GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

This volume of the *IARC Monographs* considers some traditional herbal medicines, including extracts from certain plants of the genera *Aristolochia, Rubia, Morinda* and *Senecio;* some mycotoxins, specifically aflatoxins and fumonisin B_1; and two industrial chemicals, naphthalene and styrene. Of these, the *Monographs* have previously evaluated several of the pyrrolizidine alkaloids that occur in certain species of *Senecio*, *Crotalaria* and other plant genera, including riddelliine (IARC, 1976, 1987); various mycotoxins, including the aflatoxins (IARC, 1993a) and the family of mycotoxins to which fumonisin B_1 belongs (IARC, 1993b); and styrene (IARC, 1994). These previous evaluations are summarized in Table 1.

Table 1. Previous *IARC Monographs* evaluations of substances considered[a]

Agent	Degree of evidence		Overall evaluation	Volume, year
	Human	Animal		
Riddelliine	ND	I	3	**10**, 1976; **S7**, 1987
Aflatoxins, naturally occurring mixtures of	S	S	1	**56**, 1993
Aflatoxin B_1	S	S		
Aflatoxin B_2		L		
Aflatoxin G_1		S		
Aflatoxin G_2		I		
Aflatoxin M_1	I	S	2B	**56**, 1993
Toxins derived from *Fusarium moniliforme* (now known as *F. verticillioides*)	I	S	2B	**56**, 1993
Fumonisin B_1		L		
Fumonisin B_2		I		
Fusarin C		L		
Styrene	I	L	2B[b]	**60**, 1994

[a] Abbreviations: ND, no data; I, inadequate; S7, Supplement 7 (IARC, 1987); S, sufficient; L, limited

[b] The evaluation was upgraded taking into consideration other relevant data on genetic and related effects.

Since these previous reviews, new data have become available, and these have been incorporated into the *Monographs* and considered in the evaluations. The existing Group 1 evaluation of naturally occurring aflatoxins was reaffirmed.

Traditional herbal medicines

Traditional herbal medicines encompass an extremely diverse group of preparations, and originate from many different cultures. Many herbal medicines have emerged from healing traditions around the world. Digitalis (from the dried leaf of *Digitalis purpurea* L.) and quinine (from the bark of the cinchona tree, *Cinchona pubescens* Vahl) are well-known examples of valuable therapeutic products of botanical origin. Some herbal products in current use in many parts of the world, such as ginseng (e.g., from *Panax ginseng* C.A. Mey) and valerian (e.g., from *Valeriana officinalis* L.), have long standing for their modest efficacy and few side-effects. Some, however, such as ephedra (e.g., from *Ephedra sinica* Stapf) have been imported from traditional healing systems and then used for indications (weight loss, athletic performance enhancement) never contemplated in the traditions from which they emerged.

Rather few data on possible carcinogenic hazards of any of these substances have been collected until recently. Previous *IARC Monographs* have reviewed a small number of food plants (cycad nuts, bracken fern) and some natural products that occur in these and other plants for which there were published data on carcinogenicity in experimental animals (Table 2). The only substance listed in Table 2 that has been used for medicinal purposes is dantron (1,8-dihydroxyanthraquinone), which was once widely used as a stimulant laxative. The naturally occurring glycoside derivatives of 1,8-dihydroxyanthraquinone are the pharmacologically active constituents of a herbal purgative (laxative) preparation, senna, which is obtained from the dried leaflets or seed pods of the subtropical shrubs, *Cassia (Senna) acutifolia* and *Cassia (Senna) angustifolia* (Brunton, 1996). The cathartic properties of senna have been known for centuries, and were already described in Arabic writings in the ninth century. No data were available to previous working groups on cancer risk in humans exposed to any of the substances in Table 2, except bracken fern. Several of these compounds, however, including dantron, are potent carcinogens in experimental animals.

It is clear from these examples that some natural products derived from plants are carcinogenic, including certain compounds that are present in, and may be the active ingredients of, some traditional herbal medicines. It is a reasonable inference that others may be also. Data relating to three categories of natural products used in herbal medicines are reviewed in separate sections of this volume.

The first section considers the *Aristolochia* species and some of their chemical constituents. Roots of plants of the genus *Aristolochia* have recently been imported from China and sold in Europe in powdered form, to be taken by mouth in capsules as an aid to body weight reduction. Nephrotoxicity and urothelial carcinomas have occurred in individuals who consumed these products. Carcinogenic risks associated with these

Table 2. Previous *IARC Monographs* evaluations of edible plants and of plant-derived substances occurring naturally in food or used for medicinal purposes

Agent	Degree of evidence[c]		Overall evaluation	Volume, year
	Human	Animal		
Bracken fern[a]	I	S	2B	**40**, 1986; **S7**, 1987
Shikimic acid	ND	I	3	**40**, 1986; **S7**, 1987
Ptaquiloside	ND	L	3	**40**, 1986; **S7**, 1987
Carrageenan[a]				
Native	ND	I	3	**31**, 1983; **S7**, 1987
Degraded	ND	S	2B	**31**, 1983; **S7**, 1987
Cycasin[a]	ND	S	2B	**10**, 1976; **S7**, 1987
Safrole[a]	ND	S	2B	**10**, 1976; **S7**, 1987
Dantron[b] (1,8-Dihydroxyanthraquinone)	ND	S	2B	**50**, 1990

Abbreviations: I, inadequate; S, sufficient; S7, Supplement 7 (IARC, 1987); ND, no data; L, limited

[a] Substances occurring naturally in food

[b] Substance used for medicinal purposes

preparations are evaluated for the first time. The carcinogenicity of aristolochic acids (nitrophenanthrene compounds that are natural products of this genus of plants) is also evaluated for the first time in this volume.

