



Letter to the editor

Additional support for derivation of an acute/subchronic reference level for arsenic

Tsuji et al. (2004) provide a detailed discussion of the available data for deriving an acute/subchronic oral reference level for arsenic. As part of their analysis, they summarize a series of studies in which arsenic trioxide was administered to patients with acute promyelocytic leukemia (APL) who were non-responsive to standard retinoic acid therapy. In the studies cited (Chen et al., 2001; Dombret et al., 2002; Fox et al., 2002; Niu et al., 1999; Soignet et al., 1998, 2001) arsenic was administered at doses ranging from 0.11 to 0.16 mg/kg-day. Some toxicity was observed at these doses (nausea, liver dysfunction, transient neuropathy, and facial edema). Tsuji et al. use the data from these studies to supplement the LOAEL value of 0.05 mg/kg-day obtained from the case-report of Mizuta et al. (1956) which describes a population poisoned by ingestion of arsenic contaminated soy sauce.

One APL study not cited by the authors is the study of Shen et al. (2001), which evaluated the efficacy and safety of a reduced arsenic trioxide dose, 0.08 mg/kg-day, in comparison to the typical dose of 0.16 mg/kg-day. Twenty patients received the reduced dose compared to 47 standard dose “controls.” Patients receiving the standard dose experienced facial edema (11% of patients), cardiotoxicity (17%), GI disturbance (17%), and polyneuropathy (2%), symptoms similar to those reported by Mizuta et al. (1956). These symptoms were absent in patients treated at 0.08 mg/kg-day. The only adverse effects reported from 28 days of arsenic trioxide therapy at 0.08 mg/kg-day (or 0.06 mg arsenic/kg-day) were slightly elevated liver transaminases (20% incidence) and skin rash (10% incidence).

Tsujigi et al. note that the estimate of soy sauce consumption in Mizuta et al. (1956) is quite low and suggest that the toxicity observed may have occurred primarily in members of the population with higher soy sauce intakes. The effect of such an exposure misclassification would be to introduce added conservatism into the LOAEL estimate of 0.05 mg/kg-day. The Shen et al. (2001) data appear to support their supposition. Symptoms similar to those reported by Mizuta et al. were present in Shen et al.’s 0.16 mg/kg-day treatment group but absent in the 0.08 mg/kg-day group. We also note that the 0.08 mg/kg-day dose represents a true ab-

sorbed dose while the 0.05 mg/kg-day dose estimated from Mizuta et al. is an administered dose and therefore potentially reduced by limited GI absorption and first-pass metabolism and elimination. Use of 0.05 mg/kg-day as a acute/subchronic LOAEL for arsenic therefore appears to be conservative and necessitates only limited use of uncertainty factors to obtain a reference level.

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