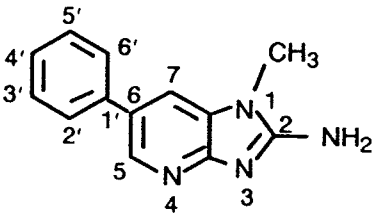
PhIP (2-AMINO-1-METHYL-6-PHENYLIMIDAZO[4,5-*b*]PYRIDINE)

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Services Reg. No.: 105650–23–5
Chem. Abstr. Name: 1-Methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridin-2-amine
IUPAC Systematic Name: 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine



$C_{13}H_{12}N_4$ Mol. wt: 224.11

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Grey-white crystals
(*b*) *Melting-point*: 327–328 °C (Knize & Felton, 1986)
(*c*) *Spectroscopy data*: Ultraviolet, mass, proton nuclear magnetic resonance, carbon-13 nuclear magnetic resonance and infrared absorbance spectra have been reported (Knize & Felton, 1986).
(*d*) *Solubility*: Soluble in methanol (Zhang *et al.*, 1988) and in dimethyl sulfoxide (Dooley *et al.*, 1992)
(*e*) *Stability*: Stable under moderately acidic and alkaline conditions (Sugimura *et al.*, 1983)

1.1.3 *Trade names, technical products and impurities*

No data were available to the Working Group.

1.1.4 *Analysis*

PhIP was originally isolated from fried beef by acid extraction, XAD-2 resin absorption and a series of preparative and analytical high-performance liquid chromatography (HPLC) purifications. The structure of PhIP was determined on the basis of data obtained by mass and proton nuclear magnetic resonance spectral analysis (Felton *et al.*, 1986a).

PhIP was isolated and identified using methanol extraction, 'blue cotton' adsorption and a series of HPLC purifications (Zhang *et al.*, 1988).

A practical, solid-phase extraction and HPLC method for the analysis of PhIP and other heterocyclic amines was devised by Gross *et al.* (1989) and used on foods and food extracts. Improvements to the method (Gross, 1990; Gross & Grüter, 1992) allow determination of PhIP 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 fluorescence detector.

1.2 Production and use

1.2.1 *Production*

The isolation and identification of PhIP were first reported by Felton *et al.* (1986a). Its structure was confirmed by chemical synthesis (Knize & Felton, 1986). Synthesis of [2-^{14}C]-PhIP from 2-amino-3-bromo-5-phenylpyridine was reported by Turteltaub *et al.* (1989). [2′-^{3}H]-PhIP was made by catalytic tritiation of 2′-bromo-PhIP. 2′-Bromo-PhIP was made by diazotization of bromobenzene and 2,5-diaminopyridine, the product of which was brominated at the 3-position of pyridine and then displaced with methylamine and cyclized with cyanogen bromide in analogy with the original synthesis of PhIP. Pentadeutero-PhIP was made from 5-amino-2-chloropyridine by a four-step synthetic route (Lynch *et al.*, 1992).

PhIP is produced commercially in small quantities for research purposes.

1.2.2 *Use*

PhIP is not used commercially.

1.3 Occurrence

PhIP was originally isolated from fried ground beef cooked at 300 °C (Felton *et al.*, 1986a). It has been reported in cooked beef, chicken, fish and pork (Table 1). In investigations of foods for the presence of multiple heterocyclic amines, PhIP is usually found to be the most abundant (see monograph on IQ, p. 168). PhIP was also isolated from a complete human diet cooked simulating 'household' conditions (Alink *et al.*, 1988).

PhIP has been produced in several model systems, including refluxed phenylalanine, glucose and creatinine (Shioya *et al.*, 1987; Skog & Jägerstad, 1991), and dry-heated reactions of phenylalanine and creatine, of phenylalanine, creatine and glucose (Taylor *et al.*, 1987; Felton & Knize, 1991) and of leucine and creatine (Övervik *et al.*, 1989).

The amount of PhIP in the urine of 10 subjects on a normal diet ranged from 0.1 to 2.0 ng/24-h urine sample. PhIP was not detected (< 0.01 ng/24-h urine sample) in the urine of three patients who were receiving parenteral nutrients (Ushiyama *et al.* (1991). Peluso *et al.* (1991) inferred that PhIP was present in the urine of smokers of black tobacco. PhIP has also been found in mainstream cigarette smoke condensate at 11–23 ng/cigarette, with an average of 16.4 ng/cigarette in six samples (Manabe *et al.*, 1991).

