

Sapphire News

Cancer Dose-Response Assessment for Acrylonitrile Based Upon Rodent Brain Tumor Incidence: Use of Epidemiologic, Mechanistic, and Pharmacokinetic Support for Nonlinearity

C.R. Kirman, MS; M.L. Gargas, Ph.d.; Gary M Marsh, Ph.d.; Dale E Strother, Ph.d.; James E Klaunig, Ph.d.; James J Collins, Ph.d.; Randy Deskin, Ph.d.

ABSTRACT

A cancer dose-response assessment was conducted for acrylonitrile (AN) using updated information on mechanism of action, epidemiology, toxicity, and pharmacokinetics. Although more than 10 chronic bioassays indicate that AN produces multiple tumors in rats and mice, a number of large, well-conducted epidemiology studies provide no evidence of a causal association between AN exposure and cancer mortality of any type. The epidemiological data include early industry exposures that are far higher than occur today and that approach or exceed levels found to be tumorigenic in animals. Despite the absence of positive findings in the epidemiology data, a dose-response assessment was conducted for AN based on brain tumors in rats. Mechanistic studies implicate the involvement of oxidative stress in rat brain due to a metabolite (2-cyanoethylene oxide or CEO, cyanide), but do not conclusively rule out a potential role for the direct genotoxicity of CEO. A PBPK model was used to predict internal doses (peak CEO in brain) for 12 data sets, which were pooled together to provide a consistent characterization of the dose-response relationship for brain tumor incidence in the rat. The internal dose corresponding to a 5% increase in extra risk ($ED_{05}=0.017$ mg/L brain) and its lower confidence limit ($LED_{05}=0.014$ mg/L brain) was used as the point of departure. The weight-of-evidence supports the use of a nonlinear extrapolation for the cancer dose-response assessment. A quantitative comparison of the epidemiology exposure-response data (lung and brain cancer mortality) to the rat brain tumor data in terms of internal dose adds to the confidence in the nonlinear extrapolation. Uncertainty factors of 200 and 220 (for the oral and inhalation routes, respectively) were applied to the LED_{05} to account for interspecies variation, intraspecies variation, and the severity of the response measure. Accordingly, oral doses below 0.009 mg/kg-day and air concentrations below 0.1 mg/m³ are not expected to pose an appreciable risk to human populations exposed to AN.