



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 56

Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins

Summary of Data Reported and Evaluation

Food items and constituents

Salted fish
Pickled vegetables
Caffeic acid
d-Limonene

Heterocyclic aromatic amines

IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)
MeIQ (2-Amino-3,4-dimethylimidazo[4,5-f]quinoline)
MeIQX (2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline)
PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine)

Mycotoxins

Aflatoxins B₁, B₂, G₁, G₂, M₁
Toxins derived from *Fusarium graminearum*, *F. culmorum* and *F. crookwellense*: zearalenone, deoxynivalenol, nivalenol and fusarenone X
Toxins derived from *Fusarium moniliforme*: fumonisins B1 and B2 and fusarin C
Toxins derived from *Fusarium sporotrichioides*: T-2 toxin
Ochratoxin A

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SALTED FISH

Chinese-style salted fish (Group 1)

Other salted fish (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 41)

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Salted fish is prepared by treating fish with dry salt or an aqueous salt solution and is often subsequently dried in the sun. It is produced and consumed primarily in Southeast Asia and northern Europe. Chinese-style salted fish is usually softened by partial decomposition before or during salting. High levels of *N*-nitrosodimethylamine have been reported in some samples of Chinese-style salted fish.

5.2 Human carcinogenicity data

The pattern of nasopharyngeal carcinoma incidence in China reflects the pattern of consumption of salted fish. Eight case-control studies consistently demonstrate that consumption of Chinese-style salted fish is strongly related to risk for nasopharyngeal carcinoma. The effect remained in studies that controlled for other risk factors. A significant dose-response relationship is seen between frequency of intake and risk for nasopharyngeal carcinoma, and the association is especially strong for intake of salted fish during childhood. Two further case-control studies, on oesophageal cancer and stomach cancer, found nonsignificant associations with consumption of Chinese-style salted fish.

The association between cancer and the consumption of other types of salted fish was examined in several studies. A study in Tunisia and one in Alaska suggested a relationship between intake of salted fish and nasopharyngeal carcinoma. Ecological studies in Japan showed a correlation between consumption of dried or salted fish and cancers of the stomach and oesophagus. One cohort study in the USA and three case-control studies in Hawaii, Japan and Italy showed positive associations between intake of dried or salted fish and risk for stomach cancer; a cohort study from Hawaii and two case-control studies from Japan found no association. In none of these studies was the effect of salt consumption evaluated independently.

Studies on cancers at other sites were not considered informative for the evaluation.

5.3 Animal carcinogenicity data

Chinese-style salted fish was tested in two studies in rats by administration in the diet or in the diet and drinking-water. A small number of carcinomas was observed in the nasal, paranasal and oral cavities in each of the studies in rats, mostly in females.

5.4 Other relevant data

Extracts of Chinese-style salted fish are mutagenic to bacteria.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of Chinese-style salted fish.

There is *inadequate evidence* in humans for the carcinogenicity of other salted fish.

There is *limited evidence* in experimental animals for the carcinogenicity of Chinese-style salted fish.

Overall evaluation

Chinese-style salted fish is *carcinogenic to humans (Group 1)*.

Other salted fish is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

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PICKLED VEGETABLES (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 83)

Chemicals found in pickled vegetables

CAS No.: 16071-96-8

Chem. Abstr. Name: Bis[μ -(methanethiolato)]tetranitrosodiiron

CAS No.: 90-19-7

Chem. Abstr. Name: 2-(3,4-Dihydroxyphenyl)-3,5-dihydroxy-7-methoxy-4*H*-1-benzopyran-4-one

CAS No.: 480-19-3

Chem. Abstr. Name: 3,5,7-Trihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4*H*-1-benzopyran-4-one

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Traditional processes for pickling vegetables in some regions of China, Japan and Korea involve fermentation of local vegetables, with or without salting. Such preparations are often eaten daily or several times a week. Among the many compounds found at low levels in pickled vegetables are *N*-nitrosamines and Roussin red methyl ester, which reacts with secondary amines to form *N*-nitrosamines.

5.2 Human carcinogenicity data

A cohort study from Japan suggests that intake of pickled vegetables is positively associated with risk for stomach cancer, but further cohort studies from Japan and Hawaii do not support an association. The methods used to determine dietary intake differed in these studies, and the types of pickled vegetables included may also have differed.

Seven case-control studies of stomach cancer have been conducted that included data on consumption of pickled vegetables. Three conducted in Japan gave negative results and another gave positive results. One study of Japanese in Hawaii showed an association, but two conducted in China did not.

A large case-control study of oesophageal cancer in Hong Kong showed a significant dose-response relationship between consumption of pickled vegetables and oesophageal cancer, after potential confounding factors were taken into account. A study in a high- and an intermediate-risk area in China showed an association with consumption of pickled vegetable juice, although there was no association with consumption of pickled vegetables; a population-based study in a high-risk area of northern China also gave negative results for pickled vegetables.

Intake of salted/pickled vegetables (leafy vegetables, roots and olives) has been investigated in two case-control studies of nasopharyngeal carcinoma from China and in one from Tunisia. One of these studies, from Guangxi, China, showed a significant association with eating salted/pickled vegetables.

