Aristolochic Acids

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Twelfth Report on Carcinogens* (2011)

Carcinogenicity

Aristolochic acids are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans and supporting data on mechanisms of carcinogenesis. Evidence of carcinogenicity from studies in experimental animals supports the findings in humans.

Cancer Studies in Humans

The evidence for carcinogenicity in humans is based on (1) findings of high rates of urothelial cancer, primarily of the upper urinary tract, among individuals with renal disease who had consumed botanical products containing aristolochic acids and (2) mechanistic studies in humans which demonstrate that aristolochic acids are the carcinogenic agents in these products.

Evidence for the carcinogenicity of aristolochic acids was first identified in studies of Belgian patients with nephropathy (progressive interstitial renal fibrosis) related to the consumption of herbal medicines. The patients had consumed Chinese herbal medicines that were inadvertently contaminated with plant species of the genus *Aristolochia*. Aristolochic acids were considered to be the cause of the nephropathy (now referred to as "aristolochic acid nephropathy," or AAN) because (1) the nephropathy developed immediately after ingestion of the herbs, (2) in most cases, the patients had not been exposed to other agents known to be risk factors for nephropathy, (3) aristolochic acids were identified in the herbal products, and (4) aristolochic acid metabolites bound to DNA (AA-DNA adducts) were found in tissues (usually kidney or urothelial tissue) from some of the patients. Over 100 cases of AAN have been reported in Belgium and over 170 cases in other locations, including the United States, Great Britain, Japan, Taiwan, and China (Arlt *et al.* 2002, NTP 2008).

Two prevalence studies in Belgium (at Cliniques Universitaires St.-Luc and Hospital Erasme) reported high rates of urothelial cancer (40% to 46%), mainly of the upper urinary tract, among female AAN patients who had received kidney transplants (Cosyns *et al.* 1999, Nortier *et al.* 2000, Nortier and Vanherweghem 2002). This rate of urothelial cancer among AAN patients is much higher than the incidence or prevalence of transitional-cell carcinoma of the urinary tract (i.e., urothelial carcinoma) (0.89% to 4%) reported in several studies of Chinese patients with renal disease, either renal-transplant patients or dialysis patients (Ou *et al.* 2000, Wu *et al.* 2004, and Li *et al.* 2008). Neither prevalence study had an unexposed comparison group. Both studies identified aristolochic acids in the botanical products consumed by the patients, and both studies detected AA-DNA adducts in kidney tissue from the patients, demonstrating that the patients had been exposed to aristolochic acids. In the study at Hospital Erasme, the rate of urothelial cancer was significantly higher among AAN patients who had consumed a high dose of the plant *Aristolochia fangchi* than among patients who had consumed a lower dose. Furthermore, AAN patients with and without urothelial cancer did not differ significantly with respect to other risk factors for urothelial cancer, such as smoking or the use of analgesics or nonsteroidal anti-inflammatory drugs. A 15-year follow-up study of AAN patients from Hospital Erasme found a rate of upper-urinary-tract urothelial cancer similar to that previously reported by Nortier and colleagues (Lemy *et al.* 2008). In addition, AAN patients with upper-urinary-tract urothelial cancer had an unusually high incidence of urinary-bladder urothelial cancer.

Additional case reports and clinical investigations of urothelial cancer in AAN patients outside of Belgium support the conclusion that aristolochic acids are carcinogenic (NTP 2008). The clinical studies found significantly increased risks of transitional-cell carcinoma of the urinary bladder and upper urinary tract among Chinese renal-transplant or dialysis patients who had consumed Chinese herbs or drugs containing aristolochic acids, using non-exposed patients as the reference population (Li *et al.* 2005, 2008).

Molecular studies suggest that exposure to aristolochic acids is also a risk factor for Balkan endemic nephropathy (BEN) and upper-urinary-tract urothelial cancer associated with BEN (Grollman *et al.* 2007). BEN is a chronic tubulointerstitial disease of the kidney, endemic to Serbia, Bosnia, Croatia, Bulgaria, and Romania, that has morphology and clinical features similar to those of AAN. It has been suggested that exposure to aristolochic acids results from consumption of wheat contaminated with seeds of *Aristolochia clematitis* (Ivic 1970, Hranjec *et al.* 2005, NTP 2008). AA-DNA adducts were found in kidney tissue from BEN patients and in urothelial and kidney (renal cortical) tissues from BEN patients who had upper-urinary-tract urothelial cancer. Furthermore, A:T to T:A transversion mutations in the *p53* tumor-suppressor gene were found in urothelial tumors from BEN patients (Grollman *et al.* 2007).

