OCHRATOXIN A

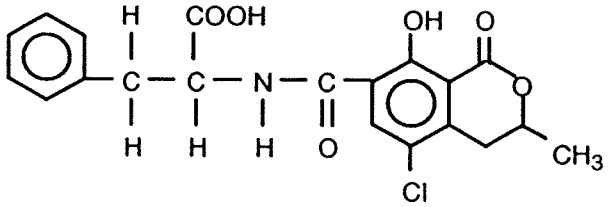
This substance was considered by previous working groups, in October 1975 (IARC, 1976), October 1982 (IARC, 1983) and March 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Services Reg. 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*)-
IUPAC Systematic Name: *N*-[[(3*R*)-5-Chloro-8-hydroxy-3-methyl-1-oxo-7-isochromanyl]carbonyl]-3-phenyl-L-alanine
Synonym: (–)-*N*-[(5-Chloro-8-hydroxy-3-methyl-1-oxo-7-isochromanyl)carbonyl]-3-phenylalanine



$C_{20}H_{18}ClNO_6$ Mol. wt: 403.8

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Crystals (recrystallized from xylene); intensely fluorescent in ultraviolet light, emitting green and blue fluorescence in acid and alkaline solutions, respectively (IARC, 1983; Budavari, 1989)

(*b*) *Melting-point*: 169 °C (recrystallized from xylene) (van der Merwe *et al.*, 1965a,b; Kuiper-Goodman & Scott, 1989)

(*c*) *Optical rotation*: $[\alpha]_D^{21}$ –46.8° (c = 2.65 mmol/l [1.07 g/l] in chloroform) (Pohland *et al.*, 1982)

(*d*) *Spectroscopy data*: Ultraviolet, infrared, mass spectral and proton nuclear magnetic resonance data have been reported (van der Merwe *et al.*, 1965a,b; Pohland *et al.*, 1982).

(*e*) *Solubility*: The free acid is moderately soluble in organic solvents (e.g., chloroform, ethanol, methanol, xylene) (WHO, 1990).

(*f*) *Stability*: Partially degraded under normal cooking conditions (Müller, 1982). Solutions of ochratoxin A are completely degraded by treatment with an excess of sodium hypochlorite solution (Castegnaro *et al.*, 1991a).

1.1.3 *Analysis*

Methods of analysis for ochratoxins in various matrices have been the subject of three recent reviews (Kuiper-Goodman & Scott, 1989; WHO, 1990; van Egmond, 1991a). Only one method (AOAC 973.37, Nesheim *et al.*, 1992) has been subject to a trial by the US Association of Official Analytical Chemists: a thin-layer chromatography method for grain, dating from 1973 (Gilbert, 1991). This and similar methods are widely used (van Egmond, 1991a). A liquid chromatographic method for determining ochratoxin A in maize, barley and kidney was tested in a IUPAC collaborative study (Nesheim *et al.*, 1992). Several high-performance liquid chromatographic methods for various commodities have been proposed and appear to be useful, and a number of enzyme-linked immunosorbent assay methods are valuable for screening and providing semiquantitative data, e.g., for cereals and porcine kidney (van Egmond, 1991a). Methods also have been reported for determining ochratoxins in blood, e.g., by fluorescence with high-performance liquid chromatographic confirmation (Hult *et al.*, 1982; Bauer & Gareis, 1987).

1.2 Production and use

Ochratoxin A was first isolated in 1965 from a culture of *Aspergillus ochraceus* Wilh. grown on sterile maize meal (van der Merwe *et al.*, 1965a). The structure was established by synthesis (Steyn & Holzapfel, 1967; Roberts & Woollven, 1970). Ochratoxin A is produced by inoculating strains of the fungi that produce this compound on autoclaved grains and oilseed (Peterson & Ciegler, 1978; Madhyastha *et al.*, 1990).

The taxonomy of *Aspergillus* and *Penicillium* has been the subject of disagreement since the 1920s. Numerous erroneous reports have been made of ochratoxin A production by more than a dozen species of these two genera (e.g., WHO, 1990; Frank, 1991). An international commission on *Aspergillus* and *Penicillium* was convened to harmonize the taxonomy (Samson & Pitt, 1990); in addition, in extensive studies of the metabolites of *Penicillium* species, their taxonomy has been made consonant with internationally accepted norms. There is now general agreement that ochratoxin A is produced by only one species of *Penicillium*, *P. verrucosum* (Frisvad & Filtenborg, 1989). Among the aspergilli, *A. ochraceus* is the most important ochratoxin-producing species; however, rare species in the *ochraceus* group, including *A. sclerotiorium*, *A. melleus*, *A. alliaceus* and *A. sulphureus*, also produce ochratoxin A (Ciegler, 1972).

Authentic strains of *P. verrucosum* produce ochratoxin A, verrucosin and often high concentrations of citrinin (Frisvad & Filtenborg, 1989). Authentic strains of *A. ochraceus* produce ochratoxin A and penicillic acid (Ciegler, 1972). Other species of *Penicillium* have been reported in grains containing ochratoxin A, including *P. aurantiogriseum* and *P. commune* (Mantle *et al.*, 1991). *P. aurantiogriseum* produces an array of toxic metabolites, including brevianamide A and B, and *P. commune* produces penicillic acid (Frisvad & Filtenborg, 1989; Frank *et al.*, 1990). Grain containing ochratoxin A probably contains additional fungal metabolites.

1.3 Occurrence

Although ochratoxin A occurs in many commodities—from grains to coffee beans—all over the world, it has been found primarily in north-temperate barley- and wheat-growing areas (Kuiper-Goodman & Scott, 1989; WHO, 1990). Representative values reported in various plant products are given in Table 1. Ochratoxin A concentrations in food-grade wheat are generally low, the highest values and frequencies of occurrence being found in some parts of Europe. One sample from Australia contained relatively high ochratoxin A concentrations, indicating that more study of this toxin outside Europe is warranted. A few studies have reported ochratoxin A in retail pork products in Europe (Table 2), suggesting that feed-grade cereals contain more ochratoxin A than is implied by Table 1. Pork products can be a significant human dietary source of ochratoxin A: ochratoxin A occurs at high frequency in the blood of swine produced in several countries (Table 3).

Table 1. Natural occurrence of ochratoxin A in plant products

Country	Product	Year	Positive samples/ total no.	Content (μg/kg)	Reference
North America					
Canada	Wheat, hay	1971–75	7/95	30–6000	Prior (1976)
Canada	Grain, forage	1975–79	5/474	30–4000	Prior (1981)
Canada	Cereals	1976–78	6/315	3–8	Williams (1985)
Canada	Cereals	1981–83	5/440	10–50	Sinha *et al.* (1986)
Canada	Peas, beans	1979	1/84	20	Williams (1985)
USA	Maize	1968–69	3/293	80–170	Shotwell *et al.* (1971)
USA	Wheat	1970–73	11/577	Trace–120	Shotwell *et al.* (1976)
USA	Barley	NR	23/182	10–29	Nesheim (1971), cited in Krogh & Nesheim (1983)
USA	Barley	NR	18/127	10–40	Nesheim (1971), cited in WHO (1990)
South America					
Brazil	Cassava flour	1985–86	2/33	30, 70	Valente Soares &
Brazil	Beans	1985–86	2/13	90, 160	Rodriguez-Amaya (1989)
Brazil	Dried white corn	1985–86	1/12	30	Rodriguez-Amaya (1989)
Chile	Maize	NR	1/28	55	Vega *et al.* (1988)
Europe					
Austria	Feed	1986	30/170	100–1000	Böhm & Leibetseder (1987)
Bulgaria	Maize	1984–89	103/264	0.2–1418	Petkova-Bocharova *et al.* (1991)
Bulgaria	Beans	1984–89	86/260	0.05–285	Petkova-Bocharova *et al.* (1991)
France	Maize	1973	18/924	5–200	Galtier *et al.* (1977)
Germany	Barley	1982–87	10/68	0.1–206	Bauer & Gareis (1987)
Germany	Wheat	1982–87	94/719	0.1–12.5	Bauer & Gareis (1987)

