National Toxicology Program (NTP) Public Meeting on Toxicology in the 21st Century: The Role of the National Toxicology Program

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Comments by
Jennifer Sass, Ph.D.
Senior scientist, Health and Environment
Natural Resources Defense Council
1200 New York Avenue, NW, suite 400
Washington, DC 20005
Email: jsass@nrdc.org

Support for a leading role of NTP, as a public health institute, in the development of a strategy to integrate* in vitro *toxicity data into regulatory policy

While we are well aware that policy makers will someday utilize these data for regulatory decisions, how this is to be done is still being discussed. Thus, we support a strong role for the NTP in the development of methodology on the use of 'omics data for human risk assessment. Without this methodology, gene expression data cannot be effectively used to predict toxicity or low-dose cancer risk. Further, we strongly support the need to include proteomics and metabonomics, in conjunction with the toxicogenomic effort, in the overall strategy.

Support for the validation and appropriate integration of* in vitro *toxicity data

We support the NTP efforts to lead the way on the validation and appropriate integration of data from 'omics and in vitro toxicity testing methods. However, we encourage the NTP to develop clear objectives as well as a comprehensive strategy to achieve that objective. For example, does the NTP envision use of these data as screening strategies, or as surrogates for existing *in vivo* endpoints. If a potential goal is to develop an alternative approach to the rodent bioassay, we strongly object. We are years, if not decades, from fully understanding the cellular and subcellular mechanisms of carcinogenicity. We therefore suggest that an appropriate goal at this time be to further characterize cellular and subcellular toxicity, in order to refine our understanding of chemicals and toxic agents on health and disease. Mechanistic-based endpoints will be most useful if data can be developed in both humans (epidemiology) and animal models. We suggest that any objective include the development of biologically based dose-response models that can be used for trans-species extrapolations of toxic or carcinogenic effects, and that can address inter-individual differences in susceptibility as well as the effects of exposures to mixtures.

To achieve any of the above objectives, extensive quantitative data on time- and dose-dependent relationships are needed. Studies on time dependence should cover the time interval between exposure and elimination of the agent under study, at least over a 24-hour cycle (longer

for bio-accumulating agents or for agents in which continuous treatment affects their metabolic elimination), and at multiple life stages to capture effects of age-related changes. Transcriptional data without information on time-dependent protein levels will be of limited value. Measurements of gene expression in conjunction with NTP sacrifice times (4, 21, 90 days or 2 years) may be useful in linking altered gene expression with clinical pathology or histopathologic effects in the same animals.

The strengths of NTP studies are the consistent genetic background of animals on study and the consistency in diet, so it may be useful to apply mechanistic methods to better characterize the effects of animal variability (e.g., use of transgenic or knockout mice) and of different dietary formulations. Collecting and interpreting this information may not lead to significant savings in cost, time, and use of animals.

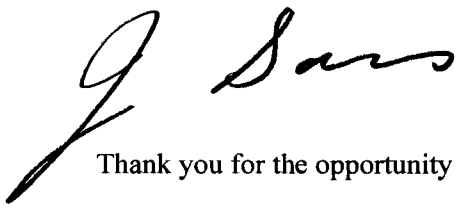
The validation and appropriate integration of microarray and 'omics technology will require a clear strategy, to contribute to the design or interpretation of NTP studies and enhance the overall goals of the NTP. As the NTP develops their mechanistic endpoints, they should consider incorporating these into low-dose testing regimes, and observe for appropriately sensitive endpoints.

Support for the NTP bioassay program, as a critical and integral part of identifying and characterizing toxic agents

It is alarming to realize that with approximately 80,000 chemicals commercially available worldwide, and 2,000 new ones introduced annually, less than 2% of these have been adequately tested for carcinogenicity. More than 2,800 chemicals are manufactured in the US in quantities exceeding one million pounds annually; of these the US Environmental Protection Agency (EPA) finds that a full set of basic toxicity information is available for only 7%, while for 43% no basic toxicity information –neither human health nor environmental toxicity -- is publicly available.[i] Without adequate laboratory testing, the default method for identifying human hazards is epidemiology. This is, unfortunately, neither rapid nor protective. Epidemiology studies are typically limited by insufficient follow-up time, uncertain exposure estimates, limited statistical power, confounding factors, and limited histopathology[ii].

The National Toxicology Program is widely considered to be the most trusted chemical testing program in the world, largely because of its tremendous work in establishing the bioassay as an effective method for identifying and characterizing carcinogens. The NTP bioassay is an accepted method because the vast majority of human carcinogens have also been shown to be carcinogenic in animals[iii], and many chemicals first identified as carcinogenic in animals were subsequently confirmed to be human carcinogens as well.[iv] Well-designed animal studies provide detailed dose-exposure information, repeatability, sufficient statistical power, and comprehensive behavior and histopathological information.[v] A baseline data set on measurements of gene expression over 24 hour intervals in different strains of rats and mice at several ages (perinatal through senescence) would be valuable information for future study designs. We encourage NTP bioassay to more routinely capture the full range of age groups, including fetal stages, puberty, and old age, and to continue for at least two full years, to allow latent tumor formation to become evident.[vi]

We encourage NTP to expand this trusted methodology, to handle an increased number of chemicals annually.



Thank you for the opportunity to present comments,

Jennifer Sass
Senior Scientist, Health and Environment

NRDC is a non-profit environmental action organization. We use law, science and the support of more than 1 million members and online activists to protect the planet's wildlife and wild places and to ensure a safe and healthy environment for all living things.

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