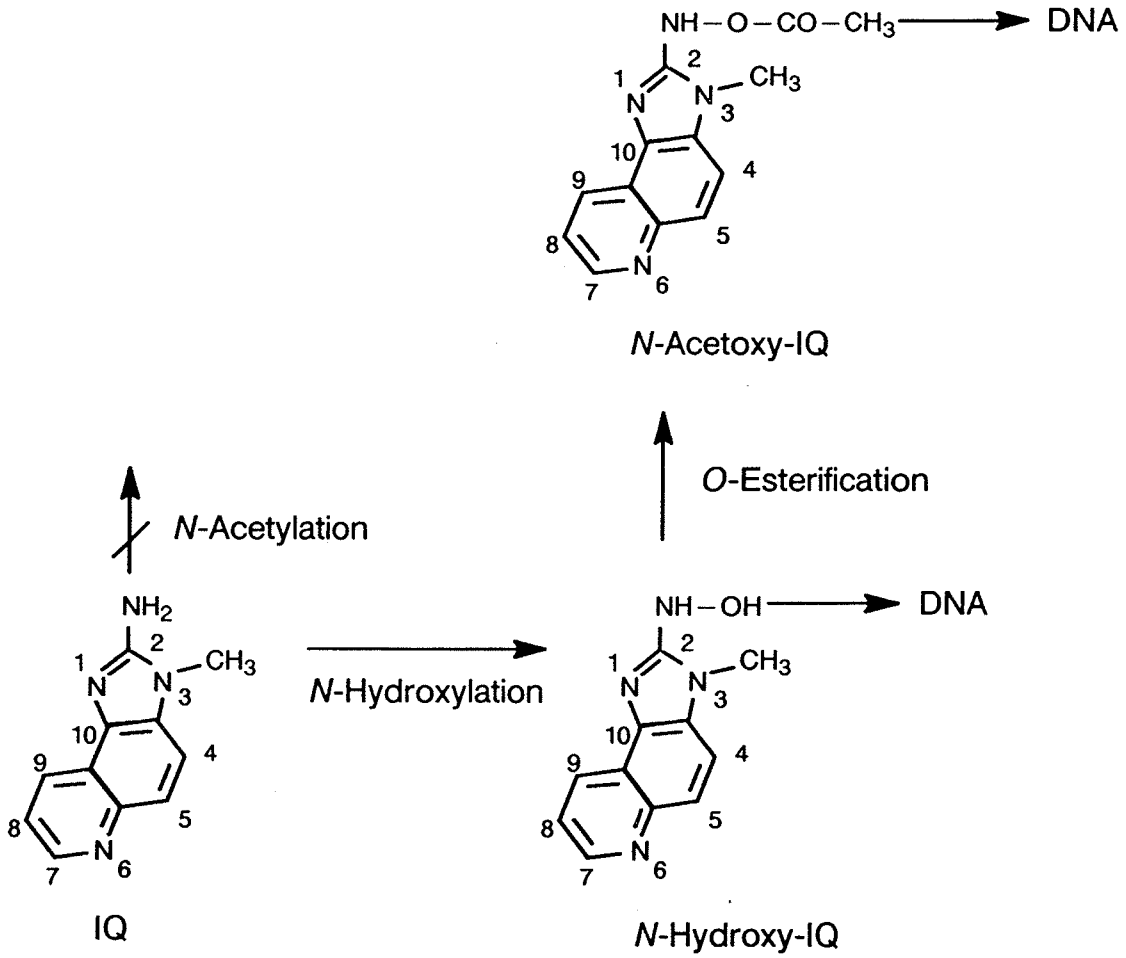
The fate of intravenously injected ^{14}C-IQ was studied in male NMRI, pregnant NMRI and female C3H mice. Whole-body autoradiograms were characterized by an accumulation of radiolabel in metabolic and excretory organs (liver, kidney, bile, urine, gastric and intestinal contents, salivary glands, nasal mucosa and Harder's gland) and in lymphomyeloid tissues (bone marrow, thymus, spleen and lymph nodes) and endocrine and reproductive tissues (adrenal medulla, pancreatic islets, thyroid, hypophysis, testis, epididymis, seminal vesicles, ampulla and prostate). The liver and kidney cortex were identified as sites of retention of nonextractable radiolabel. IQ crossed the placenta, but no radiolabel was retained in fetal tissues (Bergman, 1985).