Two correlation studies carried out in Japan and one carried out in Hawaii suggest a relationship between consumption of pickled vegetables and stomach cancer, but the results are not completely consistent. The

results of correlation studies on oesophageal cancer were also inconsistent.

No data were available on pickled vegetables made elsewhere in the world.

5.3 Animal carcinogenicity data

No adequate study on the carcinogenicity of pickled vegetables to experimental animals was available to the Working Group.

5.4 Other relevant data

In a single study, extracts of pickled vegetables from northern China induced morphological transformation of Syrian hamster embryo cells in culture. Extracts of pickled vegetables from northern China and Japan are mutagenic to bacteria.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of pickled vegetables as prepared traditionally in Asia.

There is *inadequate evidence* in experimental animals for the carcinogenicity of pickled vegetables.

Overall evaluation

Pickled vegetables (traditional Asian) are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms for Bis[μ -(methanethiolato)]tetranitrosodiiron

- Bis(methanethiolato)tetranitrosodiiron
- Roussin red methyl ester
- Roussin's red methyl ester

Synonyms for 2-(3,4-Dihydroxyphenyl)-3,5-dihydroxy-7-methoxy-4H-1-benzopyran-4-one

- C.I. 75690
- 7-Methoxyquercetin
- 7-Methylquercetin
- 7-O-Methylquercetin
- Quercetin 7-methyl ether
- Rhamnetin
- β -Rhamnocitrin
- 3,3',4',5-Tetrahydroxy-7-methoxyflavone
- 3,5,3',4'-Tetrahydroxy-7-methoxyflavone

Synonyms for 3,5,7-Trihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4H-1-benzopyran-4-one

- C.I. 75680
- Isorhamnetin
- Isorhamnetol

- 3'-Methoxyquercetin
- 3'-Methylquercetin
- 3'-O-Methylquercetin
- Quercetin 3'-methyl ether
- 3,4',5,7-Tetrahydroxy-3'-methoxyflavone

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CAFFEIC ACID (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 115)

CAS No.: 331-39-5

Chem. Abstr. Name: 3-(3,4-Dihydroxyphenyl)-2-propenoic acid

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Caffeic acid is found in many fruits, vegetables, seasonings and beverages consumed by humans, principally in conjugated forms such as chlorogenic acid.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Caffeic acid was tested for carcinogenicity by oral administration in the diet in one study in mice and one study in rats. In mice, it produced renal-cell adenomas in females and a high incidence of renal tubular-cell hyperplasia in animals of each sex. An increase in the combined incidence of squamous-cell papillomas and carcinomas of the forestomach was seen in male mice, and a high incidence of hyperplasia of the forestomach was seen in both males and females. In rats, it produced squamous-cell papillomas and carcinomas of the forestomach in animals of each sex and a few renal-cell adenomas in males.

Oral administration of caffeic acid in combination with known carcinogens resulted in enhancing or inhibiting effects depending upon the carcinogen and the time of administration.

5.4 Other relevant data

Humans and experimental animals metabolize caffeic acid to the same metabolites and hydrolyse chlorogenic acid to caffeic acid.

Caffeic acid did not induce micronuclei in mice treated *in vivo*. It produced gene mutation and chromosomal aberrations in cultured rodent cells. It did not induce gene mutation in bacteria.

5.5 Evaluation

No data were available on the carcinogenicity of caffeic acid to humans.

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

Overall evaluation

Caffeic acid is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- Caffeic acid
- 5(4)-(2-Carboxyethenyl)-1,2-dihydroxybenzene
- 4-(2'-Carboxyvinyl)-1,2-dihydroxybenzene;
- 3,4-Dihydroxybenzeneacrylic acid
- 3,4-Dihydroxycinnamic acid
- 3-(3,4-Dihydroxyphenyl)propenoic acid

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***d*-LIMONENE**

(Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 135)

CAS No.: 5989-27-5

Chem. Abstr. Name: (R)-1-Methyl-4-(1-methylethenyl)cyclohexene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

d-Limonene is found widely in citrus and many other plant species and is a major constituent of many essential oils. It is used extensively as a component of flavourings and fragrances, as a chemical intermediate and as an insect repellent. Widespread exposures occur through consumption of fruits, vegetables and products containing essential oils. Consumption of *d*-limonene has been estimated to be 0.2-2 mg/kg bw per day.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

d-Limonene has been tested for carcinogenicity by oral gavage in one study in mice and one study in rats. In mice, no treatment-related tumour was observed. It significantly increased the combined incidence of renal-cell adenomas and carcinomas and induced renal tubular hyperplasia in male rats.

In a two-stage experiment, oral treatment with *d*-limonene after administration of *N*-nitrosoethylhydroxyethylamine enhanced the development of renal adenomas and renal tubular hyperplasia in male Fischer 344 rats, which synthesize $\alpha_{2\mu}$ -globulin, but not in male NBR rats, in which there is no evidence that $\alpha_{2\mu}$ -globulin is synthesized in measurable quantities.

5.4 Other relevant data

In men, oral intake of *d*-limonene induced transient proteinuria. *d*-Limonene induced nephrotoxicity in male Fischer 344 but not NBR rats.

