Riddelliine Expert Panel Report

Part B - Recommendation for listing status for Riddelliine in the Report on Carcinogens and the scientific justification for this recommendation

The Report on Carcinogens (RoC) expert panel for riddelliine met at the Sheraton Chapel Hill Hotel on January 24 & 25, 2008, to review the draft background document on riddelliine 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
State University of New York at Stony Brook

A. Morrie Craig, Ph.D.
College of Veterinary Medicine
Oregon State University

Patricia E. Ganey, Ph.D.
Department of Pharmacology and Toxicology
Michigan State University

Yanze Liu, Ph.D.
Bio-organic and Natural Products Research Laboratory
McLean Hospital
(a Harvard Medical School Affiliate)

Albert B. Lowenfels, M.D.
Department of Community and Preventive Medicine
New York Medical College

Joëlle L. Nortier, M.D.
Department of Nephrology
Erasme Hospital
Université Libre de Bruxelles

Brian T. Schaneberg, Ph.D.
Technical Services
ChromaDex, Inc.
Boulder, CO

Bryan L. Stegelmeier, D.V.M., Ph.D.
Poisonous Plant Research Laboratory
U.S. Department of Agriculture
Agriculture Research Service
Logan, UT

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

Following discussion of the body of scientific knowledge, including the strengths and weaknesses for each section of the background document, the expert panel applied the RoC listing criteria and made a recommendation for riddelliine for the listing status “reasonably anticipated to be a human carcinogen” in the RoC. The expert panel recommended by a vote of 7 yes/0 no that riddelliine should be listed in the RoC under that status based on sufficient evidence of carcinogenicity in several species of animals at multiple target sites and supporting mechanistic data.

The major considerations discussed that led to this recommendation include (i) vascular neoplasms developed in rodents treated with riddelliine, (ii) riddelliine metabolites and structurally related pyrrolizidine alkaloids (PA) are carcinogenic in animals, and (iii) riddelliine produces DNA adducts and mutations in vivo and in vitro.

Past and present exposure to materials containing PAs, including riddelliine, remains a concern for cancer in humans.

Human Exposure

Past and present exposure to materials containing PAs remains a concern for human carcinogenicity. Riddelliine, a PA, has been detected in plants that may be used in these preparations. In 2001, the Food and Drug Administration (FDA) sent an advisory to dietary supplement manufacturers to remove comfrey products from the market. Within this advisory, the FDA stated they would take action under the authority of the Dietary Supplement Health and Education Act (DSHEA) when products containing any PAs were found on the market. There currently is low probability of exposure to PAs, but exposure is still possible in the United States. Studies have shown PA contamination in milk, meat, liver, bee pollen, honey, feeds, and other foods. There also is the possibility of contamination by misidentification and substitution of plants containing PAs for plants that are PA free. PAs have been used as herbal remedies, including for infants who may be more susceptible to PAs.

Human Cancer Studies

No studies evaluating the carcinogenicity of exposure specific to riddelliine were identified.

Studies of Cancer in Experimental Animals

There is sufficient evidence that riddelliine is carcinogenic in rats and mice. Mice dosed orally with riddelliine developed dose-related hepatic hemangiosarcomas with lower incidences of hepatocellular and pulmonary neoplasms. Similarly dosed rats also developed hepatic hemangiosarcomas in a dose-related manner. These animals also developed significant hepatocellular and renal lesions.
indicative of riddelliine toxicity. Dehydroretronecine (DHR or R-DHP) and dehydroheliotridine (DHH or S-DHP), common toxic riddelliine metabolites, produced tumors in rats, mice, and chickens. Administered orally, subcutaneously, and percutaneously, these metabolites produced a variety of neoplasms in multiple locations. Hepatocellular adenomas and carcinomas also were induced in rats and chickens dosed with riddelliine-containing plants and extracts.

Other Relevant Data

Liver microsomes from humans and rodents mainly produce riddelliine N-oxide and 6,7-dihydro-7-hydroxy-1-hydroxymethyl-5H-pyrrolizine (DHP) derivatives (R-DHP and S-DHP). DHP has been demonstrated to bind to DNA and similar DNP adducts are produced by both rat and human microsomes. Adducts also are observed in endothelial cells from liver of exposed rats, and the frequency of mutation in those cells is increased. This observation is relevant to the carcinogenicity of riddelliine, which is characterized by liver hemangiosarcomas in rodents. Riddelliine is mutagenic in prokaryotes and in vitro in mammalian cell lines. It results also in DNA damage and mutations after in vivo exposure of rodents. These data are supportive of a carcinogenic potential for riddelliine.