INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS (ICCVAM) TEST METHOD NOMINATION: THE NATIONAL TOXICOLOGY PROGRAM (NTP) TWO-YEAR RODENT BIOASSAY DRAFT ICCVAM RECOMMENDED PRIORITY

In October 2007, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) received a nomination (Appendix 1) requesting that the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) evaluate the current validation status of the NTP two-year rodent bioassay for differentiating human carcinogens from human noncarcinogens. Carcinogenicity studies (i.e., two-year bioassays) conducted at the National Toxicology Program (NTP) generally employ both sexes of rats (Fischer 344/N or Wistar Han) and mice (B6C3F1 hybrid), and generally include three dose levels of a test substance plus an untreated control using 50 animals per sex per dose group (Chhabra et al. 2003, King-Herbert and Thayer 2006). In accordance with its established test method nomination process (ICCVAM 2003), ICCVAM considered this nomination in conjunction with currently available information on this test method's usefulness and limitations, and proposed that the evaluation of this test method be assigned a "low priority", pending consideration of comments received from the public and its scientific advisory board, the Scientific Advisory Committee on Alternative Toxicological Methods. The rationale for this decision follows.

As stated in the 11th Edition of the NTP Report on Carcinogens[1], "*The strongest evidence for establishing a relationship between exposure to any given substance and cancer in humans comes from epidemiological studies—studies of the occurrence of a disease in a defined population and the factors that affect its occurrence (Bradford 1971). Epidemiological studies of human exposure and cancer are difficult (Rothman 1986). They must rely on natural, not experimental, human exposures and must therefore consider many factors that may affect cancer prevalence besides the exposure under study. One such factor is the latency period for cancer development. The exposure to a*

[1] Report on Carcinogens, 2004. Eleventh Edition; U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Introduction.

carcinogen often occurs many years (sometimes 20 to 30 years or more) before the first sign of cancer appears.

Another valuable method for identifying substances as potential human carcinogens is the long-term animal bioassay. These studies provide accurate information about dose and duration of exposure and they are less affected than epidemiology studies by possible interaction of the test substance with other chemicals or modifying factors (Huff 1999). In these studies, the substance is given to one or (usually) two species of laboratory rodents over a range of doses for nearly the animals' entire lives. Experimental cancer research is based on the scientific assumption that substances causing cancer in animals will have similar effects in humans. It is not possible to predict with complete certainty from animal studies alone which substances will be carcinogenic in humans. However, known human carcinogens that have been tested adequately in laboratory animals also cause cancer in laboratory animals (Fung et al. 1995). In many cases, a substance first was found to cause cancer in animals and later confirmed to cause cancer in humans (Huff 1993). How laboratory animals respond to substances, including developing cancer and other illnesses, does not always strictly correspond to how people will respond. Nevertheless, laboratory animal studies remain the best tool for detecting potential human health hazards of all kinds, including cancer (OTA 1981, Tomatis et al. 1997)."

The above information supports the basis for the current utility of the two-year bioassay, which is further supported by extensive literature. It is important to recognize that short-term studies are conducted when deemed appropriate on species-comparative pharmacokinetics, metabolism, and epigenetic and genetic mechanisms to extend and clarify the cancer bioassay findings. ICCVAM concluded that, in light of this information and ICCVAM priorities described in the recent NICEATM-ICCVAM 5-Year Plan[2] (ICCVAM 2008), any further evaluation of this assay should have a low priority at this time. However, while this represents the proposed current priority for this test method, ICCVAM and NICEATM recognize that future planning and priorities must be flexible in order to take advantage of opportunities resulting from advances in science and technology, development of new methods, and to respond to new testing needs.

[2] http://iccvam.niehs.nih.gov/docs/5yearplan.htm

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