Table 1. Concentrations of PhIP in foods

Sample	Concentration (ng/g)	No. of samples	Reference
Ground beef, fried			
190 °C	23.5–48.5	2	Gross (1990)
250 °C	1.2	1	Gross *et al.* (1989); Turesky *et al.* (1989)
300 °C	15	1	Felton *et al.* (1986b)
No temperature given	0.56	1	Wakabayashi *et al.* (1992)
Beef, broiled	15.7	1	Wakabayashi *et al.* (1992)
Beef extract, food-grade	3.62	1	Wakabayashi *et al.* (1992)
Chicken, broiled	38.1	1	Wakabayashi *et al.* (1992)
Mutton, broiled	42.5	1	Wakabayashi *et al.* (1992)
Fish, walleye pollack, fried at 260 °C	69.2	1	Zhang *et al.* (1988)
Salmon			Gross & Grüter (1992)
Pan-broiled at 200 °C	1.7–23	4	
Oven-cooked at 200 °C	ND–18	3	
Barbecued at 270 °C	2–73	4	

ND, not detected (< 1 ng/g)

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 PhIP itself. Cancer risks associated with consumption of broiled and fried foods, which have a high content of PhIP 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. PhIP is also a component of tobacco smoke, which has been covered in a previous IARC monograph (IARC, 1986).

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 400 mg/kg PhIP [purity unspecified] for 579 days. Animals

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

that became moribund were killed and autopsied. The first lymphoma was detected on day 236 in a female mouse given PhIP, and the numbers of mice that survived after that time were taken as the effective numbers. Higher incidences of lymphomas were found in treated than control animals: males, 11/35 *versus* 2/36; females, 26/38 *versus* 6/40. Lung tumours [histological type unspecified] were observed in two controls and in nine treated animals [sex unspecified] (Esumi *et al.*, 1989).

Groups of 10 or more female CF_1 (Charles River) mice, 27–31 days old, were treated with 35, 70 or 150 mg/kg bw PhIP ($< LD_{50}$; dissolved in medium-chain triglycerides) by gavage twice at a four-day interval. Aberrant crypts of colonic mucosa (as defined by light microscopy in methylene blue-stained mucosa; McLellan & Bird, 1988) were scored 21 days after the first treatment. Crypts (0.5 ± 0.3) were observed only after the highest dose (Tudek *et al.*, 1989). [The Working Group noted the lack of concurrent controls.]

3.1.2 *Rat*

A group of 30 male and 30 female Fischer 344 rats, six weeks old, were fed a diet containing 400 mg/kg PhIP (purity, > 99.9%) for 52 weeks. A control group of 40 males and 40 females was available. Animals that became moribund were killed. The first tumour [unspecified] was detected at week 34 in a female rat given PhIP, and the numbers of rats that survived after that time were taken as the effective numbers. At the end of the experiment, 24/30 treated males, 18/30 treated females, 40/40 control males and 40/40 control females were still alive. A total of 38 colon adenocarcinomas were found in 16/29 treated males, four in 2/30 treated females, none in 40 control males and none in 40 control females. Mammary adenocarcinomas were observed in 14/30 treated females and 0/40 controls (Ito *et al.*, 1991).

A group of 13 male Nagase analbuminaemic rats [known to be particularly sensitive to chemical carcinogens (Kakizoe & Sugimura, 1988)], eight weeks old, were fed a diet containing 400 mg/kg PhIP as the hydrochloric acid salt [purity not given] for the first 108 days. The dose was reduced to 300 mg/kg and finally to 100 mg/kg between day 144 and day 311, when the two surviving rats were sacrificed. The presence of at least 90% of the added PhIP in the diet was confirmed by HPLC analysis. Animals that became moribund were killed. The first tumours were detected in the small and large intestine of a rat autopsied on day 136. A total of 36 intestinal tumours were found in 10/13 animals; 22 were adenocarcinomas of the small intestine, two were adenomas at this site, four were carcinomas of the caecum and eight were carcinomas of the large intestine (Ochiai *et al.*, 1991). [The Working Group noted the small number of animals and that no concurrent controls were used but that historical controls were reported to have low rates of intestinal tumours.]