No data were available on the genetic and related effects of *d*-limonene in humans. In a small number of studies with a variety of endpoints, *d*-limonene showed no evidence of genotoxic activity.

5.5 Evaluation

No data were available on the carcinogenicity of *d*-limonene to humans.

There is *limited evidence* in experimental animals for the carcinogenicity of *d*-limonene.

Overall evaluation

d-Limonene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Vol. 73 \(1999\)](#)

Synonyms

- Cajaputene
- Carvene
- Cinene
- (+)-Dipentene
- *d*-(+)-Limonene
- D-(+)-Limonene
- (+)-Limonene
- (R)-Limonene
- (R)-(+)-Limonene
- (+)-*para*-Mentha-1,8-diene
- (R)-(+)-*para*-Mentha-1,8-diene
- 1-Methyl-4-isopropenyl cyclohexene-1
- Refchole

Last updated: 30 September 1999

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

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 165)

CAS No.: 76180-96-6

Chem. Abstr. Name: 3-Methyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine

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

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.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (p. 64)

MeIQ (2-AMINO-3,4-DIMETHYLIMIDAZO[4,5-f]QUINOLINE) (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 197)

CAS No.: 77094-11-2

Chem. Abstr. Name: 3,4-Dimethyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine

5. Summary of Data Reported and Evaluation

5.1 Exposure data

MeIQ (2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline) has been found in cooked meat and fish. A few determinations indicated that the levels of MeIQ were lower than those of IQ, MeIQx and PhIP.

5.2 Human carcinogenicity data

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

5.3 Animal carcinogenicity data

MeIQ was tested for carcinogenicity by dietary administration in one study in mice and in one study in rats. In mice, hepatocellular adenomas and carcinomas were induced in females and papillomas and squamous-cell carcinomas of the forestomach in animals of each sex in a dose-dependent manner. In rats, oral administration of MeIQ produced squamous-cell carcinomas of the Zymbal gland and oral cavity and adenomas and adenocarcinomas of the colon in animals of each sex, squamous-cell carcinomas of the skin in male rats and mammary adenocarcinomas in female rats.

Sequential administration of MeIQ after *N*-nitrosodiethylamine enhanced the appearance of foci of altered hepatocytes in rat liver.

5.4 Other relevant data

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

MeIQ bound to DNA and induced DNA damage and sister chromatid exchange in rodents treated *in vivo*. It induced DNA damage and gene mutation in rodent cells *in vitro* and gene mutation in insects. It induced DNA damage and mutation in bacteria.

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

5.5 Evaluation

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

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

Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (p. 65)

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

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 211)

CAS No.: 77500-04-0

Chem. Abstr. Name: 3,8-Dimethyl-3*H*-imidazo[4,5-*f*]quinoxalin-2-amine

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

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)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (p. 65)

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

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 229)

CAS No.: 105650-23-5

Chem. Abstr. Name: 1-Methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridin-2-amine

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.

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

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)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

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AFLATOXINS

Naturally Occurring Aflatoxins (Group1)

Aflatoxin M₁ (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 245)

Aflatoxin B₁

CAS No.: 1162-65-8

Aflatoxin B₂

CAS No.: 7220-81-7

Aflatoxin G₁

CAS No.: 1165-39-5

Aflatoxin G₂

CAS No.: 7241-98-7

Aflatoxin M₁

CAS No.: 6795-23-9

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Aflatoxins are a group of relatively stable toxins produced mainly by two *Aspergillus* species that are ubiquitous in areas of the world with hot, humid climates. Whether exposure is predominantly to aflatoxin B₁ or to mixed B₁ and G₁ depends on the geographical distribution of the *Aspergillus strains*. *Aspergillus flavus*, which produces aflatoxins B₁ and B₂, occurs worldwide; *A. parasiticus*, which produces aflatoxins B₁, B₂, G₁ and G₂, occurs principally in the Americas and in Africa. Exposure occurs primarily through dietary intake of maize and groundnuts. Exposure to aflatoxin M₁ occurs mainly through consumption of milk, including mother's milk. Life-time exposure to aflatoxins in some parts of the world, commencing *in utero*, has been confirmed by biomonitoring.

5.2 Human carcinogenicity data

One cohort study of a small number of Dutch oilpress workers exposed to aflatoxin-containing dusts indicated increased mortality from cancer, but no death from hepatocellular carcinoma was observed. A cohort study in China found significant excess mortality from liver cancer among individuals in villages where foods were heavily contaminated with aflatoxins. A cohort study of Danish workers exposed to aflatoxin from imported feed found an excess of hepatocellular carcinoma among those who had had major exposure to aflatoxin-contaminated feed in the period 10 or more years before diagnosis. In a cohort study in China, a significant elevation in risk for hepatocellular carcinoma was found among people with aflatoxin metabolites in the urine, after adjustment for hepatitis B surface antigen positivity. The elevation in risk was particularly high among those excreting aflatoxin B₁-guanine adducts; however, there was no association between dietary and urinary aflatoxin levels among subjects in whom both were detected.

