

Workshop 3: Mouse liver tumors: benefits and constraints on use in human health risk assessment, qualitative and quantitative aspects.

Liver cancer in humans is the most common neoplasm in many parts of the world, with more than a million new cases diagnosed annually. In mice, a primary animal model for cancer risk assessment, liver cancer is among the most common cancers. The B6C3F1 mouse strain used by the National Toxicology Program develops benign and malignant liver tumors on exposure to a variety of toxicants, including both mutagenic and non-mutagenic compounds. Susceptibility to liver cancer is highly variable among mouse strains. Fewer than 5% of B6 parental strain mice, compared with 30-50% of C3H parental strain mice, spontaneously develop hepatocellular carcinoma by two years of age. Induction of liver tumors in the B6C3F1 and other mouse strains is variously interpreted as a valuable, sensitive indicator—or as bearing little to no relationship due to mode of action (MOA) and/or dose considerations—to human cancer risk. As background, EPA's cancer risk assessment guidelines do not presume site concordance between animals and humans. Qualitative interpretations of mouse liver tumor results have been central to cancer risk evaluations for many years by DHHS, EPA, FDA, IARC and other organizations. Quantitative dose-response modeling of the mouse liver tumor results has also figured prominently in EPA's calculation of some cancer slope factors. EPA is seeking consultative advice on the extent and circumstances in which mouse liver tumors inform qualitative and quantitative human cancer risk assessment, drawing from what is currently known as to:

- § The biological basis of differential susceptibility to hepatocarcinogenesis among mouse strains
- § Commonalities in the MOAs for mouse and human cancer development
- § Kinetic and dynamic factors likely to influence inferences for human risk evaluation
- § The extent to which quantitative estimates of susceptibility between mouse strains and human variation in susceptibility to cancer can be made at this time

Specific questions are as follows:

- 1) What factors are important in considering differential sensitivity between animals and humans to a MOA, also taking into account the possibility of considerable differential sensitivity and variability of response within the human population?
- 2) Currently, some consider human relevance analysis as a qualitative binary decision. What steps might be considered for systematically and quantitatively including differential sensitivity (e.g., kinetic and dynamic factors) between and within species in the assessment of human cancer risk? How could this analysis of differences in species sensitivity be incorporated in a decision analysis framework?
- 3) If quantitative approaches are feasible at this time, what sources of uncertainty could be addressed and how (e.g., high background rates in test species, etc.)?

EPA is requesting the academy prepare a background paper addressing the first topic on the biological basis of differential susceptibility to hepatocarcinogenesis among mouse strains. In addition, this paper should discuss historical controls, the rationale for choices of background parentage of mouse strains, and the strength and weaknesses of the commonly used mouse strains used in cancer bioassays