A Hidden Paradox in Carcinogenesis Bioassays

The suitability of preclinical studies has sound implications on the toxicologic risk of drugs or environmental pollutants both during the subsequent clinical investigation and during marketing. Unfortunately, data from long-term carcinogenicity tests often give rise to limited or equivocal evidence of carcinogenicity.

Inasmuch as the procedures for chemical risk assessment used by the U.S. Environmental Protection Agency (EPA) have been criticized for many years and for many reasons, we wish to point out to the scientific community an overlooked but paradoxical aspect of assessment procedures that we only recently discovered.

Most standard risk-assessment experiments expose rodents to large doses of a test chemical for about 2 years (i.e., the natural life-span of the rodent). These animals, generally Sprague-Dawley rats, Fischer rats, or (C57BL/6 × C3H)F1 mice (hereafter called B6C3F1 mice), have a higher natural incidence of tumors than humans, and this incidence has also changed with time (1). In the 1970s, the incidence was 58%; in the 1980s, it was 44%; in the 1990s, it has dropped to 24%.

Even though the recently emphasized (2,3) role of excess weight on the health and longevity of humans or rodents (fed ad libitum) is unquestionable, we would like to bring up the question of food constituents, which can contribute to the great tumor-expression variability of tests in various laboratories (i.e., from 10% to 76% in the male B6C3F1 mice). Indeed, most standardized diet formulations that we received from numerous laboratories around the world that were conducting cancer research experiments contain the well-known mutagenic/carcinogenic element manganese (4-6) at the same level and, in some cases, at an even higher level (up to ninefold) compared to that used to study the carcinogenicity of manganese itself (7). The optimal dietary intake (8) of manganese for laboratory animals should not exceed 0.35 mg/day (0.74 mg/day for humans, who have a slower metabolism than rodents). In other words, the animal diet should contain no more than 45 mg/kg of this element per weight of the chow.

To increase the reliability of long-term bioassays, the EPA should simply establish protocols in which animal diet constituents should be more carefully considered to avoid invalidating cancer bioassays.

References


Notes

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