Male Fischer 344 rats, six weeks old, were fed a diet containing 500 mg/kg PhIP for 16 weeks. Animals were killed at weeks 2 and 4 in one experiment and at weeks 4, 8 and 12 and up to 16 weeks in the second. Aberrant crypt foci were induced at a rate of 0.3 ± 0.4 in one out of four rats at week 2 and at 1.3 ± 0.8 in four out of four rats at week 4. In the second experiment, the numbers of aberrant crypt foci induced were 1.3 ± 0.6 (3/3 rats) at week 4, 0.7 ± 0.6 (2/3 rats) at week 8, 3.0 ± 0 (3/3 rats) at week 12 and 11.3 ± 7.0 (3/3 rats) in those killed up to week 16. In age-matched controls, no aberrant crypt foci was found. The numbers of foci per colon found were almost half those induced by Glu-P-1, a known colonic carcinogen (Takahashi *et al.*, 1991).

3.2 Intraperitoneal administration

Mouse

Groups [initial numbers unspecified] of newborn male B6C3F$_1$ mice were injected intraperitoneally with PhIP (purity, 98%) at total doses of 0, 0.625 or 1.25 μmol [140 or 280 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 eight months, 1/44 in controls, 2/19 at the low dose and 7/24 at the high dose; at 12 months, 5/44 in controls, 8/16 at the low dose and 14/21 at the high dose. One hepatocellular carcinoma was found in the high-dose group at 12 months (Dooley *et al.*, 1992).

3.3 Administration with known carcinogens

Rat

Groups of 15 male Wistar rats, six weeks old, underwent a two-thirds partial hepatectomy, followed 16–19 h later by a single intraperitoneal injection of 50 or 75 mg/kg bw PhIP (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 the higher dose of PhIP (1.4 foci/cm^2) than in 17 controls given 0.9% saline instead of PhIP (0.48 foci/cm^2). The lower dose of PhIP did not induce significant development of lesions (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*

No data were available to the Working Group.

4.1.2 *Experimental systems*

In rats and mice, absorbed PhIP was rapidly distributed to most tissues, the highest concentrations being found in the liver and intestines. Over 90% of the radiolabel was eliminated from the body in the two species within 24 h. At that time, much of the retained radiolabel was in ethanol-insoluble, perhaps covalently bound, form. In mice, 11 different radioactive products were identified in the urine and two in the faeces. The profile of urinary and fecal metabolites of PhIP in rats depended on pretreatment (Turteltaub *et al.*, 1989; Watkins *et al.*, 1991).

Human liver and colon cytosols contained *O*-acetyltransferase activity that metabolized *N*-hydroxy-PhIP into a DNA-binding form. PhIP was not a substrate to liver cytosolic *N*-acetyltransferase (Turesky *et al.*, 1991). (See Fig. 1, in the monograph on IQ, p. 178).

Hepatocytes isolated from Aroclor 1254-pretreated rats activated PhIP into a mutagen, as detected in a number of systems. The activation was inhibited by α-napththoflavone, indicating involvement of the cytochrome P450 system. The active metabolite, out of at least eight different species, was concluded to be *N*-hydroxy-PhIP (Holme *et al.*, 1989).

Rabbit and human liver microsomes could activate PhIP to a mutagenic form. Mutagenic activity was increased when 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD)-induced rabbit liver and lung microsomes were used. Rabbit cytochrome P450 forms 4 and 6 were mainly responsible for the activation, suggesting involvement of polycyclic hydrocarbon-inducible enzymes (McManus *et al.*, 1989). Cytochrome P450 IA enzymes are responsible for the conversion of PhIP to mutagenic metabolites (Shimada & Guengerich, 1991). Use of purified rat and rabbit cytochrome P450 preparations led to the conclusion that the activation pathway to *N*-hydroxy-PhIP is catalysed mainly by CYP IA2 (P450 IA2) and to a lesser extent by CYP IA1 (P450 IA1) (Wallin *et al.*, 1990).