Table 1 (contd)

Country	Product	Year	Positive samples/ total no.	Content (μg/kg)	Reference
Europe (contd)					
Germany	Cereals	1973–88	24/765	Mean, 11.8	Frank (1991)
Germany	Bran	1973–88	9/84	6.8	Frank (1991)
Germany	Flour	1973–88	17/93	2.2	Frank (1991)
Italy	Bread	1976–79	1/1	80 000	Visconti & Bottalico (1983)
Norway	Cereal	1973–88	11/538	2–180	Olberg & Yndestad (1982); Kuiper-Goodman & Scott (1989)
Poland	Feed (mixed)	1966, 87	18/1240	10–200	Goliński *et al.* (1991)
Poland	Cereals	1984–85	158/1353	5–2400	Goliński *et al.* (1991)
Poland	Bread	1984–85	63/368	Mean, 1360	Goliński *et al.* (1991)
Poland	Flour	1984–85	48/215	Mean, 4370	Goliński *et al.* (1991)
Sweden	Beans	1976–79	6/91	10–442	Åkerstrand & Josefsson (1979)
Sweden	Cereals	1972	7/84	16–410	Krogh *et al.* (1974)
United Kingdom	Bread	NR	1/50	210	Osborne (1980)
United Kingdom	Barley	1976–79	51/376	< 25–5000	Buckle (1983)
United Kingdom	Wheat	1976–79	15/101	< 25–2700	Buckle (1983)
United Kingdom	Feeds	1976–79	27/812	< 25–250	Buckle (1983)
United Kingdom	Breakfast cereals	1976–79	12/243	5–108	Lindsay (1981), cited by Kuiper-Goodman & Scott (1989)
Yugoslavia	Maize	1972–76	45/542	19–140	Pavlović *et al.* (1979)
Yugoslavia	Wheat	1972–76	11/130	19– > 100	Pavlović *et al.* (1979)
Africa					
Egypt	Wheat	NR	1/3	10	Abdelhamid (1990)
Egypt	Maize	NR	1/3	12	Abdelhamid (1990)
Egypt	Mixed feed	NR	2/3	Mean, 19	Abdelhamid (1990)
Senegal	Cowpea	1984–88	5/31	Mean, 34	Kane *et al.* (1991)
Tunisia	Wheat	1982–83	8/28	34–360	Bacha *et al.* (1988)
Tunisia	Feed	1982–83	3/10	140–360	Bacha *et al.* (1988)
Australasia					
Australia	Feed	1971–80	1/25	70 000	Connole *et al.* (1981)
India	Rice	1981	2/32	8, 25	Reddy *et al.* (1983)
India	Copra	1982–83	1/384	50	Kumari & Nusrath (1987)
Indonesia	Maize	1985–86	1/26	3	Widiastuti *et al.* (1988)
Japan	Flour	1977–82	11/11	< 2.5–20	Nishijima (1984)

NR, not reported

Table 2. Occurrence of ochratoxin A in retail animal products

Country	Product	Year	Positive samples/ total no.	Content (μg/kg)	Reference
Germany	Kidneys (pork)	1983	41/300	0.5–10	Scheuer & Leistner (1986)
Germany	Sausage (pork)	1984	58/325	0.1–3.4	Scheuer & Leistner (1986)
Switzerland	Sausage	NR	1/12	0.8	Baumann & Zimmerli (1988)
Yugoslavia	Smoked meat products	NR	206	0.01–9	Pepeljnjak & Blažević (1982)
	Bacon		18.9%	37–200	
	Ham		28.9%	40–70	
	Sausages		12%	10–920	
	'Kulen' (specially prepared sausages)		13.3%	10–460	

Table 3. Occurrence of ochratoxin A in swine blood at slaughter

Country	Year	Positive samples/ total no.	Content (ng/ml)	Reference
Canada	1986	813/1006	< 10–229	Frohlich *et al.* (1991)
Germany	1982–83	93/191	0.1–67	Bauer & Gareis (1987)
Poland	1983–84	335/894	Mean, 2.03	Goliński *et al.* (1991)
Sweden	1982–83	26/122	2–62	Hult *et al.* (1984)
Yugoslavia	1979	16.6%	36–77	Pepeljnjak *et al.* (1982)

Ochratoxin A has been found in blood from individuals in several European countries (Creppy *et al.*, 1991; Hald, 1991), at levels ranging, e.g., in Sweden from 0.3 to 6 ng/ml (Breitholz *et al.*, 1991). In inhabitants of the Balkans, concentrations of up to 100 ng/ml have been found (Fuchs *et al.*, 1991; Petkova-Bocharova & Castegnaro, 1991). Concentrations found in human blood and milk are presented in Table 4. The limits of detection in these studies vary, so that the proportion of positive samples may not be a good indication of relative exposures.

1.4 Regulations and guidelines

In 1990, existing or proposed regulations for ochratoxin A were available in Brazil, Czechoslovakia, Denmark, France, Greece, Hungary, Israel, the Netherlands, Romania, Sweden and the United Kingdom, the levels ranging from 1 to 50 μg/kg in food and from 100 to 1000 μg/kg in animal feed. In Denmark, the levels of ochratoxin A in pork kidney are used to determine if the animal (25 μg/kg) or certain organs (10 μg/kg) can be used as food (van Egmond, 1991b).

Table 4. Occurrence of ochratoxin A in human blood and milk

Country	Year	Positive samples/ total no.	Content (ng/ml)[a]	Reference
Bulgaria	1984–90	82/576	1–35	Petkova-Bocharova & Castegnaro (1991)
Canada	1988	63/159	0.27–35.3	Frohlich *et al.* (1991)
Denmark	1986–88	78/144	0.1–13.2	Hald (1991)
France	NR	~ 18%	0.1–6	Creppy *et al.* (1991)
Germany	1977–85	173/306	0.1–14.4	Bauer & Gareis (1987)
Germany	NR	4/36	(0.003) 0.017–0.03 (milk)	Gareis *et al.* (1988)
Italy	1989–90	9/50	(1.2) 1.7–6.6 (milk)	Micco *et al.* (1991)
Poland		9/216	1.3–4.8	Goliński & Grabarkiewicz-Szczęsna (1985)
Poland	1983–84	77/1065	Mean, 0.10	Goliński *et al.* (1991)
Sweden	1989	38/297	0.3–6.7	Breitholtz *et al.* (1991)
Yugoslavia	1980	42/639	1–40	Hult *et al.* (1982)
Yugoslavia	1981–89	240/17175	5–100	Fuchs *et al.* (1991)

NR, not reported
[a]Lower end of range or value in parentheses is the detection limit.

In 1990, a WHO/FAO Joint Expert Committee on Food Additives reviewed the literature on ochratoxin A and recommended a provisional tolerable weekly intake of 112 ng/kg bw (WHO, 1991).

