PCRM PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

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PETA
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Dear Dr. White,

These comments on the National Toxicology Program's (NTP) Research Concept for Polycyclic Aromatic Hydrocarbons (PAHs) are submitted on behalf of the more than three million members and supporters of People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine. PETA and PCRM are committed to using the best available science to protect animals from suffering in laboratory experiments and promote the acceptance of human-relevant methods for risk assessment.

In its Research Concept, NTP notes that individual PAHs, as well as the class as a whole, have been nominated on multiple occasions to the NTP for toxicological evaluation, but it's unclear whether the Research Concept is a response to these nominations. A Nomination Search on NTP's web site returns six PAH quinones nominated by a private individual in 2005 and the PAH class nominated by Health and Welfare Canada in 1994. In addition, in its review of EPA's "Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures" EPA's Science Advisory Board (SAB) recommended that the Agency seek support from NTP to validate the RPF approach.

We are concerned that a large number of individual PAHs and mixtures may be subject to a short-term testing panel which includes a sub-acute rodent study by the gavage route of exposure. Sub-acute rodent studies are likely to produce duplicative data for many PAHs. Rather than subject all test articles to a short-term test panel which includes this animal study, we recommend that at the very least, the need for additional animal data first be evaluated individually. In its Research Concept, NTP states: "It is impractical to comprehensively assess the toxicity/ carcinogenicity of the 1500+ identified individual PAHs and the practically infinite number of mixtures containing PAHs using the traditional two-year bioassay. Therefore, shorter term animal studies, alternative animal models, and *in vitro* assays are needed to provide information on a broader subset of individual PAHs and PAH mixtures." Longer term animal studies appear to be limited to targeted assessments in the proposed research project, and its iterative testing approach promises to avoid unnecessary resource expenditure. However, minimizing *any* animal use should be considered explicitly, particularly since efforts will be made to maximize the number of PAH-related test articles that can be included.

As EPA notes in its PAH Mixtures document, there is a large PAH database on carcinogenicity in animal bioassays. For this document, the Agency's primary literature search identified over 900 individual publications for a target list of 74 unsubstituted PAHs, from which over 300 data sets were extracted, reflecting dose-response data for 51 of the 74 PAHs. In its review, the SAB expressed concern that even more high quality animal data may have been dismissed due to EPA's stipulation that benzo(a)pyrene (BaP) be tested concurrently with the target PAH and noted that bioassays also exist for nitro-aromatics and alkylated PAHs. The SAB also recommended that the International Agency for Research on Cancer (IARC) Monograph, Volume 92, in which the potential carcinogenicity of 60 PAHs is assessed, be added to the database as an additional resource. NTP also notes that scientists at Health Canada have tested nine unsubstituted PAHs as well as several mixtures for genotoxicity in 28-day oral gavage studies and that the proposed project builds upon this research. Further discussion of Health Canada's PAH research program, along with references, if available, would be helpful.

Thus, while the PAH class is large, data from numerous animal studies exist for a significant number of PAHs such that new animal data need not be developed. The assessments mentioned above are limited to carcinogenic effects; however, the bioassays on which they are based typically include evaluation of additional endpoints (for example, pathology of reproductive organs) which may address non-cancer toxicities to be investigated in the proposed research project. In some cases (possibly including the Health Canada program), archived tissue samples may also be available which could be further examined (for example, for pathology and gene expression) in place of duplicating animal studies. With regard to route of exposure, NTP claims that oral gavage is considered to be among the human-relevant exposure routes. While humans are exposed to PAHs in the diet through consumption of PAH-containing foods, the reference cited (Phillips, 1999) makes no mention of oral gavage. Oral gavage, especially for repeated dosing, has serious animal welfare implications, so this route should not be selected over dietary exposure.

With regard to elucidating mechanisms and pathways of toxicity, NTP states that despite the large number of studies dedicated to elucidating the mechanisms involved in the carcinogenesis of PAHs, these mechanisms are not yet fully understood. However, in its Monograph, IARC notes that the use of mechanistic data to classify BaP indicates the increasing strength of mechanistic data to contribute to the identification of human carcinogens and describes in considerable detail both general and specific mechanisms of PAH carcinogenesis. Therefore, a more thorough discussion of mechanisms of toxicity identifying data gaps is warranted. NTP notes that 60 individual PAHs are included in the 10K compound library being screened in nuclear receptor and stress response pathway assays in Tox21 high throughput screening (HTS) efforts, the goal of which is to identify biologically meaningful endpoints that can be used in the development of a PAH-specific toxicity profile(s). Screening a larger number of individual PAHs and mixtures should be considered.

With regard to risk characterization, in its review of EPA's PAH Mixtures document, the SAB agreed that more comparisons of the RPF approach to estimates of cancer risk derived from whole mixtures are needed. However, the SAB described an application of the RPF approach to existing data from chronic bioassays in mice for two synthesized coal tar mixtures and noted that the PAH Mixtures document discusses the availability of several additional studies on mixtures that provide data for comparing cancer risk estimates using the RPF approach. This use of existing animal data should be considered as it would provide information about the RPF approach.

Given the large scale of the proposed project and the early stage represented by this Research Concept, it is essential for the public to have another opportunity for review and comment once the initial test articles are selected.

Thank you for your attention to these comments. Joseph Manuppello can be reached at (757) 793-8941, or by e-mail at josephm@peta.org.

Sincerely,
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