4′-Hydroxy-PhIP, thought to be a detoxified metabolite in rats, was formed five times more rapidly by CYP IA1 than by CYP IA2 (Wallin *et al.*, 1990). A sulfate ester of 4′-hydroxy-PhIP was found to be the main metabolite of PhIP in cultured rat hepatocytes and in rat urine but not in bile *in vivo*. N^2-Sulfamate and N^2-acetyl derivatives of PhIP were not present in urine or bile (Alexander *et al.*, 1989); the β-glucuronide conjugate of *N*-hydroxy-PhIP is the major PhIP metabolite excreted in bile and to a smaller extent in the urine. A glutathione conjugate of *N*-hydroxy-PhIP was also identified (Alexander *et al.*, 1991).

In mice, 31% of the radiolabel was found in urine and 30% in faeces 24 h after gavage with radioactive PhIP. Following intraperitoneal exposure, the respective amounts were 39 and 12% (Turteltaub *et al.*, 1989). In rats, 51% of the total dose was recovered as unmetabolized PhIP in the faeces 24 h after gavage, representing 66% of the faecal radiolabel (Watkins *et al.*, 1991).

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 PhIP have been reviewed (de Meester, 1989; Sugimura *et al.*, 1989; Felton & Knize, 1990).

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)

PhIP was mutagenic to *Salmonella typhimurium* strains. In cultured mammalian cells, it induced DNA strand breaks; unscheduled DNA synthesis was found in rat primary hepatocytes, provided that they were derived from polychlorinated biphenyl-treated animals. In cultured repair-deficient Chinese hamster ovary cells, PhIP induced mutation at the *hprt* locus, sister chromatid exchange and chromosomal aberrations.

PhIP was reported to have induced sister chromatid exchange in bone-marrow cells from mice treated *in vivo*. [The Working Group noted that the control values in different experiments were variable.] Chromosomal aberrations were not induced in bone-marrow cells, but the frequency of aberrations was slightly increased in circulating blood cells. [The Working Group noted that a single sampling time, 50 h, was used to obtain the observations in bone marrow.]

PhIP binds covalently to the DNA of various tissues in rats and cynomolgus monkeys following oral administration. Hydrolysis of DNA from the livers of rats dosed with ^{3}H-PhIP, followed by HPLC separation, showed that the radiolabel co-chromatographed with the acid hydrolysis product of N^2-(2′-deoxyguanosin-8-yl)–PhIP (Frandsen *et al.*, 1992).

N-Hydroxy-PhIP does not react with DNA *in vitro* unless it is esterified, particularly by sulfotransferase or *O*-acetyltransferase reactions (Buonarati *et al.*, 1990). Chemical acetylation of N^2-hydroxy-PhIP produced two products, one of which reacted with DNA and with 2′-deoxyguanosine but not with 2′-deoxycytidine, 2′-deoxyadenosine or 2′-deoxythymidine. The adduct was identified as N^2-(2′-deoxyguanosin-8-yl)–PhIP (Frandsen *et al.*, 1992).

4.4.3 *Genetic changes in animal tumours*

As reported in an abstract (Ushijima *et al.*, 1992), colonic carcinomas induced in rats by PhIP contained no mutation in codons 12, 13 or 61 of Ki-*ras* or Ha-*ras*, and polymerase chain reaction and single-strand conformation polymorphism analysis showed no mutation or mutational hot spot in p53. In breast carcinomas induced in rats by PhIP, Ha-*ras* was mutated at a rate of 20%, but no p53 mutation was found.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine) has been found in cooked meat and fish at concentrations of up to 70 ng/g. A few determinations indicated that the levels of PhIP were higher than those of IQ, MeIQ and MeIQx.