The second section deals with some anthraquinone derivatives that are structurally related to the previously evaluated 1,8-dihydroxyanthraquinone. These compounds occur naturally in certain herbaceous plants that have been used in some traditional Oriental medicinal preparations.

The final section of the herbal medicines monograph concerns toxic pyrrolizidine alkaloids including riddelliine that occur in several widely distributed genera of wild plants including *Senecio*, *Crotalaria* and some others. In western North America these plants co-exist with edible forage plants and may be ingested by livestock. The alkaloids may contaminate foods derived from these animals, including meat and milk, and may be found in honey (National Toxicology Program, 2001). Riddelliine occurs in the plant *Senecio longilobus*, which has been used as a herbal tea called ‘gordolobo yerba’ by members of the Mexican-American community in the south-western region of the USA, and has been linked with acute hepatic veno-occlusive disease (Stillman *et al*., 1977; Segall & Molyneux, 1978). Pyrrolizidine alkaloids were previously reviewed by the *IARC Monographs* programme (IARC, 1976). Experimental carcinogenicity data on riddelliine available at that time were considered insufficient to evaluate the carcinogenicity of this compound, and there were no data on cancer risks in humans who might have been exposed to it either in food or as a traditional herbal medicine. Riddelliine was

subsequently placed in Group 3, *not classifiable as to its carcinogenicity to humans* (IARC, 1987) (Table 1). A recent bioassay of riddelliine for carcinogenicity conducted by the US National Toxicology Program provides important new data on this compound (National Toxicology Program, 2001) and is the basis for its re-evaluation in this volume.

Mycotoxins

Aflatoxins comprise four secondary metabolites of toxins produced by a number of species of *Aspergillus* of which *A. flavus* and *A. parasiticus* are the most common. These fungi and their toxins contaminate maize and peanuts (groundnuts) along with other commodities in the field and when improperly stored. Naturally occurring aflatoxins and aflatoxin B_1 were previously reviewed and evaluated in *IARC Monographs* Volume 56 (IARC, 1993a). Naturally occurring aflatoxins (as a group) were evaluated as *carcinogenic to humans* (Group 1). Aflatoxin M_1, the metabolite of aflatoxin B_1 found in the milk of lactating mammals, was classified in Group 2B as *possibly carcinogenic to humans* (IARC, 1993a) (Table 1). An update of the scientific literature on these substances is provided in this volume. The existing Group 1 evaluation of naturally occurring aflatoxins was reaffirmed; an update was undertaken because of the concurrent re-evaluation of another mycotoxin, fumonisin B_1.

Mention is also made in this monograph of carcinogenicity studies of materials containing aflatoxins that have been treated with ammonia by a number of methods to reduce aflatoxin content. These processes result in a number of known and unknown reaction products which are not evaluated as such in this monograph; the elimination of the carcinogenicity of aflatoxin B_1 in ammoniated feed as well as the reduction of the mutagenicity and carcinogenicity due to aflatoxin M_1 in milk from dairy cows fed ammoniated feed was noted. This monograph also contains an annex on the causes and occurrence of aflatoxin contamination and on the management of this problem.

The fungi *Fusarium verticillioides* (Sacc.) Nirenburg (formerly known as *Fusarium moniliforme* Sheldon) and *F. proliferatum* are maize endophytes. Fumonisins are toxins produced by these fungi. Under environmental conditions that result in stress of the plant, the maize disease ‘Fusarium kernel rot’ occurs and the crop may become contaminated with fumonisins. Experimental carcinogenicity data on these toxins that were cited in the previous *IARC Monographs* review (IARC, 1993b) were from studies in which crude mixtures, rather than purified individual compounds, were fed to experimental animals, and the resulting evaluation was for ‘toxins derived from *Fusarium moniliforme*’ (Table 1) (IARC, 1993b). New bioassays to assess the carcinogenicity of purified fumonisin B_1 in experimental animals have been published since the previous *IARC Monographs* evaluation. These bioassays, as well as numerous studies on the toxicity and mechanisms of action of fumonisin B_1 are reviewed and evaluated in the present volume.

Naphthalene and styrene

Naphthalene was originally planned for inclusion in *IARC Monographs* Volume 77, *Some Industrial Chemicals* (2000), but was withdrawn from consideration at that time because the *Monographs* programme became aware of new carcinogenicity studies of this compound that were nearing completion. These studies have now been published, and their results are included in the present evaluation. In addition, there are extensive new data that contribute to understanding the mechanisms of carcinogenicity of this compound.

Styrene is an important industrial chemical and a major intermediate in the manufacture of both synthetic rubber and certain plastics. It was previously evaluated by the *IARC Monographs* programme in 1994 (IARC, 1994) (see Table 1). At that time it was classified in Group 2B as *possibly carcinogenic to humans*, on the basis of *limited evidence* for carcinogenicity in experimental animals that was supported by an extensive set of other relevant data, including biomarkers of exposure and of effect. Recently, new results have been published on carcinogenicity of styrene in experimental animals by inhalation and on mechanistic aspects, which are included in the present re-evaluation.

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