Of three hospital-based case-control studies in which an attempt was made to evaluate exposure to aflatoxin

B₁, one (in the Philippines) found a significantly greater risk for hepatocellular carcinoma among people whose intake of aflatoxin was estimated to be heavy than in those with light aflatoxin intake. The other two studies, one in Hong Kong and one in Thailand, gave negative results. In Thailand, one study on hepatocellular carcinoma and another on cholangiocarcinoma also found no association with the presence of aflatoxin B₁-albumin adducts in sera.

The two cohort studies in China addressed combined exposure to hepatitis B virus and aflatoxins and suggested that each has an independent effect.

Several correlation studies have been performed, the majority showing a strong association between estimated aflatoxin intake and incidence of hepatocellular carcinoma. In only a few was it possible to evaluate simultaneously any correlation with the prevalence of hepatitis infection. Of those that did so, two - one in Swaziland and one in China - showed a stronger correlation with exposure to aflatoxin B₁ than with hepatitis B viral infection. The largest such study, in China, did not show an association with the presence of aflatoxin B₁ metabolites in urine. The study from Swaziland was the only one in which it was shown that subjects had concomitant exposure to aflatoxin B₁ and G₁.

5.3 Carcinogenicity in experimental animals

Mixtures of aflatoxins and aflatoxin B₁ have been tested extensively for carcinogenicity by various routes of administration in several strains of mice and rats, in hamsters, several strains of fish, ducks, tree shrews and monkeys. Following their oral administration, mixtures of aflatoxins and aflatoxin B₁ caused hepatocellular and/or cholangiocellular liver tumours, including carcinomas, in all species tested except mice. In rats, renal-cell tumours and a low incidence of tumours at other sites, including the colon, were also found. In monkeys, liver angiosarcomas, osteogenic sarcomas and adenocarcinomas of the gall-bladder and pancreas developed, in addition to hepatocellular and cholangiocellular carcinomas. In adult mice, aflatoxin B₁ administered intraperitoneally increased the incidence of lung adenomas. Intraperitoneal administration of aflatoxin B₁ to infant mice, adult rats and toads produced high incidences of liver-cell tumours in all of these species. Subcutaneous injection of aflatoxin B₁ resulted in local sarcomas in rats. Exposure of fish embryos to aflatoxin B₁ induced a high incidence of hepatocellular adenomas and carcinomas. Intraperitoneal administration of aflatoxin B₁ to rats during pregnancy and lactation induced benign and malignant tumours in mothers and their progeny in the liver and in various other organs, including those of the digestive tract, the urogenital system and the central and peripheral nervous systems. In several species, aflatoxin B₁ administered by different routes induced foci of altered hepatocytes, the number and size of which was correlated with later development of hepatocellular adenomas and carcinomas.

Aflatoxin B₂ induced foci of altered hepatocytes and hepatocellular adenomas following its oral administration to rats. A low incidence of hepatocellular carcinomas was observed after intraperitoneal administration of aflatoxin B₂ to rats.

Oral administration of aflatoxin G₁ induced foci of altered hepatocytes, hepatocellular adenomas and carcinomas and renal-cell tumours in rats and liver-cell tumours in fish. The hepatocarcinogenic effect of aflatoxin G₁ was weaker than that of aflatoxin B₁. Subcutaneous injection of aflatoxin G₁ in rats resulted in local sarcomas, which developed at a lower incidence and at later times than those induced by aflatoxin B₁ at the same dose level and by the same route. Oral administration of aflatoxin G₂ to trout had no hepatocarcinogenic effect in one experiment.

Aflatoxin M₁, a hydroxy metabolite of aflatoxin B₁, produced fewer hepatocellular carcinomas following its oral administration to rats and fish than aflatoxin B₁ given at the same dose level and by the same route. Aflatoxin Q₁, another metabolite of aflatoxin B₁, produced a high incidence of hepatocellular carcinomas following its oral administration to fish. Administration to rats and fish of aflatoxicol, yet another metabolite of aflatoxin B₁, induced hepatocellular carcinomas in both species; the tumour incidence was lower than that in animals

treated with aflatoxin B₁ at the same dose level.

A large number of experiments have been carried out in which aflatoxins were administered in combination (prior to, during and following) with diets, viruses, parasites, known carcinogens and a number of different chemicals in order to study the modulating effects, including chemoprevention, of the agents on aflatoxin-induced carcinogenesis. Enhancing and inhibitory effects on the carcinogenicity of aflatoxins have been observed.

5.4 Other relevant data

Aflatoxin B₁ is consistently genotoxic, producing adducts in humans and animals *in vivo* and chromosomal anomalies in rodents and, in a single study, in rhesus monkeys *in vivo*. In human and animal cells in culture, it produces DNA damage, gene mutation and chromosomal anomalies; in animal cells *in vitro*, it also induces cell transformation. In insects and lower eukaryotes, it induces gene mutation and recombination. In bacteria, it produces DNA damage and gene mutation.

Aflatoxin B₁ is hepatotoxic in humans and animals and is nephrotoxic and immunosuppressive in animals.

Aflatoxin B₂ has not been studied extensively, and most data are derived from single reports. Aflatoxin B₂ becomes bound to DNA of rats treated *in vivo*, after metabolic conversion to aflatoxin B₁. In rodent cells, it induces DNA damage, sister chromatid exchange and cell transformation, but not gene mutation. In fungi, it produces neither gene mutation nor recombination, whereas it produced gene mutation in bacteria.