5.2 Human carcinogenicity data

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

Table 2. Genetic and related effects of PhIP

Test system	Result		Dose (LED/HID)[a]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ERD, *Escherichia coli* differential toxicity	-	+	3.1 µg/ml	Knasmüller *et al.* (1992)
HMM, Host-mediated assay, *Escherichia coli* in intrasanguinous mice	+	0	2.3 mg/kg	Knasmüller *et al.* (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	0.0000	Sugimura *et al.* (1989)
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.* (1986a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	+	15	Felton & Knize (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.5000	Shioya *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	+[b]	2.2400	Holme *et al.* (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0000	Sugimura *et al.* (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.5000	Buonarati & Felton (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	0.05	Wild *et al.* (1991)
SAS, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	0	+[b]	112.0000	Holme *et al.* (1989)
SAS, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	0	+	0.5000	Buonarati & Felton (1990)
SAS, *Salmonella typhimurium* TA98/1,8-DNP_6, reverse mutation	0	+	0.0050	Wild *et al.* (1991)
SAS, *Salmonella typhimurium* TA98NR, reverse mutation	0	+[b]	112.0000	Holme *et al.* (1989)
SAS, *Salmonella typhimurium* TA97, reverse mutation	0	+	0.0000	Felton & Knize (1990)
SAS, *Salmonella typhimurium* YG1024, reverse mutation	0	+	0.0500	Wild *et al.* (1991)
SAS, *Salmonella typhimurium* TA96, reverse mutation	0	(+)	0.0000	Felton & Knize (1990)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+	0	11.2000	Holme *et al.* (1989)
DIA, DNA strand breaks, Chinese hamster V79 cells *in vitro*	-	+[b]	11.2000	Holme *et al.* (1989)
GCO, Gene mutation, Chinese hamster ovary cells (*uv5*) *in vitro*	0	+	2.0000	Thompson *et al.* (1987)

Table 2 (contd)

Test system	Result		Dose (LED/HID)[a]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SIC, Sister chromatid exchange, Chinese hamster ovary cells (*uv5*) *in vitro*	0	+	1.0000	Thompson *et al.* (1987)
SIA, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	–	+[b,c]	5.6000	Holme *et al.* (1989)
CIC, Chromosome aberrations, Chinese hamster ovary cells (*uv5*) *in vitro*	0	+	2.0000	Thompson *et al.* (1987)
SVA, Sister chromatid exchange, mouse[c] bone-marrow cells *in vivo*	+		3.1 × 1 ip	Tucker *et al.* (1989)
MVM, Micronucleus test, mouse[c] bone-marrow cells *in vivo*	?		50.0 × 1 ip	Tucker *et al.* (1989)
MVM, Micronucleus test, mouse[c] peripheral blood cells *in vivo*	?		100.0 × 1 ip	Tucker *et al.* (1989)
CBA, Chromosomal aberration, mouse[c] bone-marrow cells *in vivo*	–		100.0 × 1 ip	Tucker *et al.* (1989)
CLA, Chromosomal aberration, mouse[c] peripheral blood cells *in vivo*	(+)		100.0 × 1 ip	Tucker *et al.* (1989)
BVD, Binding (covalent) to DNA in rats (multiple organs) *in vivo*[d]	+		60 ppm diet × 2/4 wk	Takayama *et al.* (1989)
BVD, Binding (covalent) to DNA in cynomolgus monkey (multiple organs) *in vivo*[d]	+		20.00 × 9 po	Adamson *et al.* (1991)
BID, Binding (covalent) to calf thymus DNA *in vitro*	0	+	0	Peluso *et al.* (1991)

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

[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

[b]Hepatocytes

[c]Polychlorinated biphenyl-treated

[d]^{32}P-Postlabel

5.3 Animal carcinogenicity data

PhIP was tested for carcinogenicity in one experiment in mice and in two experiments in rats by oral administration in the diet. It increased the incidence of lymphomas in mice of each sex. In rats, it produced adenocarcinomas of the small and large intestine in males and mammary adenocarcinomas in females.

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

A single intraperitoneal dose of PhIP after a two-thirds hepatectomy, followed by further modulating treatment, enhanced development of foci of altered hepatocytes in the livers of rats.

5.4 Other relevant data

PhIP formed DNA adducts *in vivo* in rats and monkeys. In rodent cells *in vitro*, it induced DNA damage, gene mutation and chromosomal anomalies. It induced DNA damage and mutation in bacteria.

PhIP can be metabolized by human microsomes isolated from liver and colon to a species that damages bacterial DNA.

5.5 Evaluation[1]

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

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

Overall evaluation

PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine) *is possibly carcinogenic to humans (Group 2B).*

6. References

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

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