2. Studies of Cancer in Humans

During the 1950s, a fatal chronic renal disease was identified in certain geographically limited areas of Bulgaria, Yugoslavia and Romania (Tanchev & Dorossiev, 1991). In 1964, the disease was recognized as a new nosological entity and was referred to as Balkan endemic nephropathy (BEN). Studies in experimental animals have shown a relationship between exposure to ochratoxin A and a porcine nephropathy that has striking similarity to BEN (Krogh, 1974). The geographical distribution of BEN, in turn, is linked with areas of high incidence of urinary tract tumours. The epidemiology of BEN is therefore considered below.

2.1 Case reports

In Bulgaria, Petrinska-Venkovska (1960) reported 16 cases of urinary tract tumours among 33 autopsied patients with BEN (48%); Tanchev *et al.* (1970) reported such tumours among 6–7% of BEN patients; in 1968, urinary tract tumours represented 16% of tumours in the endemic area. Other reports appeared subsequently (Petković *et al.*, 1974; Čeović *et al.*, 1976).

2.2 Descriptive studies

The occurrence of BEN and of cancer in the populations of 27 villages in Vratza district, Bulgaria, an endemic area for BEN, during the period 1965–74 has been considered in several publications (Chernozemsky *et al.*, 1977; Stojanov *et al.*, 1977, 1978). The villages were divided into two groups: 15 villages with a high incidence of BEN (population, 147 321) and 12 villages with a low incidence (population, 120 687). Age-adjusted incidence rates for BEN in the high-incidence villages were reported to be 506 and 315 per 100 000 in women and men, respectively; and the rates for urinary system (kidney and urinary tract) tumours, 104 and 89 per 100 000, respectively. In the same villages, BEN accounted for about 30% of total mortality in women and for over 40% in men, and urinary tract tumours were the most frequent neoplasms recorded, with incidences far higher than those in other parts of Bulgaria and in Europe. A ratio of 28.3 (95% confidence interval [CI], 16.5–47.4) was computed by comparing the urinary tract tumour incidence among the patients with BEN with that in the population of the low-incidence villages. The rate ratio was particularly high for tumours of the renal pelvis and ureter (88.9; 50.0–143.2) among patients with BEN. People in the high-incidence villages not affected by BEN also had increased rates of urinary system tumours in general (4.3; 1.6–11.3) and of tumours of the renal pelvis and ureter in particular (6.7; 2.3–16.4). [The Working Group noted that the statistical analysis was not adequately described and that bias due to better tumour ascertainment among cases of BEN could not be ruled out.]

A survey of the geographical distribution of BEN and of the incidence of tumours of the urinary system was carried out in central Serbia by Radovanović and Krajinović (1979) during the period 1970–74. The population of the region was divided into two groups, each of approximately 2.6 million people, on the basis of the topographical distribution of BEN. The incidence of urinary system tumours was determined in each of the study groups from cancer registry data. The annual incidence of cancer of the renal pelvis and ureter overall was 39 per 100 000 in counties affected by BEN and 15 per 100 000 in the non-endemic counties, on the basis of 52 and 20 tumour cases, respectively. The incidence of tumours of the renal parenchyma was slightly higher in the endemic than the non-endemic area, but no difference in the incidence of urinary bladder cancer was seen between the two. It was indicated, however, that distinction of the two subpopulations according to endemic area was very crude. This may have led to an underestimate of the true differences in the incidences of urinary system tumours.

Using records of cases of urinary tract tumour collected over a period of 16 years (1974–89) at the medical centre of the County of Slavonski Brod in Croatia, Šoštarić and Vukelić (1991) studied the distribution of these tumours in the areas of the County that were endemic for BEN (population, 10 094) and in the rest of the County (96 306). A total of 67 tumours were recorded in the endemic areas (estimated cumulative incidence, 0.664%) and 126 in the non-endemic area (0.131%). The difference in the recorded relative number of cases was highest for tumours of the renal pelvis (0.287 *versus* 0.021%) and ureter (0.089 *versus* 0.013%) and only moderate for bladder cancer (0.228 *versus* 0.089%). In general, more cases were seen among women than among men in the endemic area. Tumours of the renal parenchyma were not mentioned in this survey.

In a study carried out in Bulgaria, Petkova-Bocharova and Castegnaro (1985) examined contamination by ochratoxin A of 65 samples of beans, maize or wheat flour from households in an area endemic for BEN and with a high incidence of urinary system tumours and in 65 samples from households in non-endemic areas. None of the samples was visibly mouldy. Samples from high-risk areas were collected from families in which cases of BEN and/or urinary tract tumours had been diagnosed ('affected' households), while samples from non-endemic areas were taken at random. All samples of home-produced beans and maize were taken during February and March 1982 from the 1981 harvest; wheat flour samples were purchased from local shops, which were supplied from central state stocks. Although there was no significant difference between endemic and non-endemic areas in the mean values of ochratoxin A in contaminated samples of beans (range, 25–27 μg/kg in endemic area, 25–50 μg/kg in non-endemic area) and maize (25–35 and 10–25 μg/kg, respectively), a larger proportion of samples from the endemic area were contaminated: (16.7% of beans (95% CI, 4.8–33.9) and 27.3% of maize (11.2–47.4) in endemic areas, and 7.1% of beans and 9.0% of maize in non-endemic areas). None of the samples of wheat flour analysed contained measurable amounts of ochratoxin A.

In an extension of this survey, Petkova-Bocharova *et al.* (1991) collected 524 samples of home-produced, home-stored beans and maize from the harvests of 1984–86 and 1989–90. Of these, 298 were taken from 'affected' and 'non-affected' households in the endemic areas of Bulgaria and 226 from non-affected households in non-endemic areas. Overall, significantly more samples from endemic areas than from control areas were contaminated with ochratoxin A [54 *versus* 12%].

Petkova-Bocharova *et al.* (1988) reported a study in Bulgaria of the association between BEN and/or urinary system tumours and ochratoxin A content in blood samples taken from 187 subjects living in endemic villages and 125 individuals in non-endemic villages. Among 61 patients with BEN and/or urinary system tumours, 14.8% had levels of 1–2 ng/ml and 11.5% had more than 2 ng/ml ochratoxin A in their blood. This proportion was significantly higher than that in a control group of 63 healthy individuals from unaffected families in the endemic villages (7.9 and 3.2%, respectively). The percentage of positive blood samples in the control group was similar to that measured among a random sample of healthy individuals from non-endemic villages (6.2 and 1.5% respectively). Intermediate proportions of positive blood samples were found among healthy individuals from families of patients with either endemic nephropathy and/or a urinary system tumour (9.5 and 6.3%, respectively). [The Working Group noted that no attempt was made by the authors to present separate results for the subgroup of urinary system tumours].

In an extension of this study, Petkova-Bocharova and Castegnaro (1991) collected blood samples from 576 people living inside and outside the endemic areas in Bulgaria during 1984, 1986, 1989 and 1990. Overall, a significantly larger proportion of the blood samples from 105 patients with urinary tract tumours and/or BEN [26.7%] contained ochratoxin A than those from 116 healthy people living in villages in the endemic area [12.1%], or from 119 healthy people from non-affected villages in the endemic area [10.9%] or from 125 healthy people living in non-endemic areas of Bulgaria [7.2%]; however, the proportion among the patients was not significantly higher than that among 111 healthy relatives of patients with urinary tract tumours and/or BEN living in affected villages [16.2%].

