**AFLATOXINS**
**CAS No. 1402-68-2**
First Listed in the *First Annual Report on Carcinogen*s

## CARCINOGENICITY

Aflatoxins are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans (IARC 1987, 1993). A study of a small number of Dutch oilpress workers exposed to aflatoxin-containing dusts demonstrated increased mortality from cancer, but no death from hepatocelluar carcinoma was observed. However, a positive correlation between estimated aflatoxin intake or level of aflatoxin contamination of market food samples and cooked food and incidence of hepatocellular cancer was observed in early studies in Uganda, Swaziland, Thailand, and Kenya. Similar correlations between aflatoxin intake and hepatocellular cancer incidence and mortality have been reported from Mozambique and China. Studies conducted in different regions of Africa and Asia, where hepatocellular cancer incidence or mortality and aflatoxin intake were measured, revealed a highly significant correlation between these variables. In the southeast United States, in an area with a high average daily intake of aflatoxin, a 10% excess in hepatocellular cancer incidence was observed compared with areas with low aflatoxin intake. A case-control study in the Philippines, where mean aflatoxin contamination levels in dietary items were established and individual levels of aflatoxin consumption were determined retrospectively, demonstrated an increased, dose-related risk of developing hepatocellular cancer in persons with higher ingestion of aflatoxin. One major difficulty in interpreting these studies is potential confounding due to hepatitis virus B infection, which is endemic in many areas where the relationship between aflatoxin intake and hepatocellular carcinoma has been examined. However, in three recent studies, both factors have been taken into account. In China, both dietary and urinary levels of aflatoxins were found to be related to hepatocellular cancer incidence. Serological surveys did not show corresponding differences in the prevalence of the hepatitis B virus-carrier state. In Swaziland, in a study based on surveys of levels of aflatoxin intake across four broad geographic regions, liver cancer incidence was associated strongly with estimated levels of aflatoxin. In a multivariate analysis involving ten smaller subregions, aflatoxin exposure emerged as a more important determinant of the variation in liver cancer incidence than the prevalence of hepatitis B infection.

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of aflatoxins in experimental animals (IARC 1976, 1982, 1987, 1993) Since the early report that contaminated peanut meal induced hepatomas in rats, many studies have demonstrated the carcinogenic potential of aflatoxins for the liver of rats. These compounds have been tested for carcinogenicity with many animal species by several routes of administration and found to produce tumors primarily of the liver, colon, and kidneys. When administered in the diet, aflatoxins induced hepatocellular carcinomas, carcinomas of the glandular stomach, mucinous adenocarcinomas of the colon, and kidney tumors in rats. Aflatoxins by the same route of administration induced hepatocellular carcinomas in Rhesus monkeys, a marmoset, and tree shrews. When administered in the diet, aflatoxin induced cholangiocellular carcinomas in hamsters. Following oral administration of aflatoxin, monkeys developed liver angiosarcomas, osteogenic sarcomas, adenocarcinomas of the gallbladder and pancreas, and hepatocellular and cholangiocellular carcinomas. When administered by a single intragastric injection, the compound induced neoplastic hepatic nodules in rats. When administered by intraperitoneal injection to pregnant rats, aflatoxin induced liver and other tumors in the mothers and in their progeny. When administered orally or by intraperitoneal injection, aflatoxin induced pulmonary adenomas in mice. When administered by subcutaneous injection, aflatoxin induced sarcomas in

mice and rats. Aflatoxins G1 and B2 are less potent hepatocarcinogens than aflatoxin B1 for rats dosed orally, but G1 can induce a significant incidence of kidney tumors.

## PROPERTIES

Aflatoxins are toxic metabolites produced by certain types of fungi. They are intensely fluorescent in ultraviolet light. Aflatoxins are soluble in methanol, acetone, and chloroform, while being only slightly soluble in water and hydrocarbon solvents (HSDB 2000).

## USE

Aflatoxins are used solely for research purposes. They are naturally occurring contaminants formed by specific fungi on food and agricultural products during conditions of high temperature and high humidity (IARC 1976).

## PRODUCTION

Aflatoxins are not manufactured in commercial quantities. They are produced in small quantities for research purposes by large-scale fermentation on solid substrates or liquid media, then extracted and purified by chromatography. Total annual production usually does not exceed 0.25 lb (IARC 1976, 1993). Aflatoxins occur mainly as contaminants on food and animal feed products; aflatoxin B1 is the most frequent contaminant (IARC 1976). Twenty-three current U.S. suppliers of aflatoxins B1, B2, G1, G2, and M1 were identified (Chem Sources 2001).

## EXPOSURE

The primary route of potential human exposure to aflatoxins is ingestion of contaminated food. Grains, peanuts, tree nuts, and cottonseed meal are among the foods on which aflatoxin-producing fungi commonly grow. Meat, eggs, milk, and other edible products from animals that consume aflatoxin-contaminated feed are additional sources of potential exposure. Americans may consume up to an estimated 0.15 to 0.50 µg of aflatoxins daily (IARC 1976). The discovery of the toxic and major carcinogenic metabolite of aflatoxin B1, aflatoxin M1, in breast milk from nursing mothers living in tropical countries in Africa and Asia establishes an early exposure route (Zarba *et al.* 1992, Somogyi and Beck 1993). Concentrations from 20 to 1,816 ng/L of aflatoxin M1 have been detected, while levels up to 8,218 ng/L of aflatoxin B1 have been found (Somogyi and Beck 1993). As the number of childhood illnesses continues to grow, environmental exposure assessment in children is becoming an important part of research. Biomarkers are currently being used in such an assessment of aflatoxins (Weaver *et al*. 1998).

Workers at high risk of exposure are those involved in agriculture as they are occupationally exposed to airborne aflatoxin through inhalation of grain dust (Ghosh *et al*. 1997). In measuring the airborne total aflatoxin levels in a rice processing plant and a maize processing plant, Ghosh *et al*. (1997) found mean concentrations of 12 $pg/m^3$ in the total dust samples of the workplace and 11 $pg/m^3$ in the storage area of the rice mill. In the respirable dust samples, the values were 26 $pg/m^3$ in the workplace and 19 $pg/m^3$ in the storage area. In the maize processing plant, no airborne aflatoxin was found in the total dust samples, but in the respirable dust samples, the mean levels were 816 $pg/m^3$ in the oil mill, 800 $pg/m^3$ in the loading/unloading area, and 18 $pg/m^3$ in the elevator. The high levels in the first two sites were as expected, since the

aflatoxigenic *Aspergillus flavus* strain was highly present in these areas. Furthermore, because maize is a better source for the growth of the strain, the concentrations of airborne total aflatoxin were higher in the maize processing plant than in the rice mill. Autrup *et al.* (1993), in their assessment of the exposure to aflatoxin B1 in livestock-feed processing plants, found an occupational exposure to the aflatoxin, with a mean level of exposure for a worker of 64 pg/kg/day. Three of the five workers with the highest antigenicity were involved in the discharging of a cargo with an aflatoxin B1 concentration of 26 µg/kg.

## REGULATIONS

EPA regulates aflatoxins under the Resource Conservation and Recovery Act (RCRA), which designates aflatoxins as hazardous constituents of waste. Additionally, EPA's Carcinogen Assessment Group considers aflatoxins to be potentially carcinogenic.

FDA, under the Federal Food, Drug and Cosmetic Act (FD&CA) and the Public Service Act, regulates any materials or ingredients that could be contaminated with aflatoxins.

OSHA regulates aflatoxins under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 6.

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