Ochratoxin A

CAS No. 303-47-9

Reasonably anticipated to be a human carcinogen

First listed in the Sixth Annual Report on Carcinogens (1991)

Carcinogenicity

Ochratoxin A is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to ochratoxin A caused tumors at several different tissue sites in mice and rats. Dietary administration of ochratoxin A caused benign and/or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and benign and malignant kidney tumors (renal-cell adenoma and carcinoma) in male mice (IARC 1983, 1987). When administered by stomach tube, ochratoxin A caused benign and/or metastatic malignant kidney tumors (renal-cell adenoma or carcinoma) in rats of both sexes and benign mammary-gland tumors (fibroadenoma) in female rats (NTP 1989, Huff 1991). Since ochratoxin A was listed in the Sixth Annual Report on Carcinogens, an additional study in male rats has been identified, which also found an increased incidence of kidney tumors following dietary exposure to ochratoxin A (Mantle et al. 2005).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to ochratoxin A. In descriptive ecological studies, a relatively high frequency of contamination of cereals and beans with ochratoxin A has been reported in an area of Yugoslavia where a potentially fatal chronic renal disease, Balkan endemic nephropathy (BEN), is present (IARC 1983, 1987). The geographical distribution of this disease has been linked, in turn, to areas of increased incidence and mortality from urinary-tract tumors.

Since ochratoxin A was listed in the Sixth Annual Report on Carcinogens, additional studies in humans have been identified; however, the findings concerning a relationship between exposure to ochratoxin A and cancer are mixed. Ecological studies have found correlations between the geographic distribution of urinary-tract tumors and exposure to ochratoxin A (Pfohl-Leszkowicz et al. 2002, Clark and Snedeker 2006). In addition, higher blood levels of ochratoxin A were observed in individuals with BEN or urinary-tract tumors than in unaffected residents of the same areas (Petkova-Bocharova and Castegnaro 1991), and levels of ochratoxin A were higher in a small sample of Egyptian patients with urinary-tract tumors than among healthy control subjects (Wafa et al. 1998). However, the International Agency for Research on Cancer reported that there was no clear association between ochratoxin A–contaminated foods and BEN in Bulgaria (IARC 1993), and a small study of urinary-bladder cancer in Pakistan found no differences in blood ochratoxin A concentrations between case and control subjects (Aslam et al. 2006). Exposure to aristolochic acid, which also correlates with the geographical distribution of urinary-tract tumors, has been proposed as a risk factor for BEN and the associated urinary-tract tumors (Grollman et al. 2007).

Properties

Ochratoxin A is a naturally occurring fungal toxin that occurs as a colorless crystal at room temperature under normal light, but exhibits green and blue fluorescence in ultraviolet light (IARC 1976). The free acid is insoluble in water but is moderately soluble in organic solvents such as chloroform, ethanol, methanol, and xylene (Akron 2010, HSDB 2010). It is unstable in light, especially in very humid conditions; however, it is stable in the dark in ethanol solutions (Akron 2010). Ochratoxin A is also fairly stable to heat; in cereal products, up to 35% of the toxin survives autoclaving for up to 3 hours (IARC 1976). Physical and chemical properties of ochratoxin A are listed in the following table.

<table>
<thead>
<tr>
<th>Property</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>403.8</td>
</tr>
<tr>
<td>Density</td>
<td>1.366 g/mL</td>
</tr>
<tr>
<td>Melting point</td>
<td>169°C</td>
</tr>
<tr>
<td>Log K&lt;sub&gt;a&lt;/sub&gt;</td>
<td>4.74</td>
</tr>
<tr>
<td>Water solubility</td>
<td>1.31 mg/L at 25°C</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>7.56 × 10&lt;sup&gt;-11&lt;/sup&gt; mm Hg at 25°C</td>
</tr>
<tr>
<td>Dissociation constant (pK&lt;sub&gt;a&lt;/sub&gt;)</td>
<td>3.46</td>
</tr>
</tbody>
</table>


Use

Ochratoxin A has no known commercial use. It has been used as a research chemical (HSDB 2010).

Production

Ochratoxin A is a naturally occurring mycotoxin (IARC 1976). The most important ochratoxin A–producing species is Aspergillus ochraceus (IARC 1993). Ochratoxin A is also produced by one species of Penicillium, P. verrucosum, and by rare species in the A. ochraceus group. Ochratoxin A is not produced commercially (IARC 1983); however, in 2010, it was available from 16 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2010).

Exposure

The widespread occurrence of ochratoxin A in food and animal feed results in probable human exposure (IARC 1976, 1993). Ochratoxin A is formed by Penicillium in colder climates and by Aspergillus in tropical and subtropical regions. It is found on corn, peanuts, storage grains, cottonseed, and decaying vegetation (Merck 1996). It has been detected in peanuts, coffee beans, bread, flour, rice, peas, and beans and in moldy cereals, including wheat, maize, rye, barley, and oats (IARC 1983, 1993). Concentrations in cereals ranged from 0.03 to 27.5 ppm (Scott et al. 1972, Krogh et al. 1973).

Ochratoxin A has been detected in fresh grapes, grape juice, dried vine fruits, musts, and all types of wine throughout the world. It was found in Cabernet Sauvignon grapes from Portugal at a concentration of 115.6 μg/kg (Serra et al. 2006), in grape juice at 0.337 μg/kg (Clark and Snedeker 2006), and in dried fruit (raisins, currants, and sultanas) purchased in the United Kingdom at concentrations of up to 53.6 μg/kg (Rizzo et al. 2002). Concentrations are higher in red wines than in rosé wines, and higher in rosé wines than in wines or special wines (e.g., Marsala).

Ochratoxin A has been detected in coffee throughout the world in all stages of production, from coffee cherries to brewed coffee. It was found in coffee cherries and beans in Brazil at concentrations of up to 3.3 μg/kg (Clark and Snedeker 2006). The highest concentra-
Ochratoxin A has been detected in cocoa in all stages of production, from raw beans to chocolate and chocolate cream, in the tropical areas where cocoa is produced. The highest concentration found at any stage of cocoa production was 48.02 μg/L in Bulgaria (Clark and Snedeker 2006) and up to 66.2 μg/L in Tunisia (Abid et al. 1991). The highest concentration in breast milk was 1,890 ng/L (Mus musculus) (Huff 1991). The highest concentration in urine of endemic nephropathy patients and controls in Bulgaria: Lack of detection of 4-hydroxyochratoxin A. IARC Sci Publ (115): 165-169.