The available studies are limited in their ability to formally address confounding by other factors that could increase the risk of cancer, and the case-series studies did not include unexposed controls; however, a causal association between exposure to aristolochic acids and human cancer is evidenced by the strength of the association, consistency across studies, dose-response effects, detection of AA-DNA adducts in exposed patients, timing of the exposure and disease, and specific mutations in the *p53* gene similar to the A:T to T:A transversions seen in rodents and rodent cell cultures exposed to aristolochic acids. The finding of urothelial cancer among patients who consumed a variety of botanical products from different plant species known to contain aristolochic acids provides additional support for the role of aristolochic acids as the cancer-causing agent in the botanical products. In 2000, the International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of herbal remedies containing plant species of the genus *Aristolochia* in humans (IARC 2002). In 2008, IARC concluded that aristolochic acids also were carcinogenic to humans (Grosse *et al.* 2009).

Studies on Mechanisms of Carcinogenicity

Aristolochic acids are absorbed after oral exposure; no data are available on absorption after dermal or inhalation exposure (NTP 2008). Aristolochic acids I and II (AAs I and II) are the most widely studied aristolochic acids. Aristolochic acids are metabolized to aristolactams, which are further metabolized to a cyclic *N*-acylnitrenium ion, a reactive intermediate that forms adducts with purine bases (adenine and guanine) in DNA (dA-AAI, dG-AAI, dA-AAII, and dG-AAII). A number of cytosolic and microsomal enzymes (CYP1A1, CYP1A2, NADPH:CYP reductase, prostaglandin H synthase, DT-diaphorase, xanthine oxidase, cyclooxygenase, and NAD(P)H:quinone oxidoreductase) are capable of bioactivating aristolochic acids to the reactive form (NTP 2008).

DNA adducts have been detected *in vitro* in experimental animals exposed to aristolochic acids and in human tissue from individuals exposed to aristolochic acids, including individuals with AAN, BEN, or urothelial cancer associated with AAN or BEN (Grollman *et al.* 2007, NTP 2008). In animals, adducts have been detected in the forestomach and stomach, urinary tract (kidney and urinary

bladder), liver, intestine, spleen, and lung. In humans, adducts have been detected in the urinary tract (kidney, ureter, and urinary bladder), liver, and non-target tissues such as pancreas, breast, and lung (NTP 2008). The predominant adduct, dA-AAI, persists for a lifetime in rats and at least 89 months in humans and appears to be responsible for most of the mutagenic and carcinogenic properties of aristolochic acids (NTP 2008).

Aristolochic acids (purified I or II or mixtures) have been shown to be mutagenic in bacteria, cultured cells, and rodents exposed *in vivo*. AA I has been tested the most extensively. In *in vitro* assays, purified aristolochic acids induced mutations in the bacterium *Salmonella typhimurium* and in cultured mammalian cells, including (1) *hprt* mutations in rat fibroblast-like cells and Chinese hamster ovary cells, (2) forward mutations in mouse lymphoma cells, and (3) mutations in the *p53* DNA-binding domain in two studies with fibroblast cell cultures from human *p53* knock-in (Hupki) mice (mice carrying a humanized *p53* gene sequence) (NTP 2008). Mutations were identified in the *p53* DNA-binding domain in one third (6 of 18) to one half (5 of 10) of the established Hupki mouse fibroblast cultures; A:T to T:A transversions were predominant, occurring in at least 80% of the cell lines with mutations (Liu *et al.* 2004). Aristolochic acid mixtures or plant extracts caused mutations in *S. typhimurium* and sex-linked recessive lethal mutations in the fruit fly *Drosophila melanogaster* (NTP 2008). In studies with rodents exposed *in vivo*, exposure to aristolochic acid mixtures or plant extracts caused (1) mutations in subcutaneous granulation tissue from Sprague-Dawley rats (Maier *et al.* 1985), (2) mutations of the *lacZ* transgene in forestomach, kidney, and colon tissue from transgenic Muta mice (Kohara *et al.* 2002), and (3) mutations of the *cII* transgene in liver and kidney tissue from transgenic Big Blue rats (Chen *et al.* 2006, Mei *et al.* 2006). A:T to T:A transversions were the predominant mutation type in the Muta mice and Big Blue rats. Exposure to AA I also caused mutations in granulation tissue from Sprague-Dawley rats (Maier *et al.* 1987).