Aflatoxin G₁ binds to DNA and produces chromosomal aberrations in rodents treated *in vivo*. In cultured human and animal cells, it induces DNA damage, and, in single studies, it induced chromosomal anomalies. It induces mutation in fungi and DNA damage and gene mutation in bacteria.

There are few published genetic studies on **aflatoxin G₂** and **aflatoxin M₁**. Aflatoxin G₁ produced DNA damage and sister chromatid exchange in animal cells in culture. Aflatoxin M₁ produced DNA damage in cultured rodent cells and gene mutation in bacteria.

Humans metabolize aflatoxin B₁ to an 8,9-epoxide, forming DNA and albumin adducts by the same activation pathways as susceptible animal species. Humans metabolize aflatoxin B₁ to the major aflatoxin B₁-N7-guanine and -serum albumin adduct at levels comparable to those in susceptible animal species (rat).

Glutathione S-transferase-mediated conjugation of glutathione to the 8,9-epoxide reduces DNA damage, and this mechanism is important in reducing the tumour burden in experimental animals. Animal species, such as the mouse, that are resistant to aflatoxin carcinogenesis have three to five times more glutathione S-transferase activity than susceptible species, such as the rat. Humans have less glutathione S-transferase activity for 8,9-epoxide conjugation than rats or mice, suggesting that humans are less capable of detoxifying this important metabolite.

Studies of human microsomal activation of aflatoxin B₁ show that at non-saturating concentrations of aflatoxin B₁ the rate of formation of the 8,9-epoxide is similar to that found in sensitive species (rat and monkey).

The value of aflatoxin B₁-N7-guanine as an indicator of risk for developing tumours is demonstrated by experiments with chemoprotective agents that show concordance between reduction of levels of DNA adduct formation and reduced incidence of liver tumours in rats and trout.

The presence of DNA- and protein-aflatoxin adducts in humans, the urinary excretion of aflatoxin B₁-N7-guanine adducts by humans, and the ability of human tissues to activate aflatoxin B₁ to form DNA adducts *in*

in vitro provide evidence that humans have the biochemical pathways required for aflatoxin-induced carcinogenesis. The following evidence is consistent with those biochemical mechanisms.

Studies with bacteria show that activated aflatoxin B₁ specifically induces G to T transversions. On the basis of experiments conducted *in vitro*, aflatoxin B₁ specifically targets the third and not the second nucleotide of codon 249 (AGG) of the human *p53* gene, an effect not seen with benzo[*a*]pyrene-7,8-diol-9,10-epoxide when tested at the same level of binding.

A high frequency of mutations at a mutational 'hotspot' (the third nucleotide of codon 249 in exon 7) has been found in *p53* tumour suppressor genes in hepatocellular carcinomas from patients resident in areas considered to offer a high risk of exposure to aflatoxins and where there is a high incidence of hepatocellular carcinoma. In contrast, this mutation is rare in hepatocellular carcinomas from regions of low exposure to aflatoxins (including Australia, Japan, southern Africa, Germany, Spain, Italy, Turkey, Israel, Saudi Arabia, the United Kingdom and the USA).

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of naturally occurring mixtures of aflatoxins.

There is *sufficient evidence* in humans for the carcinogenicity of aflatoxin B₁.

There is *inadequate evidence* in humans for the carcinogenicity of aflatoxin M₁.

There is *sufficient evidence* in experimental animals for the carcinogenicity of naturally occurring mixtures of aflatoxins and aflatoxins B₁, G₁ and M₁.

There is *limited evidence* in experimental animals for the carcinogenicity of aflatoxin B₂.

There is *inadequate evidence* in experimental animals for the carcinogenicity of aflatoxin G₂.

Overall evaluations

Naturally occurring aflatoxins are *carcinogenic to humans (Group 1)*.

Aflatoxin M₁ is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (p. 83)

Subsequent evaluation: [Vol. 82 \(2002\)](#)

Synonyms for Aflatoxin B₁

- 6-Methoxydifurocoumarone
- 2,3,6α,9α-Tetrahydro-4-methoxycyclopenta[*c*]furo[3',2':4,5]furo[2,3-*h*]benzopyran-1,11-dione

Synonyms for Aflatoxin B₂

- Dihydroaflatoxin B₁
- 2,3,6α,8,9,9α-Hexahydro-4-methoxycyclopenta[*c*]furo[3',2':4,5]furo[2,3-*h*][*l*]benzopyran-1,11-dione

Synonym for Aflatoxin G₁

- 3,4,7α,10α-Tetrahydro-5-methoxy-1*H*,12*H*-furo[3',2':4,5]furo[2,3-*h*]pyrano[3,4-*c*][*l*]-benzopyran-1,12-dione

Synonyms for Aflatoxin G₂

- Dihydroaflatoxin G₁
- 3,4,7α,9,10,10α-Hexahydro-5-methoxy-1*H*,12*H*-furo[3',2':4,5]furo[2,3-*h*]pyrano[3,4-*c*][*l*]-benzopyran-1,12-dione