No analytical epidemiological study was available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

A group of 10 male ddY mice (average weight, 26 g) received a diet containing 40 mg/kg diet ochratoxin A [purity unspecified] for 44 weeks. A group of 10 untreated controls were fed the basal diet. All survivors were killed 49 weeks after the start of treatment. A significant increase in the incidence of hepatocellular tumours (designated as well-differentiated trabecular adenomas) was seen in 5/9 treated mice and in 0/10 controls; hyperplastic liver nodules were found in 1/9 treated mice and in 2/10 controls. A significant increase in the incidence of renal-cell tumours (nine renal cystadenomas and two solid renal-cell tumours) was found in 9/9 treated mice, with 0/10 controls (Kanisawa & Suzuki, 1978). [The Working Group noted the small size of the experimental groups.]

Groups of 16 male ddY mice [age unspecified] received a diet containing 50 mg/kg diet ochratoxin A for 0, 5, 10, 15, 20, 25 and 30 weeks, followed by a basal diet for 40 weeks. The experiment was terminated at 70 weeks. The estimated mean cumulative doses of ochratoxin A were 0, 11, 21, 30, 33, 40 and 50 mg/mouse, respectively. Hepatomas were seen in animals fed ochratoxin A in the diet for 20 weeks or more: control 0/15; 20 weeks, 2/14; 25 weeks, 5/15; and 30 weeks, 6/17. Renal-cell tumours [not further specified] were seen in mice fed ochratoxin A in the diet for 15 weeks or more: control, 0/15; 15 weeks, 3/15; 20 weeks, 1/14; 25 weeks, 2/15; and 30 weeks, 4/17. Lung tumours [unspecified] were found in all groups, but the incidence was not related to exposure level (Kanisawa, 1984).

Two groups of 20 male DDD mice, six weeks of age, received diets containing ochratoxin A at 0 or 25 mg/kg for 70 weeks. Twenty mice exposed to ochratoxin A had renal-cell tumours, designated as cystadenomas (20 tumours) and solid renal-cell tumours (six tumours); no such tumour occurred in controls. The incidence of hyperplastic hepatic nodules was significantly increased: 16/20 in treated mice *versus* 4/17 in controls; as was that of hepatomas (exhibiting the trabecular structure): 8/20 in treated animals *versus* 1/17 in controls (Kanisawa, 1984).

Groups of 50 male and 50 female B6C3F$_1$ mice, three weeks old, received diets containing crude ochratoxin A at 0, 1 or 40 mg/kg for two years. The crude ochratoxin preparation contained 84% ochratoxin A, 7% ochratoxin B and 9% benzene. Both male and female mice in the high-dose group had terminal body weights that were about 40% lower than those of controls, but survival was not decreased after exposure to ochratoxin. The incidence of renal-cell adenomas was significantly increased (26/49) in high-dose male mice that survived 21 months, as none were found in the low-dose and control groups. A significant increase in the incidence of renal-cell carcinomas (14/49) was also found in high-dose male mice that survived at least 20 months, with none in the low-dose or control groups. Nine of the 26 mice with renal-cell adenomas also had renal-cell carcinomas. No renal tumour was observed in female mice. The incidence of hepatocellular tumours was

increased in animals of each sex: males—adenomas: 1/50, 5/47 and 6/50 [p = 0.03, Cochran-Armitage test]; carcinomas: 0/50, 3/47 and 4/50 [p = 0.03, Cochran-Armitage test]; females—adenomas: 0/47, 1/45 and 2/49; carcinomas: 0/47, 1/45 and 5/49 [p = 0.007, Cochran-Armitage test] in control, low-dose and high-dose animals, respectively. The incidences of neoplasms in other tissues were not significantly increased in treated animals compared to controls (Bendele *et al.*, 1985a).

3.1.2 *Rat*

Groups of 80 male and 80 female Fischer 344 rats, 8–10 weeks old, received 0, 21, 70 or 210 μg/kg bw (maximum tolerated dose) ochratoxin A (98% pure) in 5 ml/kg maize oil by gavage on five days per week for 103 weeks. All survivors were killed 104–105 weeks after initiation of exposure. Mean body weights of high-dose rats were generally 4–7% lower than those of vehicle controls. The survival rates of treated and vehicle control female rats were comparable, but the survival of all groups of dosed male rats was decreased. Renal-cell tumours were increased in a dose-related manner in animals of each sex: males—renal-cell adenomas: 1/50, 1/51, 6/51 and 10/50; renal-cell adenocarcinomas: 0/50, 0/51, 16/51 and 30/50; females—renal-cell adenomas: 0/50, 0/51, 1/50 and 5/50; renal-cell adenocarcinomas 0/50, 0/51, 1/50 and 3/50, in control, low-dose, mid-dose and high-dose animals, respectively. Metastasis of the renal-cell tumours occurred in 17 males and one female (US National Toxicology Program, 1989).

3.2 Administration with known carcinogens

Rat

In a medium-term carcinogenicity study, groups of 20 male Fischer 344 rats weighing about 150 g, were kept for one week on a basal diet and were then given ochratoxin A [purity unspecified] at 0 or 50 mg/kg diet for six weeks; one week after initiation of the study, the rats were given a partial hepatectomy, and during weeks 7–9 the animals received 200 mg/kg diet *N*-2-fluorenylacetamide [purity unspecified]. The rats also received carbon tetrachloride (1 ml/kg bw) at the end of week eight. The animals were killed 10 weeks after the start of the experiment. In 14 rats, 0.63 ± 0.69 hepatic hyperplastic nodules/cm^2 were observed (p < 0.02), compared to an average of 0.11 ± 0.22/cm^2 in the 20 rats that received no ochratoxin A. In the same study, groups of 20 male rats were fed the ochratoxin A diets during weeks 3–9 and received the *N*-2-fluorenylacetamide during the first two weeks and the carbon tetrachloride at week 1; the partial hepatectomy was done at week 4. Sixteen rats had an average of 0.82 ± 0.54 hepatic hyperplastic nodules/cm^2 (p < 0.05) compared with an average of 0.36 ± 0.43/cm^2 in 20 control rats that received similar treatment without exposure to ochratoxin A (Imaida *et al.*, 1982).

4. Other Relevant Data

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Ochratoxin A was injected into the lumina at various sites of the gastrointestinal tract in rats; the highest concentration in portal blood was observed after injection into the proximal jejunum (Kumagai & Aibara, 1982). Ruminants do not absorb much ochratoxin A when the concentration in the feed is low because it is hydrolysed rapidly by their ruminal flora (Galtier & Alvinerie, 1976; Hult *et al.*, 1976); however, ochratoxin A has been detected in kidney, milk and urine of cows given high doses of ochratoxin A (Ribelin *et al.*, 1978; Shreeve *et al.*, 1979).

In human plasma, ochratoxin A binds *in vitro* to certain, as yet unidentified macromolecules (relative molecular mass, 20 000) with extremely high affinity, the association constant being 2.3×10^{10}/mol (Stojković *et al.*, 1984). Saturation of these macromolecules occurs at low levels of ochratoxin A: 10–20 ng/ml of serum (Hult & Fuchs, 1986). Ochratoxin A binds to serum albumin in plasma of different animal species (Chang & Chu, 1977; Galtier, 1974), but at relatively low affinity (up to 10^6/mol) *in vivo* and *in vitro* (Chu, 1971). Studies of the binding of ochratoxin A to human plasma proteins *in vitro* showed that only 0.02% of the total concentration of 10^{-9}–10^{-6}M was unbound; 2% of ochratoxin B, the dechlorinated form of ochratoxin A, was unbound. In monkeys, 0.08% of the toxin remained in the free form (Hagelberg *et al.*, 1989).

