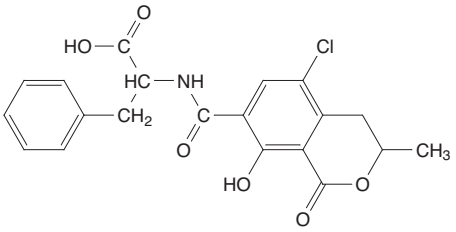
Ochratoxin A

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.

Property	Information
Molecular weight	403.8[a]
Density	1.366 g/mL[b]
Melting point	169°C[a]
Log K_{ow}	4.74[a]
Water solubility	1.31 mg/L at 25°C[c]
Vapor pressure	7.56×10^{-15} mm Hg at 25°C[c]
Dissociation constant (pK_a)	3.46[b]

Sources: [a]HSDB 2010, [b]Akron 2010, [c]SRC 2010.

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). No data were found on U.S. imports or exports of ochratoxin a.

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 concentration found in green (processed) coffee was 56 µg/kg in coffee from the Ivory Coast (Studer-Rohr *et al.* 1995). Ochratoxin A was also found in roasted coffee from Ethiopia at 2.0 µg/kg (Napolitano *et al.* 2007) and instant coffee from Brazil at 6.29 µg/kg (De Almeida *et al.* 2007). The highest concentration found in brewed coffee was 4.2 µg/L, measured in Switzerland (Studer-Rohr *et al.* 1995). Ochratoxin A has also 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/kg in wounded cocoa beans in Camaroon (Mounjouenpou *et al.* 2008). The worldwide mean concentration in cocoa cake was 2.79 µg/kg, the mean concentration in cocoa powder in Africa was 2.41 µg/kg, and the worldwide mean concentration in chocolate and chocolate cream was 0.63 µg/kg (Bonvehi 2004).

Ochratoxin A has been detected in spices and licorice flavoring and candy in many countries where these spices and flavorings are important in the diet. Although ochratoxin A from contaminated barley can occur in beer, a survey of all U.S. breweries (130 at the time) did not detect ochratoxin A in beer or malted barley (detection limit = 10 µg/kg). In moderately contaminated barley, the malting process completely degrades ochratoxin A; however, 2% to 7% of the toxin remained in the final product from heavily contaminated barley (IARC 1983). Residues of ochratoxin A were detected in samples of meat from animals slaughtered immediately after consuming contaminated feed; concentrations of 10 to 920 µg/kg were found in sausage, ham, and bacon (Krogh *et al.* 1977, IARC 1983, 1993). Ochratoxin A also was found in peas and beans from Sweden at 442 µg/kg, peanut seeds from Argentina at up to 170 µg/kg, and olives from Greece at 1.86 µg/kg (Clark and Snedeker 2006, Ghitakou *et al.* 2006, Magnoli *et al.* 2006).

In ambient air, ochratoxin A exists completely in the particulate phase (HSDB 2010). It is immobile in soil. Ochratoxin A has been measured in airborne particulates in mainly occupational settings where contaminated items were stored or processed. Where black pepper was processed, the maximum ochratoxin A concentrations were 0.43 ng/m^3 in ambient air and in 8.304 ng/m^3 personal air samples (Brera *et al.* 2002). Lower concentrations were found in ambient air and personal air monitors in workplaces where cocoa, coffee, and nutmeg were handled (Brera *et al.* 2002, Iavicoli *et al.* 2002). Ochratoxin A has also been measured in settled dust collected in residential and agricultural locations. The highest concentration was 1,581.8 µg/kg in dust in an air supply duct in a U.S. residence; other dust samples from the same residence all had high levels of ochratoxin A (Richard *et al.* 1999).

Ochratoxin A has been measured in the blood and urine of exposed individuals around the world. The concentrations are exceptionally high in Bulgaria, where BEN occurs. Concentrations of ochratoxin A in the blood have been measured at up to 100 ng/mL (100 µg/L) in Bulgaria (Clark and Snedeker 2006) and up to 66.2 µg/L in Tunisia (Abid *et al.* 2003). Urinary concentrations have been measured at up to 148 µg/L for girls in Sierra Leone (Jonsyn-Ellis 2000) and 0.604 µg/L for individuals with BEN in Bulgaria (Castegnaro *et al.* 1991). The highest concentration in breast milk was 1,890 ng/L in Egypt (Hassan *et al.* 2006). Total daily intake of ochratoxin A varies among countries, depending on food-handling methods, and has been estimated based on total diets or on consumption of specific contaminated foods or beverages. The highest estimated daily intake was 1.21 µg for adults with BEN in Bulgaria (Clark and Snedeker 2006), and the highest estimated daily intake for children was 3.6 ng/kg of body weight for Swiss children who consumed grape juice.