IQ was oxidized to *N*-hydroxy-IQ in the presence of rat and rabbit liver microsomal homogenates (Yamazoe *et al.*, 1983; Kato, 1986; McManus *et al.*, 1988a). The activity of cytochrome P450 IA2 isozyme in the liver was induced in rats by prior intraperitoneal injection of IQ and other heterocyclic amines (Degawa *et al.*, 1989); the activity of this enzyme was induced in cultured rat hepatocytes by β-naphthoflavone and polychlorinated biphenyls (Wallin *et al.*, 1992). IQ can also be oxidized *via* a prostaglandin hydroperoxidase-dependent pathway, as shown in microsomes isolated from ram seminal vesicles (Wild & Degen, 1987; Petry *et al.*, 1989).

N-Hydroxy-IQ can be esterified by *O*-acetyltransferase, sulfotransferase and prolyl-tRNA synthetase but at much lower rates than aromatic amines (Kato & Yamazoe, 1987).

N-Acetylation of IQ may not be important for DNA binding (Fig. 1; Snyderwine *et al.*, 1988a). Human liver microsomes could activate IQ into a DNA-reactive species. The isozyme involved was tentatively identified as CYP IA2 (P450 IA2) (Shimada *et al.*, 1989). The same enzyme was shown to be responsible for the formation of *N*-hydroxy-IQ in human hepatic cytosols (Butler *et al.*, 1989; McManus *et al.*, 1990). Human liver and colon cytosols catalysed the formation of *N*-hydroxylated IQ into a DNA-binding form, but *N*-acetylation was not observed under the same conditions (Turesky *et al.*, 1991). DNA-binding products were also found in human mammary epithelial cells cultured in the presence of IQ (Pfau *et al.*, 1992). In human fetal liver tissue, cytochrome P450 HFLa was the main activating enzyme of IQ (Kitada *et al.*, 1990).

Fig. 1. Schematic pathway of activation of IQ to DNA-binding products



Adapted from Snyderwine *et al.* (1988a)

IQ binds to rat haemoglobin and albumin *in vivo*. One of the haemoglobin products was identified as a sulfinamide at a cysteine residue (Turesky *et al.*, 1987).

Mixed and pure cultures of human intestinal anaerobic bacteria metabolized IQ to IQ-7-one (Carman *et al.*, 1988). In rats, the routes of detoxication of IQ include cytochrome

P450-mediated ring hydroxylation at the C5 position, followed by conjugation to a sulfate or glucuronic acid (Luks *et al.*, 1989; Vavrek *et al.*, 1989). Another pathway involves conjugation of the exocyclic amine group to a glucuronic acid or sulfate (Inamasu *et al.*, 1989). Conjugated 5-hydroxy-IQ accounted for about 40% of urinary and biliary metabolites in rats; *N*-sulfamates are another major group of excretion products (Inamasu *et al.*, 1989; Turesky *et al.*, 1986; Luks *et al.*, 1989). In the urine of monkeys, sulfate and glucuronide conjugates predominated (Snyderwine *et al.*, 1991). Treatment of rats with polychlorinated biphenyls increased the excretion of sulfate conjugates into the urine (Vavrek *et al.*, 1989).

Constituents of feed may play a role in the metabolism of IQ. Dietary fibres can bind IQ *in vitro* (Sjödin *et al.*, 1985), and a high-fat diet increased the capacity of rat liver microsomes to activate IQ (Alldrick *et al.*, 1987).

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 IQ have been reviewed (Sugimura, 1985; Hatch, 1986; de Meester, 1989; Sugimura *et al.*, 1989).

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 4 and Appendices 1 and 2)

N-Hydroxy-IQ binds nonenzymatically to DNA *in vitro* at pH 7.4. In the presence of polynucleotides, the *N*-hydroxy-IQ was bound particularly extensively with polyguanylic acid (Snyderwine *et al.*, 1988a,b). *N*-Hydroxy-IQ reacts with DNA to form up to five adducts; the major one co-chromatographs with *N*-(deoxyguanosin-8-yl)–IQ (Schut *et al.*, 1991).

IQ induced prophage, SOS repair and mutation in bacteria. Bacterial mutations were also induced in the intrasanguinous mouse host-mediated assay and following exposure to the urine of IQ-dosed rats.