Synonym for Aflatoxin M₁

- 4-Hydroxyaflatoxin B₁

Last updated 08/21/1997

**TOXINS DERIVED FROM *FUSARIUM GRAMINEARUM*,
F. CULMORUM AND *F. CROOKWELLENSIS*:
ZEARALENONE, DEOXYNIVALENOL,
NIVALENOL AND FUSARENONE X
(Group 3)**

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 397)

Zearalenone

CAS No.: 17924-92-4

Chem. Abstr. Name: 1*H*-2-Benzoxacyclotetradecin-1,7(8*H*)dione, 3,4,5,6,9,10-hexahydro-14,16-dihydroxy-3-methyl, [S-(E)]-

Deoxynivalenol

CAS No.: 51481-10-8

Chem. Abstr. Name: Trichothec-9-en-8-one, 12,13-epoxy-3,7,15-trihydroxy(3 α ,7 α)-

Nivalenol

CAS No.: 23282-20-4

Chem. Abstr. Name: Trichothec-9-en-8-one, 12,13-epoxy-3,4,7,15-tetrahydroxy(3 α ,4 β ,7 α)-

Fusarenone X

CAS No.: 23255-69-8

Chem. Abstr. Name: Trichothec-9-en-8-one, 4-(acetyloxy)-12,13-epoxy-3,7,15-trihydroxy(3 α ,4 β ,7 α)-

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The mycotoxins considered are produced by *Fusarium* species that occur primarily on wheat, barley and maize. The toxins occur whenever these cereals are grown under humid conditions. Exposure occurs through dietary consumption of contaminated cereals. Deoxynivalenol has been held responsible for large-scale human poisonings this century in China and India. Chronic exposures to deoxynivalenol, zearalenone and nivalenol occur in several parts of the world; humans are rarely exposed to fusarenone X.

5.2 Human carcinogenicity data

A few ecological studies that considered *F. graminearum* suggested no correlation with the incidence of oesophageal cancer.

5.3 Animal carcinogenicity data

Zearalenone was tested for carcinogenicity by administration in the diet in one experiment in mice and in two experiments in rats. An increased incidence of hepatocellular adenomas was observed in female mice and of pituitary adenomas in mice each sex. No increase in the incidence of tumours was observed in rats.

No data were available to the Working Group on the carcinogenicity in experimental animals of deoxynivalenol.

Nivalenol was tested for carcinogenicity in one experiment in female mice by oral administration in the diet. No increase in tumour incidence was observed.

Fusarenone X was tested for carcinogenicity in two studies in male rats by oral administration and in male mice and male rats by subcutaneous injection. The studies were inadequate for evaluation.

5.4 Other relevant data

In episodes of food poisoning in humans caused by deoxynivalenol, severe gastrointestinal involvement was the primary sign.

Zearalenone has oestrogenic effects in domestic pigs and experimental animals. Deoxynivalenol causes outbreaks of feed refusal and vomiting in domestic pigs. Deoxynivalenol and fusarenone X cause immunosuppression in mice. Nivalenol causes bone-marrow toxicity in experimental animals.

No data were available on the genetic and related effects of zearalenone, deoxynivalenol, nivalenol or fusarenone X in humans.

Zearalenone induces chromosomal anomalies in cultured rodent cells. It does not induce recombination in yeast or gene mutation or DNA damage in bacteria.

Deoxynivalenol induces cell transformation, chromosomal aberrations and inhibition of gap-junctional intercellular communication in cultured mammalian cells. It does not induce unscheduled DNA synthesis or mutation in cultured mammalian cells and does not induce mutation in bacteria.

Nivalenol and fusarenone X have not been studied adequately for genetic effects.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of toxins derived from *Fusarium graminearum*.

No data were available on the carcinogenicity to humans of toxins derived from *F. crookwellense* and *F. culmorum*.

There is *limited evidence* in experimental animals for the carcinogenicity of zearalenone.

There is *inadequate evidence* in experimental animals for the carcinogenicity of deoxynivalenol.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nivalenol.

There is *inadequate evidence* in experimental animals for the carcinogenicity of fusarenone X.

Overall evaluation

Toxins derived from *Fusarium graminearum*, *F. culmorum* and *F. crookwellense* are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (pp. 64, 74)

Synonyms for 1*H*-2-Benzoxacyclotetradecin-1,7(8*H*)-dione, 3,4,5,6,9,10-hexahydro-14,16-dihydroxy-3-methyl, [*S*-(*E*)]-

- F2
- Compound F-2
- Fermentation estrogenic substance
- FES
- (S)-(-)-3,4,5,6,9,10-Hexahydro-14,16-dihydroxy-3-methyl-1*H*-2-benzoxacyclotetradecin-1,7-(8*H*)-dione
- Mycotoxin F2
- Toxin F2
- Zearalenone
- (-)-Zearalenone
- (S)-Zearalenone
- *trans*-Zearalenone
- (10*S*)-Zearalenone
- Zenone