Regulations

No specific regulations or guidelines relevant to reduction of exposure to ochratoxin A were identified.

References

Abid S, Hassen W, Achour A, Skhiri H, Maaroufi K, Ellouz F, Creppy E, Bacha H. 2003. Ochratoxin A and human chronic nephropathy in Tunisia: Is the situation endemic? *Hum Exp Toxicol* 22(2): 77-84.

Akron. 2010. *The Chemical Database.* The Department of Chemistry at the University of Akron. http://ull.chemistry.uakron.edu/erd and search on CAS number. Last accessed: 3/8/10.

Aslam M, Beg AE, Blaszkewicz M, Degen GH, Golka K. 2006. Ochratoxin A blood concentration in healthy subjects and bladder cancer cases from Pakistan. *Toxicol Lett* 164: S280.

Bonvehi JS. 2004. Occurrence of ochratoxin A in cocoa products and chocolate. *J Agric Food Chem* 52(20): 6347-6352.

Brera C, Caputi R, Miraglia M, Iavicoli I, Salerno A, Carelli G. 2002. Exposure assessment to mycotoxins in workplaces: Aflatoxins and ochratoxin A occurrence in airborne dusts and human sera. *Microchem J* 73(1-2): 167-173.

Castegnaro M, Maru V, Petkova-Bocharova T, Nikolov I, Bartsch H. 1991. Concentrations of ochratoxin A in the urine of endemic nephropathy patients and controls in Bulgaria: Lack of detection of 4-hydroxyochratoxin A. *IARC Sci Publ* (115): 165-169.

ChemSources. 2010. *Chem Sources - Chemical Search*. Chemical Sources International. http://www.chemsources.com/chemonline.html and search on ochratoxin A. Last accessed: 3/8/10.

Clark HA, Snedeker SM. 2006. Ochratoxin A: Its cancer risk and potential for exposure. *J Toxicol Environ Health B Crit Rev* 9(3): 265-296.

De Almeida AP, Alaburda J, Shundo L, Ruvieri V, Navas SA, Lamardo LCA, Sabino M. 2007. Ochratoxin A in Brazilian instant coffee. *Braz J Microbiol* 38(2): 300-303.

EFSA. 2006. Opinion of the scientific panel on contaminants in the food chain on a request from the commission related to ochratoxin A in food. *EFSA J* 365: 1-56.

Ghitakou S, Koutras K, Kanellou E, Markaki P. 2006. Study of aflatoxin B1 and ochratoxin A production by natural microflora and *Aspergillus parasiticus* in black and green olives of Greek origin. *Food Microbiol* 23(7): 612-621.

Grollman AP, Shibutani S, Moriya M, Miller F, Wu L, Moll U, *et al.* 2007. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci U S A* 104(29): 12129-12134.

Hassan AM, Sheashaa HA, Fattah MFA, Ibrahim AZ, Gaber OA, Sobh MA. 2006. Study of ochratoxin A as an environmental risk that causes renal injury in breast-fed Egyptian infants. *Pediatr Nephrol* 21(1): 102-105.

HSDB. 2010. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 3/10.

Huff JE. 1991. Carcinogenicity of ochratoxin A in experimental animals. In *Mycotoxins, Endemic Nephropathy and Urinary Tract Tumours.* IARC Scientific Publication No. 155. Castegnaro M, Plestina R, Dirheimer G, Chernozemsky IN, Bartsch H, eds. Lyon, France: International Agency for Research on Cancer. pp. 229-444.

IARC. 1976. Ochratoxin A. In *Some Naturally Occurring Substances*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 10. Lyon, France: International Agency for Research on Cancer. pp. 191-197.

IARC. 1983. Ochratoxin A. In *Some Food Additives, Feed Additives and Naturally Occurring Substances*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 31. Lyon, France: International Agency for Research on Cancer. pp. 191-206.

IARC. 1987. Ochratoxin A. In *Overall Evaluations of Carcinogenicity.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, suppl. 7. Lyon, France: International Agency for Research on Cancer. pp. 271-272.

IARC. 1993. Ochratoxin A. In *Some Naturally Occurring Substances: Food Items And Constituents, Heterocyclic Aromatic Amines and Mycotoxins*. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 56. Lyon, France: International Agency for Research on Cancer. pp. 489-521.

Iavicoli I, Brera C, Carelli G, Caputi R, Marinaccio A, Miraglia M. 2002. External and internal dose in subjects occupationally exposed to ochratoxin A. *Int Arch Occup Environ Health* 75(6): 381-386.