IQ induced somatic and sex-linked recessive lethal mutations in *Drosophila melanogaster*. It formed DNA adducts and DNA strand breaks in cultured mammalian cells and induced unscheduled DNA synthesis in primary hepatocytes cultured from mice, rats and Syrian hamsters, but not in those from guinea-pigs. Responses in other cultured mammalian cell assays were complex. IQ induced gene mutation to diphtheria toxin resistance and at the *hprt* locus; mutations at the *hprt* locus were observed only in single studies in repair-deficient cell lines and in a repair-proficient cell line co-cultured with hepatocytes from poly-

Table 4. Genetic and related effects of IQ

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, *Escherichia coli* K12, prophage λ induction	0	+	1.0000	Nagao *et al.* (1983a)
PRB, *Salmonella typhimurium* TA1535, SOS repair	0	+	0.0300	Nakamura *et al.* (1987)
PRB, *Salmonella typhimurium*, SOS repair, with human microsomes	0	+	2.0000	Kitada *et al.* (1990)
PRB, *umu* expression, *Salmonella typhimurium* TA1535/pSK 1002	0	+	2.0000	Shimada *et al.* (1989)
ERD, *Escherichia coli rec* strains, differential toxicity	-	+	0.2600	Knasmüller *et al.* (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	0.0500	Nagao *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	0.0050	Wild *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	0.0000	Barnes *et al.* (1985)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	0.0000	Felton & knize (1990)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+	0.0000	Grivas & Jägerstad (1984)
SA2, *Salmonella typhimurium* TA102, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SA4, *Salmonella typhimurium* TA104, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	25.0000	Wild *et al.* (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	0.0025	Wild *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	+	0.0005	Thompson *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	+	0.0003	Wild *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	+	0.1500	Felton & Knize (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0050	Nagao *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	0.0003	Wild *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0015	Barnes *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+[b]	0.0050	Ishida *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	0.3125	Loprieno *et al.* (1991)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+[c]	0.2000	Holme *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	0.0017	Lin *et al.* (1992)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0010	Nagao *et al.* (1983b)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.1250	Hayashi *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0003	Wild *et al.* (1991)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0005	Buonarati & Felton (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+	0.0010	Grivas & Jägerstad (1984)
SAS, *Salmonella typhimurium* TA96, reverse mutation	0	+	0.0000	Felton & Knize (1990)

Table 4 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SAS, *Salmonella typhimurium* TA97, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	+	0.0017	Lin *et al.* (1992)
SAS, *Salmonella typhimurium* TA97, reverse mutation[d]	+	+	0.0017	Lin *et al.* (1992)
SAS, *Salmonella typhimurium* TA98, reverse mutation[d]	+	+	0.0017	Lin *et al.* (1992)
SAS, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	0	–	0.0250	Nagao *et al.* (1983b)
SAS, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	0	–	0.0005	Buonarati & Felton (1990)
SAS, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	0	–	0.0015	Wild *et al.* (1991)
SAS, *Salmonella typhimurium* TA1535/pSK 1002	0	+	2.0000	Ubukata *et al.* (1992)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	0	+	0.0500	Thompson *et al.* (1983)
SAS, *Salmonella typhimurium* TA1978, reverse mutation	0	(+)	0.0050	Wild *et al.* (1985)
SAS, *Salmonella typhimurium* YG1024, reverse mutation	0	+	0.0001	Wild *et al.* (1991)
DMM, *Drosophila melanogaster*, somatic mutation and recombination	+	0	25.0000	Yoo *et al.* (1985)
DMM, *Drosophila melanogaster*, somatic mutation and recombination	+	0	250.0000	Graf *et al.* (1992)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	200.0000	Wild *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	200.0000	Graf *et al.* (1992)
DMM, *Drosophila melanogaster*[f], wing spot test	+	0	250.0000	Graf *et al.* (1992)
DIA, DNA strand breaks, radiation-induced mouse leukaemic cells *in vitro*	–	+	1.9800	Caderni *et al.* (1983)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+	0	0.9900	Caderni *et al.* (1983)
DIA, DNA strand breaks, mouse hepatocytes *in vitro*	+	0	2.0000	Hayashi *et al.* (1985)
DIA, DNA strand breaks, Chinese hamster V79 cells *in vitro*	–	–[c,e]	100.0000	Holme *et al.* (1987)
DIA, DNA strand breaks, rat hepatocytes[e] *in vitro*	+	0	20.0000	Holme *et al.* (1987)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	0	0.0250	Barnes *et al.* (1985)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	+	0	0.1000	Yoshimi *et al.* (1988)
UIA, Unscheduled DNA synthesis, mouse hepatocytes *in vitro*	+	0	1.0000	Yoshimi *et al.* (1988)
UIA, Unscheduled DNA synthesis, Syrian hamster hepatocytes *in vitro*	+	0	1.0000	Yoshimi *et al.* (1988)
GCL, Gene mutation, Chinese hamster lung cells, DT^r, *in vitro*	–	+	5.0000	Nakayasu *et al.* (1983)
GCL, Gene mutation, Chinese hamster lung cells *in vitro*	0	+	1.0000	Sugimura *et al.* (1989)
GCO, Gene mutation, Chinese hamster ovary cells (*uv-5*) *hprt* locus *in vitro*	0	+	50.0000	Thompson *et al.* (1983)
GCO, Gene mutation, Chinese hamster ovary cells (*uv-5*) *aprt* locus *in vitro*	0	+	50.0000	Thompson *et al.* (1983)

