Captafol/*o*-Nitrotoluene Expert Panel Report

Part B – Recommendation for listing status for Captafol in the RoC and Scientific Justification for the Recommendation

The Report on Carcinogens (RoC) expert panel for Captafol/*ortho*-Nitrotoluene met at the Sheraton Chapel Hill Hotel on October 15 & 16 2007, to peer review the draft background document on captafol and make a recommendation for its listing status in the 12th Edition of the RoC. Members of the expert panel are as follows:

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Office of Environmental Health Hazard Assessment

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The recommendation follows this page.

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Overall Evaluation

Following a discussion of the body of 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 the listing status of captafol in the RoC. The expert panel recommended by a vote of 8 yes/0 no that captafol should be listed in the RoC as *reasonably anticipated to be a* human carcinogen based on sufficient evidence of carcinogenicity in experimental animals and strong supporting mechanistic evidence. The expert panel also voted (8 yes/0 no) that there is evidence that a significant number of people in the United States are or have been exposed to captafol. The potential long latency period of cancer makes past exposures of concern for current and future risks.

The major considerations discussed that led to this recommendation include:

Human Exposure

Past captafol exposures in the United States associated with its manufacture, formulation, application, and field reentry are still of concern. The U.S. population has probably been exposed in the past to low concentrations of captafol from environmental (air, water, soil) and food sources, judging from the low environmental concentrations reported in the NTP document in countries where use still occurred in the recent past. Exposure to the U.S. population may still occur from imported food and products from countries that continue to use captafol. Individuals including research and technical personnel may currently be exposed to captafol in spite of the cessation of use in agriculture and the 2006 revocation of the remaining tolerances.

Human Cancer Studies

The available epidemiologic evidence is insufficient to establish carcinogenicity of captafol in humans. There is only one epidemiologic study that directly addressed captafol exposure. This study was based upon ecologic (group-level) exposure assessment and had several potential sources of bias and did not account for multiple comparisons (18 pesticides were studied). Studies of captan or mixtures of fungicides (e.g., phthalimides) are of limited value in addressing carcinogenicity of captafol. This limited scientific database has the following significant shortcomings: (1) most of the studies addressed only a single cancer site; (2) none addressed the specific cancer sites implicated in laboratory animal studies (kidney, liver, small intestine, heart, etc.), (3) none addressed exposure from food or food products, environmental contamination, or directly evaluated occupational exposure; (3) none addressed genetic susceptibility relevant to the proposed mechanisms of action (e.g., inherited variation in DNA repair as

susceptibility factors for genotoxic effects); and (4) exposure assessments in general were crude and subject to misclassification.

Studies in Experimental Animals

There is sufficient evidence of carcinogenicity in experimental animals. Long-term carcinogenicity studies were conducted in both sexes of two strains of mice and two strains of rats. All studies were adequate for evaluating the carcinogenicity of captafol in these experimental animals. Captafol was tested for carcinogenicity in feeding studies in CD-1 mice, $B6C3F_1$ mice, Crl:CD rats, and F344 rats. Significant increased incidences of hemangiosarcoma (all sites) (male and female), Harderian gland adenoma (male) and lymphosarcoma (male and female) were observed in CD-1 mice exposed to captafol. Male and female $B6C3F_1$ mice exposed to captafol had increased incidences of benign and malignant tumors of the vascular system (primarily heart), forestomach, small intestine, and liver. In rats, the primary tumor sites were the liver and kidney. In Crl:CD rats, exposure to captafol increased the incidences of renal-cell carcinoma in males and females, and benign and combined benign and malignant hepatocellular tumors and mammary-gland fibroadenoma in females. In F344 rats, exposure to captafol induced hepatocellular adenomas of the liver and renal-cell adenomas in males and females; renal-cell carcinomas were also significantly increased in males; and nonsignificant increases of hepatocellular carcinomas were observed in females. Captafol also showed significant activity as both an initiator and a promoter of preneoplastic glutathione *S*-transferase placental form positive foci (GST-P+) in the liver of male rats. In addition to the $GST\text{-}P^+$ foci, promotion with captafol significantly increased the incidences of forestomach hyperplasia and small intestinal adenoma, thyroid follicular adenoma, and the expression of the proliferating cell nuclear antigen in the kidney.

Other Relevant Data

The metabolic activation and disposition of captafol are anticipated to be similar in experimental animals and humans. The preponderance of evidence from short-term genotoxicity studies *in vivo* and *in vitro* supports mutagenicity as a mode of action for captafol. In addition, non-mutagenic modes of action may apply as evidenced by the induction of duodenal tumors by captan. The results of the few genotoxicity studies conducted with human tissues are consistent with the larger body of data but are not sufficient to support a *known human carcinogen* listing.

Report Appropved __s/ Lauren Zeise_____ Date _____1/11/08_____
Lauren Zeise, Ph.D. (Chair)

Proper Signatures
Treat as signed, § 1.4(d)(2)