National Toxicology Program
U.S. Department of Health and Human Services

Center For The Evaluation Of Risks To Human Reproduction

PUBLIC COMMENTS ON THE METHANOL EXPERT PANEL REPORT

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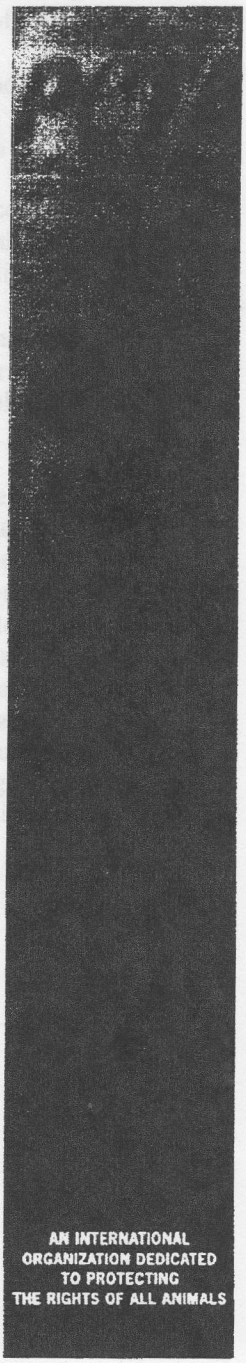

AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

VIA ELECTRONIC TRANSMISSION TO: shelby@niehs.nih.gov

On behalf of the 750,000 members and supporters of People for the Ethical Treatment of Animals (PETA), I am again submitting comments in opposition to the National Toxicology Program's (NTP) highly inappropriate proposal to conduct still more animal-based toxicity studies on methanol. PETA is the largest animal rights organization in the world, and is committed to using the best available science to protect animals from suffering and to promote the acceptance of alternatives to activities that harm animals.

Although it is acknowledged in Section 5.9 of the NTP report that further animal testing of methanol is not "critical," the report concludes that more "studies are needed to elucidate the basis for the developmental toxicity of methanol," and calls for "data from developmental toxicity studies using concurrent exposures to methanol and ethanol." For the reasons cited below, this recommendation is seriously flawed on both scientific and policy grounds.

Methanol is among the most over-studied chemicals in existence — having been subject to a veritable laundry-list of cruel and non-validated animal-poisoning tests, both in rodents as well as dogs and non-human primates. The NTP has truly refined the process of "paralysis by analysis" to an art form— subjecting chemicals to a useless and bottomless pit of study with little or no regulatory action in the end. This situation is appalling on a policy level, given the extremely high costs of NTP-mandated testing — both financially and in terms of animal suffering and death. In addition, the NTP's current paradigm represents the least public health protective application of the precautionary principle, which often results in protracted delays in risk management decisions, which can in turn have a serious adverse impact on human health.

From a scientific perspective, the NTP's report is replete with references to the fact that "the rodent data are *assumed* to be relevant for humans." However, such an arbitrary and chronically unconfirmed leap of faith does not befit a supposedly science-based institution. Because none of the NTP's laundry list of animal-poisoning tests used has ever been validated for its relevance to humans, calling for more such tests will only confuse matters further and prolong testing *ad infinitum*. We call your attention to a publication by the National Academy of Sciences in 2000, entitled Scientific Frontier in Developmental Toxicology and Risk Assessment, and highly recommend that your expert panel review the section on limitations in developmental toxicity risk assessments. The report discusses at great length the dubious relevance of animal tests to the

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understanding of human development, the major limitations of the default assumption that "outcomes for rodent tests are relevant for human risk prediction," and the failure of animal tests to generate useful mechanistic data — a fact which could not be more clear based on the NTP's current recommendations regarding methanol.

Other widely recognized limitations to animal-based studies of reproductive and developmental toxicity include, but are not limited to the following:

- the fact that human and test species' reproductive systems and cycles are very different;
- the influence of immune, physiological and dietary status on the interpretation of results of testing is fraught with problems;
- genetic constitution profoundly affects the reproductive toxicity of chemicals and this varies in humans and animals;
- organs such as the testes and ovaries respond to the test substances differently in human and animal species;
- the time course of the metabolism and elimination of any test substance influences the ways that repeat doses elicit a response, for example, in some animals but not others, the chemical accumulates in the body over time causing a more toxic effect which will complicate any extrapolation to humans; and
- the binding of the test substance to various organs and cells within the body means that there will be different distribution and concentration of the toxic substance in the internal organs of different species which will affect the interpretation of both single and multiple doses and the necessary extrapolation to humans.

Given all the admitted problems in interpreting the results of animal tests for developmental and reproductive toxicity, it is appalling that the NTP fails to consider non-animal test methods. For example, the European Centre for the Validation of Alternative Methods (ECVAM) recently validated an *in vitro* embryonic stem cell test as a sensitive and reliable method for detecting chemicals with embryotoxic potential — making it a valuable screen for potential developmental toxicants. The test uses rodent-derived stem cells, which survive in culture indefinitely and can develop into specialized cells such as heart cells. Embryotoxicity is determined by the ability of a test substance to prevent or limit the development of embryonic stem cells into specialized heart cells in culture (Genschow et al. 2002). Several *in vitro* methods are also available to study the mechanisms by which toxicity to reproduction occurs. The NTP should be championing their further development, validation and regulatory acceptance, per the NIEHS implementation guidelines developed pursuant to the NIH Revitalization Act.

We strongly urge the NTP to retract its call for further, unnecessary testing of methanol on animals.

Sincerely,

Jessica Sandler
Federal Agency Liaison