Synonyms for Trichothec-9-en-8-one, 12,13-epoxy-3,7,15-trihydroxy-(3 α ,7 α)-

- Dehydronivalenol
- Deoxynivalenol
- 4-Deoxynivalenol;
- 12,13-Epoxy-3 α ,7 α ,15-trihydroxy-9-trichothecen-8-one
- Rd toxin
- Spiro[2,5-methano-1-benzoxepin-10,2'-oxirane], trichothec-9-en-8-one derivative
- Vomitoxin

Synonyms for Trichothec-9-en-8-one, 12,13-epoxy-3,4,7,15-tetrahydroxy-, (3 α ,4 β ,7 α)-

- Nivalenol
- Spiro[2,5-methano-1-benzoxepin-10,2'-oxirane], trichothec-9-en-8-one derivative
- 3 α ,4 β ,7 α ,15-Tetrahydroxy-12,13-epoxytrichothec-9-en-8-one

Synonyms for Trichothec-9-en-8-one, 4-(acetyloxy)-12,13-epoxy-3,7,15-trihydroxy(3 α ,4 β ,7 β)-

- Fusarenon
- Fusarenon X
- Fusarenone X
- Nivalenol 4-*O*-acetate
- Nivalenol monoacetate
- 3,7,15-Trihydroxy-4-acetoxy-8-oxo-12,13-epoxy- Δ^9 -trichothecene
- 3,7,15-Trihydroxy-scirp-4-acetoxy-9-en-8-one

TOXINS DERIVED FROM *FUSARIUM MONILIFORME*: FUMONISINS B₁ AND B₂ AND FUSARIN C (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 445)

Fumonisin B₁

CAS No.: 116355-83-0

Chem. Abstr. Name: 1,2,3-Propanetricarboxylic acid, 1,1'-[1-(12-amino-4,9,11-trihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediyl] ester

Fumonisin B₂

CAS No.: 116355-84-1

Chem. Abstr. Name: 1,2,3-Propanetricarboxylic acid, 1,1'-[1-(12-amino-9,11-dihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediyl] ester

Fusarin C

CAS No.: 79748-81-5

Chem. Abstr. Name: 3,5,7,9-Undecatetraenoic acid, 2-ethylidene-11-[4-hydroxy-4-(2-hydroxyethyl)-2-oxo-6-oxa-3-azabicyclo-[3.1.0]hex-1-yl]-4,6,10-trimethyl-11-oxo, methyl ester, [1R-[1 α (2E,3E,5E,7E,9E),4 α ,5 α]]-

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Fumonisin B₁, fumonisin B₂ and fusarin C are produced by *Fusarium* species that occur primarily on maize. These toxins may occur particularly when maize is grown under warm, dry conditions. Exposure occurs through dietary consumption of contaminated maize. Populations that eat milled or ground maize as a dietary staple can therefore be exposed to significant amounts of fumonisins and to lesser amounts of fusarin C.

5.2 Human carcinogenicity data

The only studies available were correlation studies, most of which indicated some relationship between oesophageal cancer rates and the occurrence of *F. moniliforme* or its toxins in maize.

5.3 Animal carcinogenicity data

Cultures of *F. moniliforme* were tested by oral administration in two experiments in male rats of one strain. A culture of *F. moniliforme* known to produce significant amounts of fumonisins B₁ and B₂ induced neoplastic nodules, hepatocellular carcinomas and cholangiocellular carcinomas; in addition, forestomach papillomas and carcinomas were observed. A culture of *F. moniliforme*, known to contain mainly fusarin C, did not induce such tumours.

Two studies in which male rats were fed maize naturally contaminated with *F. moniliforme* were inadequate for evaluation.

Fumonisin B₁ was tested for carcinogenicity by oral administration in the diet in one experiment in male rats,

producing hepatocellular carcinomas. It induced the formation of foci of altered (γ -glutamyltranspeptidase-positive) hepatocytes.

No data were available to the Working Group on the carcinogenicity of fumonisin B₂.

Fusarin was tested in one study in female mice and female rats by oral gavage. It induced papillomas and carcinomas of the oesophagus and forestomach in mice and rats.

5.4 Other relevant data

Fumonisin B₁ causes outbreaks of leukoencephalomalacia in horses and pulmonary oedema in pigs. It is toxic to the central nervous system, liver, pancreas, kidney and lung in a number of animal species. Fumonisin B₂ is hepatotoxic in rats.

Fumonisin B₁ and B₂ do not induce unscheduled DNA synthesis in rat hepatocytes *in vivo* or *in vitro* or mutation in bacteria.

In single studies, fusarin C induces chromosomal anomalies, gene mutation and DNA damage in cultured rodent cells. It induces mutations in bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of toxins derived from *F. moniliforme*.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cultures of *F. moniliforme* that contain significant amounts of fumonisins.

There is *limited evidence* in experimental animals for the carcinogenicity of fumonisin B₁.

There is *inadequate evidence* in experimental animals for the carcinogenicity of fumonisin B₂.

There is *limited evidence* in experimental animals for the carcinogenicity of fusarin C.