JECFA. 2002. Ochrotoxin A. In *Evaluation of Certain Mycotoxins in Food.* 56th Report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization. http://whqlibdoc.who.int/trs/WHO_TRS_906.pdf, pp. 27-35.

Jeswal P. 1998. Antidotal effect of grape juice *(Vitis vinifera)* on ochratoxin A caused hepatorenal carcinogenesis in mice *(Mus musculus)*. *Cytobios* 1998(373): 123-128.

Jonsyn-Ellis FE. 2000. Aflatoxins and ochratoxins in urine samples of school children in Mokonde, Southern Sierra Leone. *J Nutr Environ Med* 10(3): 225-231.

Krogh P, Hald B, Pedersen EJ. 1973. Occurrence of ochratoxin A and citrinin in cereals associated with mycotoxic porcine nephropathy. *Acta Pathol Microbiol Scand B Microbiol Immunol* 81(6): 689-695.

Krogh P, Hald B, Plestina R, Ceovic S. 1977. Balkan (endemic) nephropathy and foodborn ochratoxin A: Preliminary results of a survey of foodstuffs. *Acta Pathol Microbiol Scand B Microbiol Immunol* 85(3): 238-240.

Magnoli C, Astoreca A, Ponsone L, Fernández-Juri MG, Chiacchiera S, Dalcero A. 2006. Ochratoxin A and the occurrence of ochratoxin A-producing black aspergilli in stored peanut seeds from Córdoba, Argentina. *J Sci Food Agric* 86(14): 2369-2373.

Mantle P, Kulinskaya E, Nestler S. 2005. Renal tumourigenesis in male rats in response to chronic dietary ochratoxin A. *Food Addit Contam* 22(suppl. 1): 58-64.

Merck. 1996. Ochratoxins. In *The Merck Index*, 12th ed. Rahway, NJ: Merck & Company. p. 6839.

Mounjouenpou P, Gueule D, Fontana-Tachon A, Guyot B, Tondje PR, Guiraud JP. 2008. Filamentous fungi producing ochratoxin a during cocoa processing in Cameroon. *Int J Food Microbiol* 121(2): 234-241.

Napolitano A, Fogliano V, Tafuri A, Ritieni A. 2007. Natural occurrence of ochratoxin A and antioxidant activities of green and roasted coffees and corresponding byproducts. *J Agric Food Chem* 55(25): 10499-10504.

NTP. 1989. *Toxicology and Carcinogenesis Studies of Ochratoxin A (CAS No. 303-47-9) in F344/N Rats (Gavage Studies)*. Technical Report Series no. 358. Research Triangle Park: National Toxicology Program. 146 pp.

Petkova-Bocharova T, Castegnaro M. 1991. Ochratoxin A in human blood in relation to Balkan endemic nephropathy and urinary tract tumours in Bulgaria. *IARC Sci Publ* (115): 135-137.

Pfohl-Leszkowicz A, Petkova-Bocharova T, Chernozemsky IN, Castegnaro M. 2002. Balkan endemic nephropathy and associated urinary tract tumours: A review on aetiological causes and the potential role of mycotoxins. *Food Addit Contam* 19(3): 282-302.

Richard JL, Plattner RD, May J, Liska SL. 1999. The occurrence of ochratoxin A in dust collected from a problem household. *Mycopathologia* 146(2): 99-103.

Rizzo A, Eskola M, Atroshi F. 2002. Ochratoxin A in cereals, foodstuffs and human plasma. *Eur J Plant Pathol* 108(7): 631-637.

Scott PM, Van Walbeek W, Kennedy B, Anyeti D. 1972. Mycotoxins (ochratoxin A, citrinin, and sterigmatocystin) and toxigenic fungi in grains and other agricultural products. *J Agric Food Chem* 20(6): 1103-1108.

Serra R, Mendonca C, Venancio A. 2006. Ochratoxin A occurrence and formation in Portuguese wine grapes at various stages of maturation. *Int J Food Microbiol* 111, suppl 1: S35-S39 (ePub).

SRC. 2010. *Interactive PhysProp Database Demo*. Syracuse Research Corporation. http://www.syrres.com/what-we-do/databaseforms.aspx?id=386 and search on CAS number. Last accessed: 3/9/10.

Studer-Rohr I, Dietrich DR, Schlatter J, Schlatter C. 1995. The occurrence of ochratoxin A in coffee. *Food Chem Toxicol* 33(5): 341-355.

Wafa EW, Yahya RS, Sobh MA, Eraky I, El-Baz M, El-Gayar HAM, Betbeder AM, Creppy EE. 1998. Human ochratoxicosis and nephropathy in Egypt: A preliminary study. *Hum Exp Toxicol* 17(2): 124-129.