The Use of Genetically Altered Animals in Carcinogen Identification by the National Toxicology Program

June 1, 2002

Introduction

The National Toxicology Program (NTP) routinely investigates the potential for chemical and physical agents to increase the incidence of cancer in rodent models. This core activity of the NTP has produced over 500 technical reports providing data and analyses on cancer incidence and has provided public health agencies with summary decisions regarding the potential for the agents studied to induce cancer in rodents. For several years, many agencies, including the NTP, have been studying the potential use of genetically altered mouse models (GAMMs) as an alternative and/or enhancement to the standard use of wild-type rats and mice in cancer screening. These GAMMs have the potential to reduce the time needed to complete an assay (6 to 9 months rather than 2 years), to use lessanimals (the models tend to respond with fewer animals) and to potentially provide greater mechanistic insight into the basis for a particular cancer finding. After careful review, the NTP has decided to refine its testing paradigm to formally include GAMMs in the battery of tests used to evaluate agents for carcinogenicity.

How will GAMM be used by the NTP?

Figure 1 illustrates the process by which agents nominated to the NTP are chosen for carcinogenicity testing. When a nomination of a chemical or physical agent is reviewed for carcinogenicity testing by the Board of Scientific Counselors (BSC), the NTP will seek a recommendation from the BSC and the public concerning the use of GAMMs as a first tier screen for carcinogenicity instead of the usual two-year chronic carcinogenicity screen. Following the NTP Executive Committee (EC) Review, the NTP will make a decision regarding the types of models to be used for screening a particular agent. In general, unless there is scientific reason to choose otherwise, the NTP will proceed as outlined in Figure 2.

As illustrated in Figure 2, the first step in the NTP Cancer Screening Process is to decide on the data gaps being addressed by a particular study, the designs to be used for these studies and the priorities and resources to be assigned to these studies. Unless otherwise indicated, the initial phase of testing will include the standard subchronic assays in mice and rat (generally 90 days of continuous exposure) followed by or simultaneous with subchronic assays in one or more GAMMs (generally 180 days of continuous exposure). Appropriate toxicokinetic studies will also be performed during this phase of testing. Upon completion of these studies, a technical report will be developed and reviewed by the NTP BSC at an open public meeting. At a public meeting, the BSC will be asked to comment on the need for a chronic exposure two-year carcinogenicity study based upon the findings from the GAMM studies. Similarly, the NTP EC will also be asked to comment on the need for additional studies. Recommendations from the public, the BSC and the EC will be used by the NTP to determine if additional studies are needed; if yes,

the chemical will return to the design phase and the previous findings will be used to design, if necessary, additional GAMM studies and/or two-year chronic exposure carcinogenicity studies. Occasionally, the NTP will initiate the two-year studies prior to board review and/or without GAMM studies if there is a compelling scientific and/or public health reason to rapidly move forward.

Which GAMMs will be used?

In general, the NTP will attempt to determine the best GAMMs to be used on an agent-specific basis based upon the scientific data available at the time the study design is developed. However, this may not always be possible and certain models will be routinely used. The most promising performance based on recent reviews of the literature was shown by the p53+/- GAMM for genotoxic chemicals, and the RasH2 GAMM for chemicals irrespective of their genotoxicity. The Tg.AC was found to be an acceptable model for many situations.

Under what conditions will NTP not likely use GAMM for cancer screening?

In general, the NTP intends to use GAMMs as an initial screen in most cases. However, the first few chemicals in large structural classes for which little is known and for which extensive testing is planned are likely targets for the traditional two-year cancer studies. In addition, agents that are anticipated to be at most weak carcinogens and for which a negative outcome in a GAMM would likely be considered as inadequate test for carcinogenic potential, such as herbal medicines, are more likely to proceed directly to the traditional 2-year bioassay.