Overall evaluation

Toxins derived from *Fusarium moniliforme* are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms for 1,2,3-Propanetricarboxylic acid, 1,1'-[1-(12-amino-4,9,11-trihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediyl] ester

- Fumonisin B₁
- Macrofusine

Synonym for 1,2,3-Propanetricarboxylic acid, 1,1'-[1-(12-amino-9,11-dihydroxy-2-methyltridecyl)-2-(1-methylpentyl)-1,2-ethanediyl] ester

- Fumonisin B₂

Synonyms for 3,5,7,9-Undecatetraenoic acid, 2-ethylidene-11-[4-hydroxy-4-(2-hydroxyethyl)-2-oxo-6-oxa-3-azabicyclo-[3.1.0]hex-1-yl]-4,6,10-trimethyl-11-oxo, methyl ester, [1R-[1 α (2E,3E,5E,7E,9E),4 α ,5 α]]-

- Fusarin C
- 6-Oxa-3-azabicyclo[3.1.0]hexane, 3,5,7,9-undecatetraenoic acid derivative

Last updated 08/21/1997

TOXINS DERIVED FROM *FUSARIUM SPOROTRICHIOIDES*: T-2 TOXIN (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 467)

CAS No.: 21259-20-1

Chem. Abstr. Name: Trichothec-9-ene-3,4,8,15-tetrol, 12,13-epoxy, 4,15-diacetate 8-(3-methylbutanoate), (3 α ,4 β ,8 α)-

5. Summary of Data Reported and Evaluation

5.1 Exposure data

T-2 Toxin is produced primarily by *Fusarium sporotrichioides*, which occurs rarely on cereals such as wheat and maize. The toxin is considered to have played a role in largescale human poisonings in Siberia during this century.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

T-2 Toxin was tested for carcinogenicity in mice and in trout by oral administration in the diet and in rats by intragastric administration. In mice, it increased the incidences of pulmonary and hepatic adenomas in males. The studies in trout and rats were inadequate for evaluation.

5.4 Other relevant data

T-2 Toxin causes outbreaks of haemorrhagic disease in animals and has been associated with alimentary toxic aleukia in humans.

No data were available on the genetic and related effects of T-2 toxin in humans.

Experimental data were drawn mainly from single studies. T-2 Toxin induced DNA damage and chromosomal aberrations in rodents *in vivo*, in cultured human cells and in cultured rodent cells. It inhibited protein synthesis in various mammalian and human cell types *in vitro*. Chromosomal aberrations were also induced in insects. It induced gene mutation in cultured rodent cells but not in bacteria. It did not induce DNA damage in bacteria.

5.5 Evaluation

No data were available on the carcinogenicity to humans of toxins derived from *Fusarium sporotrichioides*.

There is *limited evidence* in experimental animals for the carcinogenicity of T-2 toxin.

Overall evaluation

Toxins derived from *Fusarium sporotrichioides* are *not classifiable as to their carcinogenicity to humans*

(Group 3).

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (p. 73)

Synonyms

- Fusariotoxin T2
- Insariotoxin
- $8\alpha(3\text{-Methylbutyryloxy})4\beta,15\text{-diacetoxy}$ scirp-9-en-3 α -ol
- Mycotoxin T2
- NSC 138780
- T-2 Mycotoxin
- Toxin T2
- T₂-Toxin
- T₂-trichothecene
- 3 α -Hydroxy-4 $\beta,15$ -diacetoxy-8 α -(3-methylbutyryloxy)-12,13-epoxy- δ 9-tricothecene

Last updated 08/21/1997

OCHRATOXIN A (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 56 (1993) (p. 489)

CAS No.: 303-47-9

Chem. Abstr. Name: L-Phenylalanine, *N*-[(5-chloro-3,4-dihydro-8-hydroxy-3-methyl-1-oxo-1*H*-2-benzopyran-7-yl)-carbonyl]-, (R)-

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ochratoxin A is produced by *Aspergillus ochraceus* and *Penicillium verrucosum*. Human exposure occurs mainly through consumption of contaminated grain and pork products, as confirmed by detection of ochratoxin A in human blood and milk.

5.2 Human carcinogenicity data

A number of descriptive studies have suggested a correlation between exposure to ochratoxin A and Balkan endemic nephropathy and have found a correlation between the geographical distribution of Balkan endemic nephropathy and a high incidence of and mortality from urothelial urinary tract tumours. In the only study in which ochratoxin A was measured, levels were higher in the blood of patients with Balkan endemic nephropathy and/or urothelial urinary tract tumours than in unaffected people; no distinction was made between the two diseases.

5.3 Animal carcinogenicity data

Ochratoxin A was tested for carcinogenicity by oral administration in mice and rats. It increased the incidence of hepatocellular tumours in mice of each sex and produced renal-cell adenomas and carcinomas in male mice and in rats of each sex.

5.4 Other relevant data

Ochratoxin A caused renal toxicity, nephropathy and immunosuppression in several animal species.

No adequate data were available on the genetic and related effects of ochratoxin A in humans. It induces DNA damage in rodents *in vivo* and in rodent cells *in vitro*.

5.5 Evaluation

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

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

Overall evaluation

Ochratoxin A is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (p. 271)

Synonym

- (-)-*N*-[(5-Chloro-8-hydroxy-3-methyl-1-oxo-7-isochromanyl)carbonyl]-3-phenylalanine

Last updated 08/21/1997