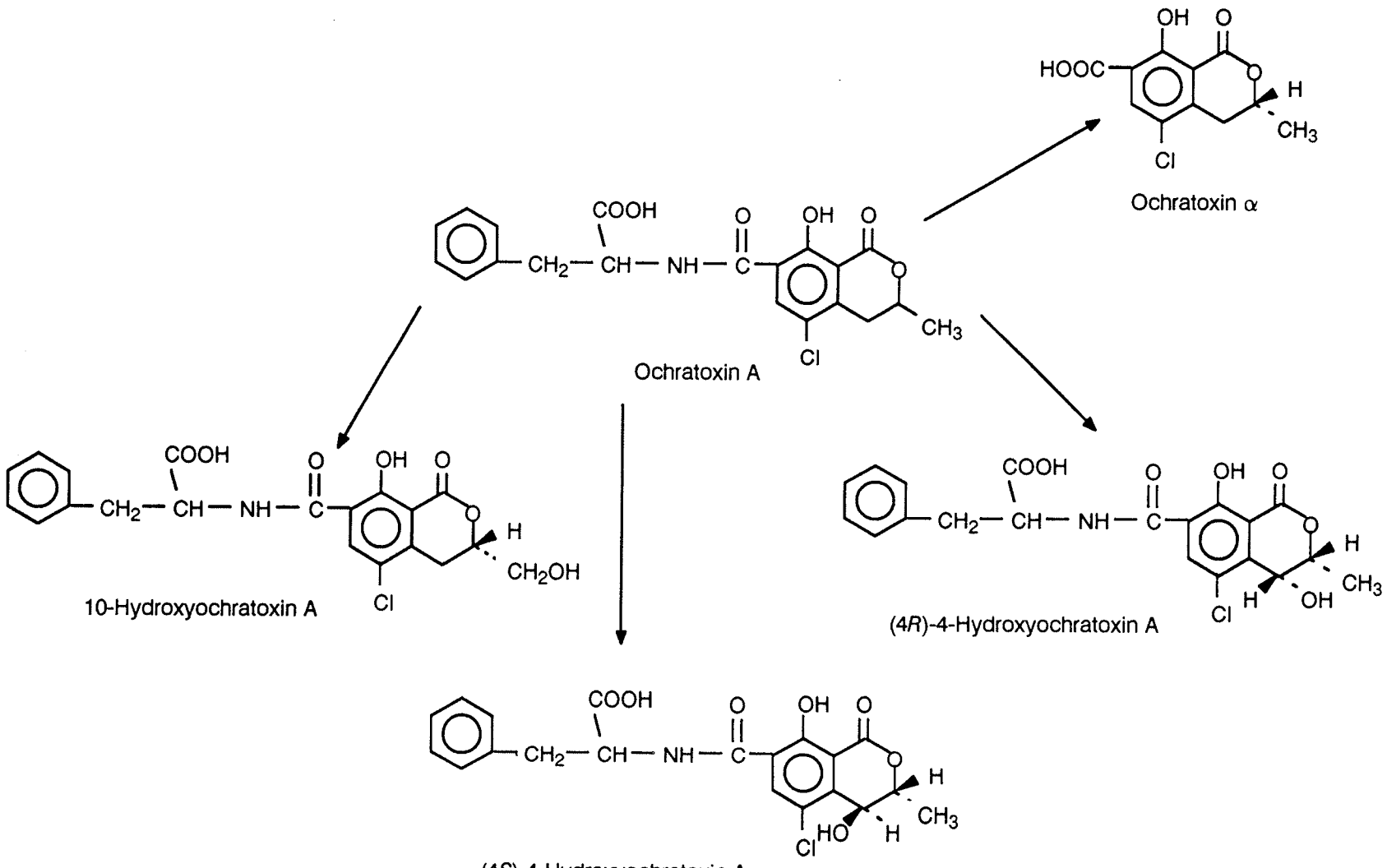
In rats given ochratoxin A by gavage at levels corresponding to the parts per million range found in contaminated foodstuffs (~ 4 ppm), the compound was found after 24 h in the following tissues (in decreasing order of concentration): fat, small intestine, testis, kidney, liver, lung, heart, spleen, stomach, muscle and brain. After 48 h, the concentrations had decreased in all tissues except fat, where increased concentrations were found (Kane *et al.*, 1986a). Intravenous administration of 2.5 mg/kg bw to rats resulted after 48 h in the following distribution (in decreasing order of concentration): thyroid, skin, parotid gland, lung, submaxillary gland, heart, seminal vesicle, kidney, large intestine, testis, liver and lachrymal gland (Galtier *et al.*, 1979a). A similar distribution pattern of labelled ochratoxin A was found in mice and rats (Fuchs *et al.*, 1988b; Breitholtz-Emanuelsson *et al.*, 1992).

Secondary distribution peaks of radiolabel in the intestinal contents and serum of rats and mice after oral or intramuscular administration of ^{3}H-ochratoxin A are a consequence of enterohepatic circulation, since the biliary excretion of ochratoxin A is very efficient (Fuchs *et al.*, 1988a; Roth *et al.*, 1988).

The apparent plasma elimination half-time of ochratoxin A after oral administration at 50 µg/kg bw varied from 0.68 h in fish to 120 h in rats and 510 h in monkeys (Hagelberg *et al.*, 1989).

When ochratoxin A was incubated with rat, rabbit, pig and human liver microsomes, (4*R*)- and (4*S*)-4-hydroxyochratoxin A were formed (see Fig. 1), the ratio between the two epimers depending on the animal species (Størmer *et al.*, 1981, 1983). The transformations are cytochrome P450-dependent (Størmer *et al.*, 1981, 1983; Oster *et al.*, 1991). Thus, liver and kidney microsomes from female dark Agouti rats (poor metabolizers of debrisoquine) had three to four times less ochratoxin A 4-hydroxylase activity than liver and kidney microsomes from female Lewis rats (extensive metabolizers of debrisoquine). The ochratoxin A hydroxylase was highly inducible by phenobarbital and 3-methylcholanthrene (Hietanen

Fig. 1. Ochratoxin A and its metabolites



From Støren *et al.* (1982); Størmer *et al.* (1983)

et al., 1986). When primary rat hepatocytes were incubated at 37 °C with ochratoxin A, (4*R*)-4-hydroxyochratoxin A was detected in the incubation medium and in the cells, but only small amounts of (4*S*)-4-hydroxyochratoxin A were found (Hansen *et al.*, 1982). 10-Hydroxyochratoxin A was formed from ochratoxin A with a rabbit liver microsomal system (Størmer *et al.*, 1983). The presence of 4-hydroxyochratoxin A was observed in intestine, liver and bile of mice given ochratoxin A by gavage. Up to 68% of ochratoxin A in bile was in a conjugated form after 24 h (Roth *et al.*, 1988). Ochratoxin A is also hydrolysed to the non-toxic ochratoxin α (Chakor *et al.*, 1988) at various sites, particularly by homogenates of duodenal, ileal, pancreatic (Suzuki *et al.*, 1977) and caecal tissues (Galtier, 1978).

Both biliary excretion and glomerular filtration are important in the plasma clearance of ochratoxin A, but tubular secretion might also be active (Stein *et al.*, 1985); the relative contribution of each excretory route varies with species (Kuiper-Goodman & Scott, 1989). In albino rats, regardless of the route of administration, 6% of a given dose was excreted in urine as ochratoxin A, 1–1.5% as (4*R*)-4-hydroxyochratoxin A and 25–27% as ochratoxin α (Støren *et al.*, 1982).