Figure 1: NTP Nomination and Selection Process

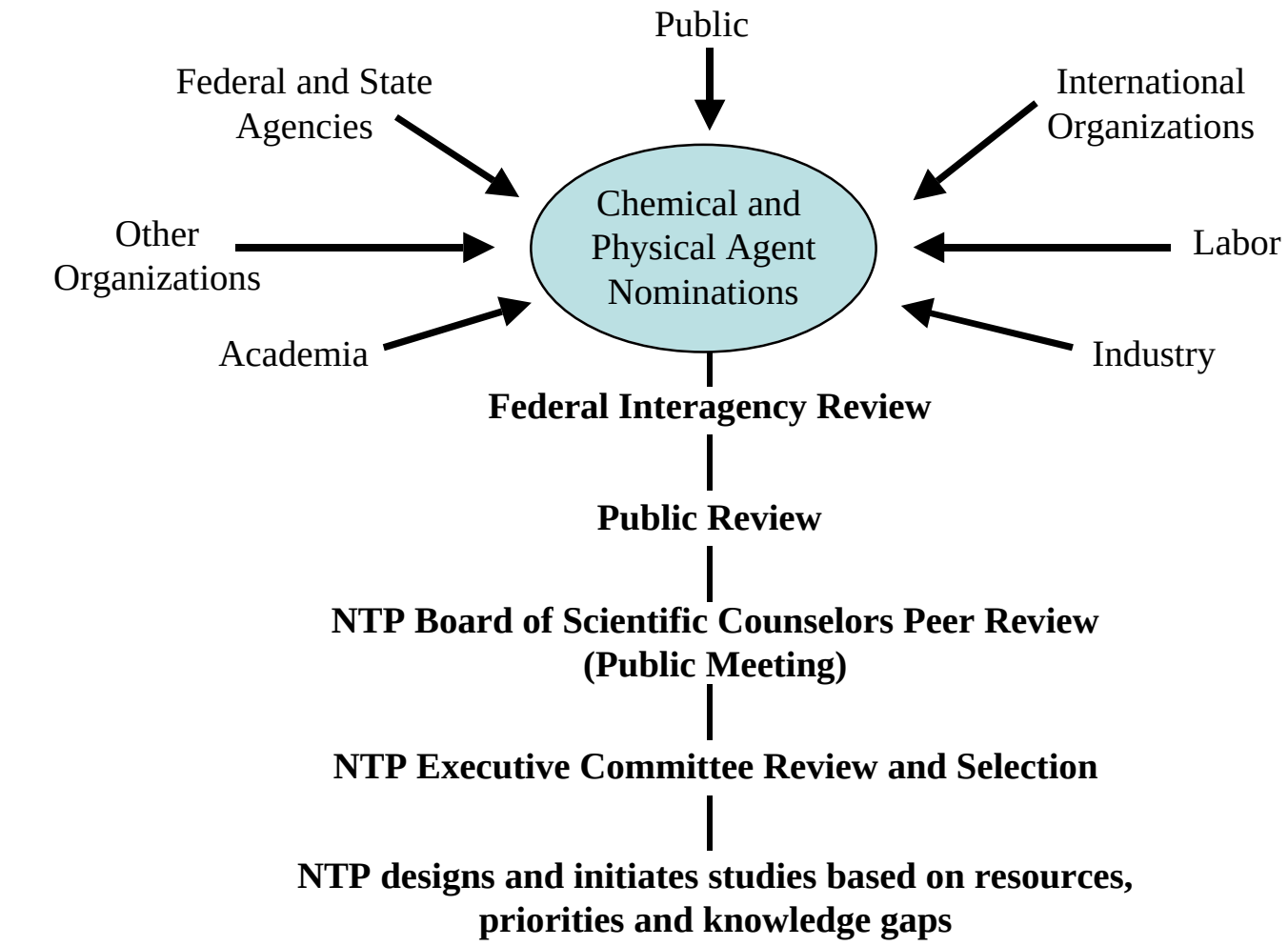

Figure 2: NTP Cancer Screening Process