

**Ernest E. McConnell, D.V.M., M.S. (Path), DACVP, DABT
President, ToxPath, Inc.**

Office Telephone/FAX
919-848-1576

3028 Ethan Lane
Laurdane Est.
Raleigh, NC 27613

8 July 2008

To: Dr. Suhair Shallal
shallal.suhair@epa.gov

Subject: on EPA SAB draft Report on acrylamide.

I want to take this opportunity to briefly respond to the EPA SAB Report on Acrylamide (ACR) dated 6-27-08

In my opinion it is obvious that sections of this report are not in concert with, and are in fact, counter to contemporary pathology doctrine. I have tried to understand why this is still in the document after my testimony before the panel on March 11, 2008 where I pointed some of the flaws in the SABs evaluation of the pathology data on ACR. The only explanation I can come up with for why my comments were totally ignored in the SAB report is because there was no experienced rodent pathologist on the panel. However, I can appreciate how this can happen having been on the EPA Science Advisory Panel for ~10 years and chairing it for the last 5 years. From that tenure I found that any panel is to some degree a prisoner of the panel's scientific expertise. I feel certain that if a veterinary pathologist with experience in rodent carcinogenicity bioassays had been part of this panel, this problem would have been corrected in the SAB report.

Let me reiterate on a couple of the comments I made to the SAB and possibly provide further incite on these matters. I have discussed these comments with several of my ACVP colleagues and all agree with me.

1. On page 38 line 5, the report says *Primary CNS tumors as a group, which are discussed at considerable length in the draft document, should be restored to the list of experimental tumors produced by acrylamide ...bioassay, the so-called "malignant reticulosis," are identified only on the basis of their histologic pattern and not by definitive histogenetic criteria that identify their cell of origin. In fact, this pattern overlaps with the histologic pattern of malignant astrocytomas, and the argument that only CNS tumors of unequivocally glial origin should be counted is unjustified.* . I have discussed this with the pathologist (Dr. Michael Stedham, Pathology Associates, Inc. - PAI) that did the original evaluation of the pathology from this study. Even though he is now retired he told me he clearly remembers the study. He further told me that he used standard rodent pathology nomenclature to make his diagnosis of malignant reticulosis. In addition, due to the unusual morphology of this tumor, Dr. Stedham sought a consensus opinion from several other pathologists at PAI on each and every slide with this lesion

before arriving at his final diagnosis. Therefore, changing Dr. Stedham's diagnosis from malignant reticulosis to glioma is not proper, unless the person that made the change examined the slides him/herself. Even then, it would be customary to convene a Pathology Working Group to confirm his/her opinion in light of the fact that these are radically different diagnoses. In my original presentation and comments to the SAB I pointed out that malignant reticulosis is a tumor of the reticuloendothelial lymphatic system which is of endodermal origin. In contrast, gliomas are derived from ectodermal stem cells. Therefore, scientifically-based contemporary pathology convention suggests that it is improper to combine these two vastly different tumors for statistical analysis of a treatment-related effect. At the very least, the SAB should have contacted Dr. Stedham, who conducted the pathology in the Friedman *et al.* study in order to understand his rationale for making this diagnosis.

2. The SAB concluded that the tunica vaginalis mesotheliomas (TVMs) are a result of genotoxicity without reviewing the morphology of the tumors in question. On page 38 line 16, SAB states "*the spectrum of tumors consistently seen in acrylamide exposed rats is completely consistent with a DNA-reactive MOA, based on published data about other substances that induce or initiate the same kinds of neoplasms. The only agents known conclusively to induce tumors of the brain and peritesticular mesothelium in rats are all DNA-reactive*". A PWG was convened to review the TVMs from the study of Johnson, et al... It is my understanding that a copy of this report was submitted to the SAB prior to their meeting. The PWG report concluded that these tumors were more probably a result of a hormonal mode of action (MOA) rather than a result of genotoxicity for several reasons that are discussed in that report. In addition, I understand that a copy of a "white paper" on TVMs is currently being provided to the SAB on the human relevance of TVMs. I encourage the SAB to take a careful look at this report because it was written by Dr. Robert Maronpot, a highly competent board certified veterinary pathologist and toxicologist and recent Chief of the Pathology Branch of the NIEHS. In this white paper Dr. Maronpot did an extensive review of the chemical induction of peritoneal mesotheliomas and found that Fischer 344 rat mesotheliomas can be broken down into robust (high incidence) and non-robust (low incidence) tumors in terms of their incidence within a given chemical study. From his analysis, it appears that the robust tumors appear to be the result of genotoxicity while the non-robust do not.

Considering the above I still conclude that:

- A. Peritoneal mesotheliomas related to ACR are a result of a non-genotoxic MOA.
- B. Malignant reticulosis neoplasms and gliomas should not be combined for evaluation of the potential carcinogenic potential of ACR or any other chemical for that matter.

Thank you for allowing me to comment on this most important document. Should you have questions concerning this brief report, please feel free to contact me. Unfortunately, I will not be able to participate in your conference call on this subject because I will be participating in a Homeland Security Agency meeting during that time.

Sincerely,

Gene McConnell