The amount of 4-hydroxyochratoxin A found in urine depends on the rat strain: the ratio of ochratoxin A:4-hydroxyochratoxin A is two to five times higher in dark Agouti female rats than Lewis rats (Castegnaro *et al.*, 1989).

4.2 Toxic effects

4.2.1 *Humans*

Krogh (1974) suggested that excessive exposure to ochratoxin A plays a role in the development of BEN; however, the causal role of other nephrotoxic agents cannot be excluded (for review, see Castegnaro *et al.*, 1991b). Evidence for a causal relationship between exposure to ochratoxin A and BEN derives from (i) similarities in the morphological and functional renal impairments induced by BEN and those induced by ochratoxin A in animals, and (ii) the finding that food from endemic areas is more heavily contaminated with ochratoxin A than food from disease-free areas (Pavlović *et al.*, 1979; Pleština *et al.*, 1990; Petkova-Bocherova *et al.*, 1991). BEN is a bilateral, non-inflammatory, chronic nephropathy, in which the kidneys are extremely reduced in size and weight and show diffuse cortical fibrosis extending into the corticomedullary junction, hyalinized glomeruli and severely degenerated tubules (Vukelić *et al.*, 1991). The clinical picture is characterized by progressive hypercreatininaemia, hyperuraemia and normo- or slightly hypochromic anaemia, but blood pressure is generally not elevated (Radovanović, 1991; Tanchev & Dorossiev, 1991).

4.2.2 *Experimental systems*

The toxicokinetic parameters of ochratoxin A vary considerably with dose and between species (for review, see Galtier, 1991). Species also vary in their susceptibility to acute poisoning by ochratoxin A, with oral LD_{50} values ranging from 0.2 to 50 mg/kg bw. Dogs and pigs are the most sensitive species (0.2 and 1 mg/kg bw, respectively) (for review, see Frank *et al.*, 1990). Simultaneous oral administration of phenylalanine either prevents death

(Creppy *et al.*, 1980) or raises the oral LD_{50} in mice (Moroi *et al.*, 1985). Pretreatment of mice with phenobarbital or 3-methylcholanthrene also raises the LD_{50} (Moroi *et al.*, 1985; Chakor *et al.*, 1988), while treatment with piperonyl butoxide lowers it (Chakor *et al.*, 1988). Synergistic effects of ochratoxin A with citrinin and with penicillic acid on the LD_{50} were seen in mice following intraperitoneal injection (Sansing *et al.*, 1976).

Ochratoxin A has a nephrotoxic effect on all mammalian species tested. The nephropathy is characterized by polyuria, glucosuria, proteinuria, enzymuria, decreased osmolarity of the urine, impaired tubular function and histopathological changes in the proximal convoluted tubule (for review, see Delacruz & Bach, 1990). Dogs and pigs are very sensitive to the nephrotoxic effects of ochratoxin A following oral exposure (Kuiper-Goodman & Scott, 1989). In pigs, dietary levels as low as 0.2 mg/kg (equivalent to approximately 8 μg/kg bw per day) for 90 days caused a reduction in the activity of several renal enzymes and decreased kidney function (Krogh & Elling, 1977; Elling, 1979, 1983; Elling *et al.*, 1985; Meisner & Krogh, 1986). The presence of ochratoxin A in feed is believed to be the most important cause of spontaneous mycotoxic porcine (Krogh, 1978) and poultry nephropathy (Elling *et al.*, 1975).

In a 90-day study, rats given 2 mg/kg ochratoxin A in the diet (equivalent to 145 μg/kg bw per day) showed increased levels of urinary enzymes originating from the brush border of the proximal convoluted tubules (Kane *et al.*, 1986b).

In chronic toxicity studies, progressive nephropathy but no renal failure was seen in female pigs fed diets containing 1 mg/kg ochratoxin A (equivalent to approximately 41 μg/kg bw per day) for two years (Elling, 1979). In rats, the no-observed-effect level for ability to concentrate urine in a 6–12-month gavage study was 70 μg/kg bw per day for males and 21 μg/kg bw for females (Kuiper-Goodman & Scott, 1989; US National Toxicology Program, 1989).

Ochratoxin A induced haematological changes in rats and mice (Galtier *et al.*, 1979b; Gupta *et al.*, 1983), but the doses used were relatively high (4–5 mg/kg bw over 4–10 days in rats).

Several studies have shown that ochratoxin A affects structural components of the immune system in several species (for reviews, see Kuiper-Goodman & Scott, 1989; Frank *et al.*, 1990). Chickens fed 2 mg/kg ochratoxin A in the diet for 20 days showed depression of immunoglobulin (Ig) G, IgA and IgM in lymphoid tissues and serum (Dwivedi & Burns, 1984); complement activity was slightly affected when ochratoxin A was fed at 2 mg/kg in the diet for five to six weeks (Campbell *et al.*, 1983). Very low levels of ochratoxin A (one intraperitoneal injection of 1 μg/kg bw) suppressed both the IgG and the IgM response in BALB/c mice to a single injection of sheep red blood cells in the standard plaque counting assay for estimation of antibody-producing spleen lymphocytes. (4R)-4-Hydroxyochratoxin A is as effective as ochratoxin A in immunosuppression, whereas ochratoxin α has no effect. Phenylalanine can prevent the effect (Haubeck *et al.*, 1981; Creppy *et al.*, 1983a).

The biochemistry and molecular aspects of the action of ochratoxin A in prokaryotes and eukaryotes have been reviewed (Dirheimer & Creppy, 1991). On the basis of work in prokaryotes (Konrad & Röschenthaler, 1977; Bunge *et al.*, 1978), eukaryotic microorganisms (Creppy *et al.*, 1979a), mammalian cell cultures (Creppy *et al.*, 1979b, 1983b) and

experimental animals *in vivo* (Creppy *et al.*, 1984), the initial action of ochratoxin A has been shown to be inhibition of protein synthesis by competition with phenylalanine in the phenylalanyl-tRNA synthetase-catalysed reaction. This inhibition can be reversed by an increased phenylalanine concentration both *in vitro* and *in vivo*. The degree of inhibition of protein synthesis is greater in Madin Darby canine kidney (MDCK) cells than in hepatoma cells (Creppy *et al.*, 1986). It also varies *in vivo* within different organs, with 26% inhibition in the liver, 68% in the kidney and 75% in the spleen 5 h after intraperitoneal injection of 1 mg/kg bw ochratoxin A to mice (Creppy *et al.*, 1984). (4R)-4-Hydroxyochratoxin A is as effective as ochratoxin A in inhibiting protein synthesis, whereas ochratoxin α has no effect (Creppy *et al.*, 1983b). Ochratoxin A also inhibits phenylalanine hydroxylase both *in vitro* and *in vivo* (Creppy *et al.*, 1990).

Synthetic analogues of ochratoxin A in which the phenylalanine moiety was replaced by other amino acids also inhibited protein synthesis *in vitro* and *in vivo* (Creppy *et al.*, 1983c).

Ochratoxin A has been reported to decrease mitochondrial oxidative phosphorylation and respiration by impairing mitochondrial transport carriers located in the inner membrane (Moore & Truelove, 1970; Meisner & Chan, 1974; Wei *et al.*, 1985). Moreover, Elling (1979) suggested that ochratoxin A induces a reduction in the activity of enzymes in the tricarboxylic acid cycle. These suggestions were corroborated by Jung and Endou (1989), who showed in isolated S_2 segments of the nephron of rats that ATP-dependent reactions were significantly inhibited by incubation with ochratoxin A at a concentration of 10^{-8}M, the ID_{50} being reached with a concentration of 10^{-6}M.

