

NTP Host Susceptibility Initiative

Goal: To establish a mechanism within the NTP to plan, conduct, and analyze multi-strain assessment of chemical toxicity. Endpoints and agents to be examined will be identified in standard NTP studies. The focus of this effort will be identification of mouse strains particularly sensitive and insensitive to the test agents or toxicants. These analyses will provide the basis for partnerships with DIR and/or extramural scientists for identification of specific genes that confer sensitivity or resistance to a given toxic agent, and ultimately for an understanding of the key genes and pathways involved in the toxic and disease responses to chemicals. Such understanding will lead to more specific, targeted tests for evaluation and prediction of the toxic potential of new chemicals as they come into use.

Process: Testing of agents will be carried out via a contract, interagency agreement, or a similar mechanism. Initial identification of strains to be used and scope of studies to be undertaken will be established by NIEHS staff, familiar with the NTP, in consultation with outside experts in a multi-strain assessment of the genetic basis of strain differences (e.g., Drs. Kenneth Paigen of Jackson Laboratories, David Threadgill of UNC, Robert Williams of the University of Tennessee, and Tim Wiltshire of Novartis). These staff members will be familiar with those disciplines likely to be involved in the study design and interpretation. Once the strains and scope of host susceptibility studies are defined and approved by NIEHS Leadership, the NIEHS members of this working group will consider candidate chemicals to be screened and will present a prioritized list of agents to NTP and NIEHS Leadership.

Since it is anticipated that chemicals selected for host susceptibility assessment will be identified based on prior NTP studies, it is probable that study design for the multi-strain assessment will be assigned to the study scientist who designed the original work on that chemical, or in some cases to the NTP scientist who was responsible for the specific toxic effect (e.g., reproductive or immune system toxicity). Thus, the lead staff member for each host susceptibility study will be drawn from the overall NTP staff and will vary from study to study. Assessment and reporting of study outcomes from each study will be similar to that used for NTP studies, with the appropriate NTP experts performing chemistry, pathology, pharmacokinetics, and bioinformatics. Findings will be summarized and published by the lead study scientist and his/her team. Those studies that identify clear differences in strain susceptibility will be reported directly to DIR and DERT scientists through seminars and meeting presentations. It is intended that translation of the Host Susceptibility findings into the focused identification of specific genes contributing to sensitivity or resistance to test chemicals will be carried out by DIR and extramural scientists and will provide an increased understanding of the genetic basis for toxic and disease responses.

Structure: A newly constituted Host Susceptibility Branch will be charged with leading this effort. However, because much of the work of this Branch will be accomplished through existing NTP staff, it is proposed that the staff needs of the Host Susceptibility Branch will be minimal and will be drawn from existing NTP and NIEHS staff.