Aristolochic acids have been shown to bind to adenine in codon 61 in the H-*ras* mouse oncogene and to purines in the human *p53* gene. Mutations identified in tumors of rodents exposed to aristolochic acids include A:T to T:A transversions in codon 61 of the c-Ha-*ras* gene in forestomach tumors (from rats and mice), lung tumors (from rats and mice), and ear-duct tumors (from rats). No mutations were identified in tissues from rats with chronic renal failure that had not been exposed to aristolochic acids (Schmeiser *et al.* 1990, 1991). Similar findings have been reported in humans. A:T to T:A transversion mutations of the *p53* gene were identified in a urothelial tumor from an AAN patient (Lord *et al.* 2004) and at a high frequency (78%) in BEN patients with upper-urinary-tract urothelial cancer. The frequency of A:T to T:A transversions of *p53* mutations in bladder and ureter tumors not caused by aristolochic acid exposure was approximately 5% (Grollman *et al.* 2007). Moreover, there was concordance between the location of the *p53* A to T transversions and mutations identified in fibroblast cell cultures from human *p53* knock-in (Hupki) mice treated with AA I (Nedelko *et al.* 2009).

Aristolochic acids also caused other types of genetic damage in other test systems with and without mammalian metabolic activation. Aristolochic acids I and II and mixtures caused DNA damage in the SOS chromotest in the bacterium *Escherichia coli,* and aristolochic acid mixtures caused sex-chromosome loss and somatic recombination in *D. melanogaster*. In mammalian cells exposed *in vitro*, aristolochic acid mixtures caused chromosomal aberrations, sister chromatid exchange, and micronucleus formation in human lymphocytes. AA I also caused chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells. Neither AA I nor AA II induced DNA strand breaks in rat liver cells, but aristolochic acids caused DNA damage in a pig kidney cell line (proximal tubular epithelial cells) and in human hepatocellular carcinoma cells. In mammalian *in vivo* studies, aristolochic acids (composition not specified) did not induce unscheduled DNA synthesis in the pyloric mucosa of male rats. DNA damage was reported in kidney cells isolated from male Sprague-Dawley rats administered a single oral dose of an aristolochic acid mixture. One study reported that intravenous injection of aristolochic acid mixtures increased micronucleus formation in polychromatic erythrocytes in bone marrow from NMRI male and female mice, but another study found no increase in micronucleus formation in peripheral blood reticulocytes from male Muta mice exposed orally to a mixture of AAs I and II (NTP 2008).

Together, these findings strongly suggest that exposure to aristolochic acids causes urothelial cancer in humans through formation of DNA adducts (specifically, through binding of the reactive metabolite with adenine) and the resulting transversion mutations in oncogenes.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of aristolochic acids in experimental animals based on studies showing that aristolochic acids caused tumors in rodents and rabbits at several different tissue sites and by several different routes of exposure. Although the studies in which aristolochic acids were administered orally or by injection typically were small and of short duration, they showed clear evidence of carcinogenicity. In nearly all of the studies, aristolochic acids caused urothelial tumors, as they did in humans.

Oral exposure to aristolochic acids caused predominantly forestomach and urinary-tract tumors, and administration by injection caused mainly urinary-tract tumors and connective-tissue tumors (sarcoma) at the injection site (NTP 2008). In female mice, oral exposure to aristolochic acids caused tumors of the forestomach, stomach, kidney, lung, and uterus and malignant lymphoma (Mengs 1988). In several studies in rats, oral exposure to aristolochic acids caused tumors of the forestomach, kidney (renal-cell and renal-pelvis tumors), urinary bladder, ear duct, thymus, small intestine, and pancreas. Single instances were also reported of tumors of the hematopoietic (blood-producing) system, heart, lung, mammary gland, pituitary gland, and peritoneum (NTP 2008). Male Wistar rats receiving daily subcutaneous injections of aristolochic acids developed urothelial carcinoma of the renal pelvis and malignant fibrohistiocytic sarcoma at the injection site (Debelle *et al.* 2002). A single intraperitoneal injection of aristolochic acids initiated liver carcinogenesis in male F344 rats that had also received treatment to stimulate proliferation of liver cells (Rossiello *et al.* 1993). Aristolochic acids administered to female New Zealand White rabbits by intraperitoneal injection caused kidney tumors, a urinary-tract tumor, and mesothelioma of the peritoneal cavity (Cosyns *et al.* 2001).

