International Agency for Research on Cancer (IARC) - Summaries & Evaluations

AFLATOXINS

Naturally Occurring Aflatoxins (Group1)

Aflatoxin M_1 (Group 2B)

For definition of Groups, see Preamble Evaluation.

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Aflatoxin B_1

CAS No.: 1162-65-8

Aflatoxin B_2

CAS No.: 7220-81-7

Aflatoxin G_1

CAS No.: 1165-39-5

Aflatoxin G_2

CAS No.: 7241-98-7

Aflatoxin M_1

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 B_1 or to mixed B_1 and G_1 depends on the geographical distribution of the *Aspergillus strains*. *Aspergillus flavus*, which produces aflatoxins B_1 and B_2, occurs worldwide; *A. parasiticus*, which produces aflatoxins B_1, B_2, G_1 and G_2, occurs principally in the Americas and in Africa. Exposure occurs primarily through dietary intake of maize and groundnuts. Exposure to aflatoxin M_1 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 B_1-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 B_1, 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 B_1-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 were 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 B_1 than with hepatitis B viral infection. The largest such study, in China, did not show an association with the presence of aflatoxin B_1 metabolites in urine. The study from Swaziland was the only one in which it was shown that subjects had concomitant exposure to aflatoxin B_1 and G_1.

5.3 Carcinogenicity in experimental animals

Mixtures of aflatoxins and aflatoxin B_1 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 B_1 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 B_1 administered intraperitoneally increased the incidence of lung adenomas. Intraperitoneal administration of aflatoxin B_1 to infant mice, adult rats and toads produced high incidences of liver-cell tumours in all of these species. Subcutaneous injection of aflatoxin B_1 resulted in local sarcomas in rats. Exposure of fish embryos to aflatoxin B_1 induced a high incidence of hepatocellular adenomas and carcinomas. Intraperitoneal administration of aflatoxin B_1 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 B_1 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 B_2 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 B_2 to rats.

Oral administration of aflatoxin G_1 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 G_1 was weaker than that of aflatoxin B_1. Subcutaneous injection of aflatoxin G_1 in rats resulted in local sarcomas, which developed at a lower incidence and at later times than those induced by aflatoxin B_1 at the same dose level and by the same route. Oral administration of aflatoxin G_2 to trout had no hepatocarcinogenic effect in one experiment.

Aflatoxin M_1, a hydroxy metabolite of aflatoxin B_1, produced fewer hepatocellular carcinomas following its oral administration to rats and fish than aflatoxin B_1 given at the same dose level and by the same route. Aflatoxin Q_1, another metabolite of aflatoxin B_1, 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 B_1, induced hepatocellular carcinomas in both species; the tumour incidence was lower than that in animals treated with aflatoxin B_1 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 B_1 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 B_1 is hepatoxic in humans and animals and is nephrotoxic and immunosuppressive in animals.

Aflatoxin B_2 has not been studied extensively, and most data are derived from single reports. Aflatoxin B_2 becomes bound to DNA of rats treated *in vivo*, after metabolic conversion to aflatoxin B_1. 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 G_1 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 G_2** and **aflatoxin M_1**. Aflatoxin G_1 produced DNA damage and sister chromatid exchange in animal cells in culture. Aflatoxin M_1 produced DNA damage in cultured rodent cells and gene mutation in bacteria.
Humans metabolize aflatoxin B_1 to an 8,9-epoxide, forming DNA and albumin adducts by the same activation pathways as susceptible animal species. Humans metabolize aflatoxin B_1 to the major aflatoxin B_1-*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 B_1 show that at non-saturating concentrations of aflatoxin B_1 the rate of formation of the 8,9-epoxide is similar to that found in sensitive species (rat and monkey).
The value of aflatoxin B_1-*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 B_1-*N7*-guanine adducts by humans, and the ability of human tissues to activate aflatoxin B_1 to form DNA adducts *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 B_1 specifically induces G to T transversions. On the basis of experiments conducted *in vitro*, aflatoxin B_1 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 B_1.
There is *inadequate evidence* in humans for the carcinogenicity of aflatoxin M_1.
There is *sufficient evidence* in experimental animals for the carcinogenicity of naturally occurring mixtures of aflatoxins and aflatoxins B_1, G_1 and M_1.
There is *limited evidence* in experimental animals for the carcinogenicity of aflatoxin B_2.
There is *inadequate evidence* in experimental animals for the carcinogenicity of aflatoxin G_2.

Overall evaluations

Naturally occurring aflatoxins are *carcinogenic to humans (Group 1)*.
Aflatoxin M_1 is *possibly carcinogenic to humans (Group 2B)*.
For definition of the italicized terms, see Preamble Evaluation.
Previous evaluation: Suppl. 7 (1987) (p. 83)

Synonyms for Aflatoxin B_1

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

Synonyms for Aflatoxin B_2

- Dihydroaflatoxin B_1
- 2,3,6aα,8,9,9aα-Hexahydro-4-methoxycyclopenta[*c*]furo[3´,2´:4,5]furo[2,3-*h*][*l*]benzopyran-1,11-dione

Synonym for Aflatoxin G_1

- 3,4,7aα,10aα-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 G_2

- Dihydroaflatoxin G_1
- 3,4,7aα,9,10,10aα-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 M_1

- 4-Hydroxyaflatoxin B_1

Last updated 08/21/1997

See Also:

Toxicological Abbreviations

Aflatoxins (WHO Food Additives Series 40)

Aflatoxins (IARC Summary & Evaluation, Volume 56, 1993)