Oral administration of ochratoxin A (2 mg/kg bw for two days) decreased the level of cytosolic phosphoenolpyruvate carboxykinase in rat kidneys. The decrease correlated well with that in renal gluconeogenesis (Meisner & Selanik, 1979; Meisner & Meisner, 1981). Krogh *et al.* (1988) showed that the level of cytosolic phosphoenolpyruvate carboxykinase was also decreased in renal cytosol of pigs fed low concentrations of ochratoxin A in capsules (corresponding to 0.2 and 1.00 mg/kg diet) for one to five weeks.

Rahimtula *et al.* (1988) found that addition of ochratoxin A to rat liver and kidney microsomes greatly enhanced the rate of NADPH-dependent lipid peroxidation.

4.3 Reproductive and developmental toxicity

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Ochratoxin A causes embryofetal lethality and induces gross structural malformations in mice, rats and hamsters.

After a single intraperitoneal injection of 5 mg/kg bw ochratoxin A on day 11 or 13 of pregnancy to ICR mice, concentrations of the toxin reached highest levels in maternal serum and tissues within 2 h. The half-times in serum were 29 h on day 11 and 24 h on day 13. Concentrations in the embryos increased up to 48 h and 30 h after injection on days 11 and 13, respectively, and reached maximal levels of 360 and 492 ng/g wet weight, respectively.

The peak incidence of pyknotic cells in the embryonic telencephalon coincided with the peak concentration of the toxin in the embryo (Fukui *et al.*, 1987).

A single intraperitoneal injection of 5 mg/kg bw ochratoxin A to pregnant SAF/ICR mice on one of days 7–12 of gestation increased the frequencies of prenatal mortality and fetal malformations and decreased fetal weight. The largest number of malformations was seen in fetuses of animals treated on day 8 of gestation (35% dead or resorbed; 58% grossly malformed; 84% with skeletal malformations) (Hayes *et al.*, 1974).

A single intraperitoneal injection of 2, 3 or 4 mg/kg bw ochratoxin A to CD-1 or Jcl:ICR mice induced craniofacial malformations when given on day 7 or 8, but not when given on day 10 of gestation. Typical findings were exencephaly, median facial clefts, anophthalmia, microphthalmia and other ocular abnormalities (Hood *et al.*, 1978; Shirai *et al.*, 1984; Ohshika *et al.*, 1988).

Hoshino *et al.* (1988) injected mice intraperitoneally with either 2 or 3 mg/kg bw ochratoxin A on day 10 of gestation and found significant decreases in brain weight, brain size and cerebral cortical thickness in offspring six weeks after birth.

Cerebral necrosis occurred in most fetuses of CD-1 and ICR mice treated orally or intraperitoneally with 3–5 mg/kg bw on days 15–17 of gestation (Szczech & Hood, 1981). Doses of 1.25 and 2.25 mg/kg bw ochratoxin A given by intraperitoneal injection on days 15, 16 and 17 to ICR mice decreased body weight and induced developmental delay in offspring, as indicated by the results of behavioural tests. The effects were more pronounced in female offspring. No compound-related brain alteration was found by histological examination under these conditions (Poppe *et al.*, 1983).

The teratogenic effect of ochratoxin A in CBA mice treated orally was decreased when zearalenone was given concomitantly on day 9 of gestation (Arora & Frölén, 1981; Arora *et al.*, 1981, 1983). Maternal protein deprivation was associated with an increased incidence of malformed fetuses in ochratoxin A-treated CD-1 mice (Singh & Hood, 1985).

In several studies, pregnant Wistar and Sprague-Dawley rats were treated with ochratoxin A on various days during the period of organogenesis. Single oral doses of 6.25, 12.5 or 25 mg/kg bw on day 10 of gestation induced high resorption rates (25, 82 and 78%, respectively) in Sprague-Dawley rats (Still *et al.*, 1971). An abnormal proportion of haemorrhagic fetuses, significant decreases in fetal body weight, an increased resorption rate and decreased litter size were noted after intraperitoneal or oral doses of 4 or 5 mg/kg bw to Wistar rats (Moré & Galtier, 1974, 1975; Moré *et al.* 1978). Furthermore, multiple oral doses of 0.75 mg/kg bw on days 6–15 were embryotoxic, inducing various gross, visceral and skeletal anomalies (Brown *et al.*, 1976).

The effects of single subcutaneous injections of 0.5–5.0 mg/kg bw on one of days 4–10 of gestation were studied in rats. The minimal teratogenic dose was 1.75 mg/kg bw, which caused decreased fetal weight and various fetal malformations; higher doses caused fetal resorption. Ochratoxin A had the greatest effect when given on day 5, 6 or 7 of gestation (Mayura *et al.*, 1982). In a rat whole-embryo culture system, concentrations of $\geq$ 75 mg/l ochratoxin A in the medium impaired the development of 10-day-old embryos (Mayura *et al.*, 1989).

Several combination experiments have been performed to study the teratogenic action of ochratoxin A in rats more closely. An increased prevalence of gross and skeletal malformations was seen in Sprague-Dawley rats maintained on a 10% protein diet (normal, 27%) after treatment with 1.75 mg/kg bw ochratoxin A on day 6 of gestation (Mayura *et al.*, 1983). Simultaneous treatment with a sub-threshold teratogenic dose of 1 mg/kg bw ochratoxin A and 30 mg/kg bw of the mycotoxin citrinin on days 5, 6, 7, 8, 10, 11 or 14 of gestation was lethal to 22–40% of treated females and resulted in a significant increase in the frequency of malformations (Mayura *et al.*, 1984a). The teratogenic action of a single subcutaneous injection of 1.75 mg/kg bw ochratoxin A on day 7 of gestation was enhanced in rats with surgically impaired renal function in comparison with sham-operated rats (Mayura *et al.*, 1984b). In contrast, phenylalanine given in combination with a single subcutaneous injection of 1.75 mg/kg bw ochratoxin A on day 7 of gestation partially inhibited its prenatal toxicity (Mayura *et al.*, 1984c).

Ochratoxin A also induced prenatal toxicity in golden hamsters after single intraperitoneal injections of 2.5–20 mg/kg bw on one of days 7–10 of gestation; days 8 and 9 were the most critical with regard to malformations. There was no skeletal malformation, but micrognathia, hydrocephalus, short tail, oligodactyly, syndactyly, cleft lip, micromalia and cardiac defects were observed. The fetal mortality rate was significantly increased in litters exposed to the highest dose on day 7, 8 or 9 (Hood *et al.*, 1976).

4.4 Genetic and related effects

4.4.1 *Humans*

No adequate data were available to the Working Group.

4.4.2 *Experimental systems* (see also Table 5 and Appendices 1 and 2)

The genotoxicity of ochratoxin A has been reviewed (Kuiper-Goodman & Scott, 1989; Dirheimer & Creppy, 1991). Ochratoxin A induced mixed responses in tests for DNA repair activity in *Escherichia coli*: it gave a positive result in one study but negative results in three others. It did not induce DNA damage in *Bacillus subtilis* and did not generally induce mutation in *Salmonella typhimurium*. Positive results were obtained in several strains of *S. typhimurium* incubated for 2 h with cell-free medium obtained from 24-h incubations of primary rat hepatocytes with 100 μM ochratoxin A. The frequency of mitotic crossing-over was not increased in yeast.