Three studies investigated the carcinogenicity of extracts of *Aristolochia* (one study each for *A. manshuriensis*, *A. clematitis*, and *A. contorta*) when administered to rats orally or by injection. Following oral administration, tumors of the forestomach and kidney were the most prevalent findings (Hwang *et al.* 2006), but one study reported tumors of the mammary gland, thyroid gland, and skin (Qiu *et al.* 2000), and one study reported injection-site polymorphocellular sarcoma (Ivic 1970). In one study, rats of both sexes were exposed to a weight-loss regimen of herbal ingredients that contained aristolochic acids; the males developed forestomach tumors (papilloma and squamous-cell carcinoma) (Cosyns *et al.* 1998).

Properties

Aristolochic acids are a family of nitrophenanthrene carboxylic acids that occur naturally in plants in the family Aristolochiaceae. The

aristolochic acid content of plants or botanical preparations varies depending on the plant species, where it was grown, the time of year, and other factors. However, aristolochic acid I (also called aristolochic acid A) and its demethoxylated derivative, aristolochic acid II (also called aristolochic acid B) are the predominant forms. AA I is a crystalline solid that is slightly soluble in water. The molar extinction coefficient (ε) for AA I in ethanol is 6,500 at 390 nm, 12,000 at 318 nm, and 27,000 at 250 nm (O'Neil *et al.* 2006). Other selected physical and chemical properties of AA I are listed in the table below. No information was located on the physical or chemical properties of AA II other than its molecular weight of 311.3 (IARC 2002).

Property	Information for AA I
Molecular weight	341.3
Melting point	281°C to 286°C
Log K_{ow}	3.48

Source: IARC 2002.

Use

Aristolochia plants have been used since ancient times in traditional herbal medicines in many parts of the world, and aristolochic acids have been reported to have antibacterial, antiviral, antifungal, and antitumor effects (Kupchan and Doskotch 1962, Zhang *et al.* 2004). The name *Aristolochia* (meaning the best delivery or birth) is thought to be of ancient Greek origin and reflects centuries of use in obstetrics. Other traditional uses include treatment for snakebite, scorpion stings, fever, infection, diarrhea, and inflammation (Arlt *et al.* 2002, Jiménez-Ferrer *et al.* 2005). In contemporary medicine, *Aristolochia* plant extracts have been used in therapies for arthritis, gout, rheumatism, and festering wounds, but these uses were discontinued in Germany and other countries after the carcinogenic and mutagenic properties of aristolochic acids were first reported in the early 1980s (Arlt *et al.* 2002). Other uses of *Aristolochia* plants include cultivation as ornamental plants. Aristolochic acids also have been used in studies of toxicity and carcinogenicity and in biochemical studies as relatively selective inhibitors of the enzyme phospholipase A2 (NTP 2008).

Occurrence and Production

Aristolochic acids have been detected only in plant species belonging to the family Aristolochiaceae, primarily of the genera *Aristolochia* and *Asarum*. More than 30 *Aristolochia* species are native to the United States, and they are present in most states (USDA 2005). The most widely distributed native species include *A. serpentaria* (Virginia snakeroot), *A. tomentosa* (woolly Dutchman's pipe), *A. macrophylla* (pipevine), and *A. clematitis* (birthwort). In addition, some non-native species are grown as ornamentals or have escaped cultivation and become naturalized. Worldwide, there are an estimated 200 to 350 *Aristolochia* species, and virtually all of them contain aristolochic acids (NTP 2008). *Asarum* species (wild gingers) also are widely distributed in the United States. Plants of the genus *Hexastylis,* a group of rare plants endemic to the southeastern United States, were reported to have "unexpectedly high levels" of aristolochic acids (Schaneberg *et al.* 2002)

A number of studies have reported concentrations of AAs I and II in medicinal plants, including several species used in traditional Chinese medicine. Concentrations ranged from 3 to 12,980 ppm for AA I and from not detected to 6,325 ppm for AA II. In *Asarum* species, concentrations of AAs I and II ranged from trace levels to 3,377 ppm. Other studies detected AA IVa at concentrations of 79 to 3,360 ppm of crude drug, aristolactam I at 6 to 358 ppm, and aristolactam II at 14 to 91 ppm (NTP 2008). Hong *et al.* (1994) identified 11 aristolochic acid derivatives, including aristolactams and other compounds, in extracts from *Aristolochia cinnabarina* roots, and Wu *et al.* (1994) identified 14 aristolochic acid derivatives in extracts from stems and roots of *Aristolochia kankauensis*.