Table 4 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
GCO, Gene mutation, Chinese hamster ovary cells (AA8) *hprt* locus *in vitro*	0	-	300.0000	Thompson *et al.* (1983)
GCO, Gene mutation, Chinese hamster ovary cells (AA8) *aprt* locus *in vitro*	0	-	300.0000	Thompson *et al.* (1983)
GCO, Gene mutation, Chinese hamster ovary cells (*uv-5*) *in vitro*	0	(+)	26.0000	Brookman *et al.* (1985)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	0	(+)[c,e]	20.0000	Holme *et al.* (1987)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	0	-	25.6000	Loprieno *et al.* (1991)
G90, Gene mutation, Chinese hamster lung V79 cells, ouabain[r] *in vitro*	0	-	50.0000	Takayama & Tanaka (1983)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	-	+[c,e]	20.0000	Holme *et al.* (1987)
SIC, Sister chromatid exchange, Chinese hamster ovary cells (*uv-5*) *in vitro*	0	+	50.0000	Thompson *et al.* (1983)
SIC, Sister chromatid exchange, Chinese hamster ovary cells (AA8) *in vitro*	0	(+)	300.0000	Thompson *et al.* (1983)
CIC, Chromosome aberration, Chinese hamster ovary cells *in vitro*	0	+	12.8000	Loprieno *et al.* (1991)
CIC, Chromosome aberration, Chinese hamster ovary cells (*uv-5*) *in vitro*	0	-	80.0000	Thompson *et al.* (1983)
CIC, Chromosome aberration, Chinese hamster ovary cells (AA8) *in vitro*	0	-	300.0000	Thompson *et al.* (1983)
G1H, Gene mutation, human lymphocytes, *hprt* locus *in vitro*	0	-	200.0000	McManus *et al.* (1988b)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	-	+	0.2000	Aeschbacher & Ruch (1989)
MIH, Micronucleus test, human lymphocytes *in vitro*	0	(+)	200.0000	McManus *et al.* (1988b)
CHL, Chromosomal aberration, human lymphocytes *in vitro*	0	-	1000.0000	Aeschbacher & Ruch (1989)
CHL, Chromosomal aberration, human lymphocytes *in vitro*	-	+	116.2000	Loprieno *et al.* (1991)
BFA, Body fluids from rats, mutagenicity to *S. typhimurium* TA98, TA100	-	+	7.0000	Barnes & Weisburger (1985)
HMM, Host-mediated assay, intrasanguinous NMRI mouse, *S. typhimurium* TA98	+	0	0.198 × 1 ip, po	Wild *et al.* (1985)
HMM, Host-mediated assay, intrasanguinous Swiss albino mice, *Escherichia coli* strains M343/753, M343/765	+	0	2.3 × 1 ip, po	Knasmüller *et al.* (1992)
DVA, DNA strand breaks, mouse liver cells *in vivo*	+		10.0000	Hayashi *et al.* (1985)
GVA, Gene mutation, mouse melanocytes *in vivo*	-		400.0 × 1 in utero	Wild *et al.* (1985)
MST, Mouse coat colour spot test *in vivo*	-		20.0 × 1 ip	Wild *et al.* (1985)
GVA, Gene mutation, rat granuloma cells, *hprt* locus *in vivo*	+		10.0 into pouch	Radermacher *et al.* (1987)

