Aristolochic Acid Related Exposures Expert Panel Report

Part B - Recommendation for listing status for “aristolochic acids” in the Report on Carcinogens and scientific justification for the recommendation

The Report on Carcinogens (RoC) expert panel for aristolochic acid-related exposures met at the Sheraton Chapel Hill Hotel, Chapel Hill, NC on January 24 - 25, 2008, to peer review the draft background document on aristolochic acid-related exposures and make a recommendation for the listing status in the 12th Edition of the RoC. Members of the expert panel are as follows:

Arthur P. Grollman, M.D. (Chair)  
Department of Pharmacological Sciences  
Stony Brook University  
Albert B. Lowenfels, M.D.  
Department of Community and Preventive Medicine  
New York Medical College  

A. Morrie Craig, Ph.D.  
College of Veterinary Medicine  
Oregon State University  
Joëlle L. Nortier, M.D.  
Department of Nephrology  
Erasme Hospital  
Université Libre de Bruxelles  

Patricia E. Ganey, Ph.D.  
Department of Pharmacology and Toxicology  
Michigan State University  
Brian T. Schaneberg, Ph.D.  
Technical Services  
ChromaDex, Inc.  
Boulder, CO  

Yanze Liu, Ph.D.  
Bio-organic and Natural Products Research Laboratory  
McLean Hospital  
(a Harvard Medical School Affiliate)  
Bryan L. Stegelmeier, D.V.M., Ph.D.  
Poisonous Plant Research Laboratory  
U.S. Department of Agriculture  
Agriculture Research Service  
Logan, UT

1nonmember, technical expert

The recommendation for listing status and scientific justification for the recommendation follows this page.
Overall Evaluation

After discussing the body of knowledge in the Draft Background Document, the expert panel voted (6 yes/0 no) to redefine the proposed candidate substances: (1) “aristolochic acid” and (2) “botanical plants containing aristolochic acid” as a single candidate substance, namely, “aristolochic acids.” Aristolochic acids are nitrophenanthrene carboxyclic acids found primarily in the Aristolochiaceae family of plants. The panel concluded that aristolochic acids are responsible for the carcinogenic effects observed in humans who consume *Aristolochia* or herbal remedies prepared from these plants.

The expert panel applied the RoC listing criteria to the current body of knowledge, recommending (6 yes/0 no) that “aristolochic acids” be listed in the RoC as a substance “known to be a human carcinogen” based on sufficient evidence of carcinogenicity in humans and experimental animals, together with mechanistic data demonstrating its carcinogenic potential.

The major considerations that led the panel to its recommendation include (i) detection of aristolactam-DNA adducts in renal tissues of patients with aristolochic acid nephropathy (AAN), (ii) the association of AAN in humans with urothelial (transitional-cell) carcinomas of the upper urinary tract, (iii) the finding of an A:T to T:A transversion mutation (the signature mutation for aristolactam-DNA adducts) in the p53 gene of an urothelial tumor of a patient with AAN, and (iv) the clear demonstration that aristolochic acid induces cancer in experimental animals.

The expert panel concluded that now, and in the past, there is/was significant opportunity for human exposure to aristolochic acid in the United States, primarily through usage as a traditional herbal remedy.

Human Exposure

Exposure to aristolochic acids and botanical products containing aristolochic acids is associated with human cancer. Until very recently, entries for birthwort (*A. clematitis*) appear in most textbooks on herbal remedies. Cancer could develop in individuals exposed over a lifetime to aristolochic acid. The 2005 Physician's Desk Reference for Herbal Medicines contains an entry on birthwort, noting its toxic potential. The import alert by the FDA on botanical products containing aristolochic acids does not cover products formulated domestically. Also, over 30 *Aristolochia* and *Asarum* species grow natively in the United States. It is possible that human foods, native or imported, may be consumed by individuals without their knowledge. Both *A. serpentaria* and *A. canadensis* are currently used as flavorings in alcoholic beverages in the United States. Botanical products containing aristolochic acids continue to be advertised for sale on the Internet. Products containing *Asarum* species are regularly consumed in the United States. Importantly, individuals from Asia, Central and South America, and Europe migrating to the United States may have been exposed to
aristolochic acids in their homeland and/or may continue the traditional use of aristolochic acid-containing herbal remedies in the United States.

**Human Cancer Studies**

Aristolochic acids are known to be human carcinogens based on evidence from three independent regions: Belgium, the Balkans, and Asia. In Belgium, a high prevalence of upper tract urothelial carcinoma was found in women inadvertently exposed to aristolochic acids while participating in a slimming regimen. The panel estimated the increased relative risk for the exposed subjects in this cohort to be > 20. The presence of aristolactam-DNA adducts in renal tissues confirmed prior exposure of these women to aristolochic acids. With reference to the Balkans, a recent paper (Grollman et al. 2007) reported that exposure of a rural population in Croatia to aristolochic acids was associated with renal failure and transitional-cell carcinomas (TCC). These studies revealed a high relative risk of TCC in patients with Balkan endemic nephropathy. In most cases, A-T transversions associated with aristolactam-DNA adducts were detected in the p53 gene. A similar mutation had been reported previously in one case of urothelial carcinoma associated with aristolochic acid nephropathy in the United Kingdom. Evidence also comes from several Asian countries where widely used traditional herbal medicines often contain aristolochic acids. Reports from these countries reveal an elevated risk of TCC in patients suffering from renal failure as a result of consuming traditional herbal remedies containing aristolochic acids.

In all of these regions, further evidence comes from the unusual site specificity of tumors associated with exposure to aristolochic acids. Such tumors are invariably located in the upper urinary tract (renal pelvis or upper ureter). The latent period between exposure to aristolochic acid and development of TCC may be long or as short as a few years. These findings agree with the epidemiologic evidence that aristolochic acids are powerful human carcinogens.

**Studies of Cancer in Experimental Animals**

There is sufficient evidence of carcinogenicity of aristolochic acids in experimental animals. Carcinogenic effects of aristolochic acids and mixtures of botanical products containing aristolochic acids have been demonstrated in mice, rats, and rabbits. In long-term studies, the incidence of neoplastic lesions in rats was dose and time related with incidences in high-dose animals approaching 100% by 16 months. Tumors induced by aristolochic acids in rats, mice and rabbits included carcinomas of the bladder, stomach, and lung. Similar tumors were induced by extracts of herbal mixtures containing aristolochic acids. Various tissues contained the same aristolactam-DNA adducts observed in human aristolochic acid-associated nephropathy associated with urothelial (transitional cell) carcinomas.
Other Relevant Data

Experimental studies demonstrate that aristolochic acids are absorbed after oral administration, distributed throughout the body and excreted through the gastrointestinal tract and kidney. The metabolic pathways in humans and rodents are similar but not identical. Aristolochic acids produce nephrotoxicity in animal models and in humans. Aristolochic acids are mutagenic in prokaryotic systems and in human and animal cells in vitro. In addition, they are associated with a dose-related increase in mutation frequency in rodents. Characteristic mutations are observed in animals exposed to aristolochic acids and in individuals with aristolochic acid nephropathy associated with urothelial carcinomas. Exposure of experimental animals or humans to aristolochic acids produces aristolactam-DNA adducts and a similar mutation spectrum.

Report Approved

Arthur P. Grollman, M.D. (Chair)