Aristolochic acids are produced commercially as reference standards and as research chemicals (IARC 2002). No data were found on U.S. producers or production volume, but in 2004, aristolochic acids were available from nine U.S. suppliers of aristolochic acid A (AA I), one supplier each of aristolochic acids B and D (AAs II and IV), three suppliers of aristolochic acid C (AA IIIa), and three suppliers of aristolochic acid, sodium salt (ChemSources 2004). No specific data on U.S. production, imports, or sales of botanical products that might contain aristolochic acids were found; however, many U.S. suppliers offer products that could contain aristolochic acids. Gold and Slone (2003) identified 112 botanical products that could contain aristolochic acids and were available for purchase over the Internet.

Exposure

Exposure to aristolochic acids may occur through ingestion as a result of intentional or inadvertent use of herbal or botanical products that contain *Aristolochia* or *Asarum* species. Exposure to aristolochic acids through ingestion of flour from wheat contaminated with *A. clematitis* has been proposed as a cause for BEN. Herbal preparations are available in several forms (e.g., capsules, extracts, teas, or dried herbs). Exposure also could potentially occur through direct contact with the plants, either in their natural habitats or as cultivated ornamentals. Direct contact with the leaves of *Asarum canadense* (Canadian snakeroot or wild ginger) has been reported to cause dermatitis (PFAF 2005).

Schaneberg and Khan (2004) purchased from Internet Web sites 25 herbal products suspected of containing aristolochic acids, of which nine were manufactured in the United States and the rest in China. AAs I and II were detected in six of the products, each of which contained six or more types of plants. The U.S. Food and Drug Administration has reported recalls of products containing aristolochic acids beginning in 2000 and continuing with the report of a recall of two products in 2008 (Tou Tong San [Headache Formula] and Du Huo Ji Sheng Tang [Du Huo Joint Relief]) (FDA 2008). Two herbal remedies prepared from *Aristolochia debilis* or *A. contorta* appeared in the official 2005 Chinese pharmacopeia, and three additional entries for drugs derived from *A. debilis, A. fangchi*, and *A. manshuriensis* were cancelled in 2003 and 2004 because the content of aristolochic acid in the drugs was high enough to cause AAN (Zhang *et al.* 2006).

In addition to the intentional uses of aristolochic acid-containing plants, herbal preparations can pose a number of quality-related problems, which can lead to inadvertent exposures. These include contamination with prohibited or restricted substances, substitution of ingredients, contamination with toxic substances, and differences between the labeled and actual product contents (MCA 2002).

The complexity of herbal nomenclature systems used in traditional medicines (particularly traditional Chinese medicines) can lead to confusion and increased risk of inadvertent exposure to aristolochic acids (Flurer *et al.* 2001), which was reported for cases in Hong Kong (Liang *et al.* 2006), Belgium (Vanherweghem 1998), and Singapore (Koh *et al.* 2006). Substitutions arising because of name confusion have also been reported between botanicals used in Japanese herbal medicines and botanicals with similar names used in Chinese herbal medicines (Tanaka *et al.* 2001, EMEA 2005). The most extensive exposure resulting from name confusion occurred in the early 1990s in Belgium, where *A. fangchi* was inadvertently substituted for *Stephania tetrandra* to prepare diet pills. The Chinese name for *S. tetrandra* is "fang ji," which is similar to the name for aristolochic acid–con-

taining *A. fangchi* ("guang fang ji"). An estimated 1,500 to 2,000 individuals (primarily women) were exposed to the *Stephania*-labeled powders that contained aristolochic acids ranging from below the detection limit (< 0.02 mg/g) to 2.9 mg/g (2,900 ppm) (Vanherweghem 1998). The resulting maximum dose of aristolochic acids was estimated at 0.025 mg/kg received over an average of 13 months (Grollman *et al.* 2009).