Ochratoxin A induced DNA single-strand breaks in cultured mouse and Chinese hamster cells, but not in rat fibroblasts. It slightly increased the frequency of unscheduled DNA synthesis in one study in rat and mouse primary hepatocytes *in vitro* but not in another study with rat hepatocytes. [The Working Group noted that the concentration range was lower in the latter study.] Gene mutations were not induced in mouse cells *in vitro*. Ochratoxin A weakly increased the frequency of sister chromatid exchange in the presence of an exogenous metabolic system in Chinese hamster ovary cells; no increase was seen in cultured human lymphocytes in the absence of exogenous metabolic activation.

DNA single-strand breaks were induced after treatment with ochratoxin A *in vivo* in mouse kidney, liver and spleen and in rat kidney and liver. Ochratoxin A also formed DNA

Table 5. Genetic and related effects of ochratoxins

Test system	Result		Dose (LED/HID)[a]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Ochratoxin A				
PRB, SOS spot test, *Escherichia coli* PQ37	–	–	0.0000	Auffray & Boutibonnes (1986)
PRB, SOS chromotest test, *Escherichia coli*	–	–	0.0000	Reiss (1986)
PRB, SOS chromotest test, *Escherichia coli* PQ37	–	–	100.0000	Krivobok *et al.* (1987)
PRB, SOS chromotest test, *Escherichia coli* PQ37	+	+[b]	800.0000	Malaveille *et al.* (1991)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	0	100 µg/plate	Ueno & Kubota (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5.0000	von Engel & von Milczewski (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.0000	Nagao *et al.* (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	150.0000	Wehner *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	100.0000	Bartsch *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	300.0000	Bendele *et al.* (1985b)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50.0000	Zeiger *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	50.0000	US National Toxicology Program (1989)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+[c]	40.0000	Hennig *et al.* (1991)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	–	500.0000	Würgler *et al.* (1991)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50.0000	Kuczuk *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	150.0000	Wehner *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	300.0000	Bendele *et al.* (1985b)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50.0000	Zeiger *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	50.0000	US National Toxicology Program (1989)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+[c]	40.0000	Hennig *et al.* (1991)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	150.0000	Wehner *et al.* (1978)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	300.0000	Bendele *et al.* (1985b)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–[c]	40.0000	Hennig *et al.* (1991)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	5.0000	von Engel & von Milczewski (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	50.0000	Kuczuk *et al.* (1978)

Table 5 (contd)

Test system	Result		Dose (LED/HID)[a]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	100.0000	Bartsch *et al.* (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	300.0000	Bendele *et al.* (1985b)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	+[c]	40.0000	Hennig *et al.* (1991)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5.0000	von Engel & von Milczewski (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.0000	Nagao *et al.* (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	150.0000	Wehner *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	300.0000	Bendele *et al.* (1985b)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50.0000	Zeiger *et al.* (1988)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	50.0000	US National Toxicology Program (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–[c]	40.0000	Hennig *et al.* (1991)
SAS, *Salmonella typhimurium* G46, reverse mutation	–	–	500.0000	Bendele *et al.* (1985b)
SAS, *Salmonella typhimurium* C3076, reverse mutation	–	–	500.0000	Bendele *et al.* (1985b)
SAS, *Salmonella typhimurium* D3052, reverse mutation	–	–	500.0000	Bendele *et al.* (1985b)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	50.0000	Zeiger *et al.* (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	50.0000	US National Toxicology Program (1989)
ECW, *Escherichia coli* WP2 *uvrA*$^-$, reverse mutation	–	–	1000 µg/plate	Bendele *et al.* (1985b)
EC2, *Escherichia coli* WP2, reverse mutation	–	–	1000 µg/plate	Bendele *et al.* (1985b)
SCH, *Saccharomyces cerevisiae* D-3, mitotic crossing over, *ade2* locus	–	–	100.0000	Kuczuk *et al.* (1978)
DIA, DNA single-strand breaks, BALB/c mouse spleen cells *in vitro*	+	0	10.0000	Creppy *et al.* (1985)
DIA, DNA single-strand breaks, Chinese hamster ovary cells *in vitro*	+	0	200.0000	Štětina & Votava (1986)
DIA, DNA single-strand breaks, AWRF rat fibroblasts *in vitro*	–	0	200.0000	Štětina & Votava (1986)
URP, Unscheduled DNA synthesis, ACI rat primary hepatocytes *in vitro*	+	0	0.4000	Mori *et al.* (1984)
URP, Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	0	0.0250	Bendele *et al.* (1985b)
UIA, Unscheduled DNA synthesis, C3H/HeN mouse primary hepatocytes *in vitro*	+	0	4.0000	Mori *et al.* (1984)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	12.5000	Bendele *et al.* (1985b)

Table 5 (contd)

Test system	Result		Dose (LED/HID)[a]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
GIA, Gene mutation, C3H mammary carcinoma cells, 8-aza^r *in vitro*	-	0	10.0000	Umeda *et al.* (1977)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	-	(+)	16.0000	US National Toxicology Program (1989)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	-	0	10.0000	Cooray (1984)
SHL, Sister chromatide exchange, human lymphocytes *in vitro*	0	+[c]	0.0400	Hennig *et al.* (1991)
BVD, Binding (covalent) to DNA, Swiss mouse kidney cells[d] *in vivo*	+		0.6 × 1 mg/kg p.o.	Pfohl-Leszkowicz *et al.* (1991)
BVD, Binding (covalent) to DNA, Swiss mouse liver cells[d] *in vivo*	+		0.6 × 1 mg/kg p.o	Pfohl-Leszkowicz *et al.* (1991)
BVD, Binding (covalent) to DNA, Swiss mouse spleen cells[d] *in vivo*	+		0.6 × 1 mg/kg p.o.	Pfohl-Leszkowicz *et al.* (1991)
DVA, DNA single-strand breaks, BALB/c mouse kidney cells *in vivo*	+		2.5 × 1 i.p.	Creppy *et al.* (1985)
DVA, DNA single-strand breaks, BALB/c mouse liver cells *in vivo*	+		2.5 × 1 i.p.	Creppy *et al.* (1985)
DVA, DNA single-strand breaks, BALB/c mouse spleen cells *in vivo*	+		2.5 × 1 i.p.	Creppy *et al.* (1985)
DVA, DNA single-strand breaks, Wistar rat kidney cells *in vivo*	+		0.2 × 1 p.o.	Kane *et al.* (1986a)
DVA, DNA single-strand breaks, Wistar rat liver cells *in vivo*	+		0.2 × 1 p.o.	Kane *et al.* (1986a)
SVA, Sister chromatid exchange, Chinese hamster bone marrow *in vivo*	-		400 × 1 p.o.	Bendele *et al.* (1985b)
Ochratoxin α				
PRB, SOS chromotest, *Escherichia coli* PQ37	-	-	400.0000	Malaveille *et al.* (1991)

+, positive; (+), weak positive; -, negative; 0, not tested

[a]In-vitro tests, μg/ml; in-vivo tests, mg/kg bw; 0.0000, dose not given

[b]Rat liver or kidney S9 mix decreased genotoxicity

[c]Conditioned medium of rat hepatocyte cultures treated with ochratoxin A

[d]^{32}P-Post-labelling

adducts in mouse kidney and to a lesser extent in liver and spleen. The incidence of sister chromatid exchange was not increased in the bone marrow of Chinese hamsters treated *in vivo*.

In a single study, ochratoxin α did not damage DNA.

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[1]

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.

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[1]For definition of the italicized terms, see Preamble, pp. 26–29.

Overall evaluation

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

6. References

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