Table 4 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SVA, Sister chromatid exchange, mouse bone-marrow cells[e] *in vivo*	+		20.0 × 1 ip	Minkler & Carrano (1984)
SVA, Sister chromatid exchange, rat hepatocytes *in vivo*	+		50.0 × 1 ip	Sawada *et al.* (1991)
MVM, Micronucleus test, mouse bone-marrow cells *in vivo*	-		594.0 × 1 ip	Wild *et al.* (1985)
MVM, Micronucleus test, mouse bone-marrow cells *in vivo*	-	0	40.0 × 1 po	Loprieno *et al.* (1991)
CBA, Chromosomal aberration, mouse bone-marrow cells[e] *in vivo*	-		160.0 × 1 ip	Minkler & Carrano (1984)
CVA, Chromosomal aberration, rat hepatocytes *in vivo*	+		50.0 × 1 ip	Sawada *et al.* (1991)
BID, Binding (covalent) to DNA in *S. typhimurium*[g] *in vitro*	+	0	0.0000	Schut *et al.* (1991)
BID, Binding (covalent) to DNA *in vitro* (bacterial DNA)[g]	0	+	100.0000	Asan *et al.* (1987)
BID, Binding (covalent) to DNA *in vitro* (rat hepatocytes)[g]	+		24.0000	Dirr *et al.* (1989)
BID, Binding (covalent) to DNA *in vitro* (Syrian hamster embryo)[g]	0	+	10.0000	Asan *et al.* (1987)
BID, Binding (covalent) to DNA *in vitro* (rat hepatocytes)	+	0	10.0000	Wallin *et al.* (1992)
BVD, Binding (covalent) to DNA in rats (multiple organs) *in vivo*[g]	+		5.00 × 1 ip	Schut *et al.* (1988)
BVD, Binding (covalent) to DNA in mice (multiple organs) *in vivo*[g]	+		25.00 × 1 po	Hall *et al.* (1990)
BVD, Binding (covalent) to DNA in mice (multiple organs) *in vivo*[g]	+		5.00 × 1 po	Zu & Schut (1991a)
BVD, Binding (covalent) to DNA in rats (multiple organs) *in vivo*[g]	+		5.00 × 1 po	Zu & Schut (1991b)
BVD, Binding (covalent) to DNA in rats liver and heart *in vivo*[g]	+		36.0000 × 4 wk diet	Övervik *et al.* (1991)
BVD, Binding (covalent) to DNA in liver of cynomolgus monkeys *in vivo*[g]	+		20.00 × 15 po	Snyderwine *et al.* (1988c)
BVD, Binding (covalent) to DNA in mice (multiple organs) *in vivo*[h]	+		40.0 × 1 po	Loprieno *et al.* (1991)
BVD, Binding (covalent) to DNA in rat liver *in vivo*[g]	+		100.0 × 1 po	Yamashita *et al.* (1988)
BVD, Binding (covalent) to DNA in mouse liver *in vivo*[g]	+		50.0 × 1 po	Schut *et al.* (1991)
BVD, Binding (covalent) to DNA in rat liver *in vivo*[g]	+		50.0 × 1 po	Schut *et al.* (1991)

+, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

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

[b] Rhesus liver S9

[c] Hepatocytes

[d] IQ reacted with nitrite (not on profile)

[e] Polychlorinated biphenyl-treated

[f] Nitro-IQ synthesized

[g] ^{32}P-Postlabel

[h] ^{14}C-Label

chlorinated biphenyl-treated rats. No *hprt* locus or ouabain-resistance mutations were observed in other studies, in which exogenous metabolic activation systems were provided by rat liver homogenates. IQ induced sister chromatid exchange in Chinese hamster cells. Chromosomal aberrations were induced in one study with Chinese hamster ovary cells but not in studies in which a repair-deficient cell line and a repair-proficient cell line were used (Thompson *et al.*, 1983).

In cultured human lymphocytes, IQ did not induce *hprt* locus mutations but did induce sister chromatid exchange and micronucleus formation. Inconsistent results were obtained for chromosomal aberrations in metaphases.

IQ–DNA adducts were formed *in vivo* in multiple organs of rats and mice and in the liver (only organ examined) of cynomolgus monkeys given oral doses of IQ. These results obtained *in vivo* confirm that the major DNA adduct co-chromatographs with *N*-(deoxyguanosin-8-yl)–IQ (Schut *et al.*, 1991).