For botanical products, high concentrations or intake of aristolochic acids have been reported in studies from China (AA I at 700 ppm, with estimated AA intake of 110 mg), Taiwan (AA I at up to 19.97 nmol/g and AA II at up to 3.95 nmol/g), Hong Kong (intake of herb from 100 mg to 800 g), Japan (total AA at up to 15.1 ppm), Australia (AA I at up to 40 ppm and AA II at up to 210 ppm), and Switzerland (AA I at up to 440 ppm) (NTP 2008). Chinese patients who developed chronic renal failure had ingested an estimated 0.7 to 1.5 mg of aristolochic acids per day intermittently for 1 to 10 years (Grollman *et al*. 2009).

No estimates were found of the number of people in the United States who are exposed to aristolochic acids in herbal medicines, but two U.S. cases of renal failure resulting from ingestion of herbal products containing aristolochic acids have been reported (Meyer *et al.* 2000, Consumer Reports 2004, Grollman *et al.* 2007). The use of all complementary and alternative medicines increased in the 1990s and 2000s (Barnes *et al.* 2004, Bent and Ko 2004). The Centers for Disease Control and Prevention reported that 10% of adults in the United States ingested herbal medicines in 1999 (Straus 2002), and the total spent on herbs and other botanical remedies in 2001 was $4.2 billion (Marcus and Grollman 2002).

The possibility also exists for exposure to aristolochic acids in food. It has been suggested that contamination of wheat flour by *Aristolochia* species growing as weeds adjacent to wheat fields might be responsible for BEN (Ivic 1970, Hranjec *et al.* 2005). Indeed, seeds of *A. clematitis* have been found commingled with wheat grain during harvest in regions where BEN is endemic (Grollman and Jelaković 2007). It has been estimated that at least 25,000 individuals are suspected of having BEN and that over 100,000 individuals residing in endemic regions could be at risk (DeBelle *et al.* 2008). As noted above, AA-DNA adducts were found in kidney tissue from BEN patients and in urothelial and kidney (renal cortical) tissues from BEN patients who had upper-urinary-tract urothelial cancer. Because *Aristolochia* species are widely distributed and wheat can be traded internationally, there is the potential for worldwide exposure from this source; however, no data were found to support this hypothesis.

Extracts from *Asarum canadense* and *Aristolochia serpentaria* are permitted for use in the United States as flavoring substances in foods or beverages (FDA 2003); *A. serpentaria* has been reported to be used as a spice and to flavors liqueurs or bitters, such as Angostura or Boonekamp bitters, but no information was found on the concentrations of aristolochic acid in these products.

Although occupational exposure to aristolochic acids has not been documented, herbalists potentially are exposed while gathering plants or while preparing or applying botanical products. Gardeners, landscapers, or nursery workers who handle or transplant *Aristolochia* or *Asarum* plants could potentially be exposed to aristolochic acids. Handling *Aristolochia* or *Asarum* plants could result in dermal exposure, which, as of 2010, has been associated only with dermatitis. To reduce the likelihood of accidental ingestion, workers should wash their hands before eating, drinking, or smoking.

Regulations

Food and Drug Administration (FDA, an HHS agency)

Federal Food, Drug, and Cosmetic Act as amended by the Dietary Supplement Health and Education Act

Manufacturers and distributors as of 2007 must record adverse events and report to the FDA serious adverse events reported to them about their products.

Label requirements for dietary supplements have been established.

Manufacturers must establish and meet specifications for identity, purity, strength, and composition and for limits on contamination of dietary supplements under current Good Manufacturing Practices (cGMP) regulations published in 2007.

Warnings and Alerts

Food and Drug Administration (FDA, an HHS agency)

Warnings issued in 2000 and 2001 (FDA 2000, 2001a,b) covered botanical products that contain aristolochic acids:

- Practitioners who prescribe botanical remedies urged to discard those products containing aristolochic acids.
- Manufacturers and distributors urged to ensure that botanical products are free of aristolochic acids.
- Consumers urged to immediately discontinue use of botanical products that contain or likely contain aristolochic acids.

An import alert issued in 2000 and revised in 2007 provided for the detention of products labeled as *Aristolochia* or any that could be confused with it unless analytical evidence shows no aristolochic acids.

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