After administration *in vivo*, IQ induced DNA strand breaks in mouse liver, but it did not induce unscheduled DNA synthesis in rat stomach. Gene mutations were induced in neither the mouse coat colour spot test nor in a transplacental assay in mice, but IQ induced *hprt* locus mutations in a single granuloma pouch assay. Sister chromatid exchange was induced in mouse bone marrow and rat liver. Whereas chromosomal aberrations were induced in rat liver, neither these nor micronuclei were induced in mouse bone marrow.

(*a*) *IQ–nitrite interaction*

Reaction mixtures of IQ and nitrite were mutagenic to *Salmonella typhimurium* strains TA97 and 98 both in the absence and presence of an exogenous metabolic activation system. Nitro-IQ induced somatic mutation in *Drosophila melanogaster*.

(*b*) *Genetic changes in animal tumours*

Activated c-Ha-*ras* proto-oncogenes were found in four of seven Zymbal gland tumours induced in rats by IQ. The mutations were G to C transversions at the first base of codon 13 (two tumours), a G to T transversion at the second base of codon 13 (one tumour) and an A to T transversion (one tumour) at the second base of codon 61 (Kudo *et al.*, 1991). p53 Gene mutations were found in four of 15 Zymbal gland tumours induced in rats by IQ. These involved changes of *C*GT to *G*GT, T*G*C to T*T*C, *G*TG to *T*TG and *G*AA deletion at codons 156, 174, 214 and 256, respectively (Makino *et al.*, 1992).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

IQ (2-Amino-3-methylimidazo[4,5-*f*]quinoline) has been found in cooked meat and fish. A few determinations indicated that the levels of IQ were lower than those of MeIQx (2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline) and PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine). IQ was reported in the only sample of cigarette smoke condensate tested.

5.2 Human carcinogenicity data

No data directly relevant to an evaluation of the carcinogenicity to humans of IQ were available; however, several studies that were potentially relevant were considered.

The only cohort study in which detailed results were presented showed a significantly increased risk for cancers at all sites and for gastric cancer associated with the consumption of broiled fish.

Two case–control studies, in Sweden and the USA, in which consumption of meat cooked in different ways was addressed and in which consumption of a number of nutrients was controlled did not show increased risks for colorectal cancer associated with consumption of fried meat; however, the study from Sweden showed an association with a preference for browned meat. One case–control study on gastric cancer in Japan showed no association with consumption of broiled fish or grilled meat.

The available information was insufficient to establish whether cooking methods that result in the formation of heterocyclic amines are a risk factor for cancer independent of the food item itself.

5.3 Animal carcinogenicity data

IQ was tested for carcinogenicity by oral administration in one experiment in mice, in two experiments in rats and in one study in monkeys. Hepatocellular adenomas and carcinomas, adenomas and adenocarcinomas of the lung and squamous-cell papillomas and carcinomas of the forestomach were produced in mice. In rats, hepatocellular carcinomas, adenocarcinomas of the small and large intestine, and squamous-cell carcinomas of the Zymbal gland were produced in animals of each sex. A high incidence of mammary adenocarcinomas was observed in females. In addition, squamous-cell carcinomas were found in the skin of males and in the clitoral gland of females. Hepatocellular carcinomas were produced in one study in monkeys.

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

Single dose or short-term oral treatment of rats with IQ followed by phenobarbital, with or without further modulating procedures, increased the numbers of foci of altered hepatocytes and of carcinomas in the liver. Sequential administration of IQ 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 IQ in humans.

IQ bound to DNA in many organs of cynomolgus monkeys and rodents dosed *in vivo*. In rodents treated *in vivo*, IQ induced DNA damage, gene mutation and chromosomal anomalies. It induced chromosomal anomalies in human cells *in vitro* and chromosomal anomalies, gene mutation and DNA damage in animal cells *in vitro*. It induced mutations in *Drosophila melanogaster* and DNA damage and mutations in bacteria. Gene mutations in c-Ha-*ras* and p53 genes were found in some Zymbal gland carcinomas induced in rats by IQ.

5.5 Evaluation[1]

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

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

Overall evaluation

IQ (2-Amino-3-methylimidazo[4,5-*f*]quinoline) *is probably carcinogenic to humans (Group 2A).*

In arriving at the overall evaluation, the Working Group took into consideration the following contributory information:

IQ is comprehensively genotoxic, and this activity can be expressed *in vivo* in rodents. IQ can be metabolized by human microsomes to a species that damages bacterial DNA.

6. References

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

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