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Comments on the SAB Review

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My name is Bob Maronpot. I am a board certified veterinary pathologist (ACVP) and toxicologist (ABT) and have designed, conducted, and evaluated rodent carcinogenesis studies for 40 years, including 26 years at NIEHS/NTP where I was responsible for the quality and diagnostic accuracy of NTP bioassay pathology. I am a senior pathologist at Experimental Pathology Laboratories, Inc. in Research Triangle Park, NC and in that capacity I recently reviewed studies involving 21 compounds in which there was a tunica vaginalis mesothelioma response.

Based on the incidence of tunica vaginalis mesotheliomas in treated rats, mostly in F344 rats, I classified the mesothelioma response as robust or marginal-to-non-significant. When available the time to first mesothelioma, as a measure of latency, and the presence of a clear dose response were also factors that assisted with the classification of the response. After this classification based on the pathology results was completed, the genotoxicity data was provided by a genetic toxicologist. The results are presented in Table 30 of my report provided to the SAB; the tabulation is ranked in decreasing order based upon the maximal mesothelioma response in treated rats.

What is clear from the tabulated data is that not all tunica vaginalis mesothelioma responses are associated with genotoxic compounds. The majority of the robust responses are associated with genotoxic compounds and the

majority of the non-robust responses are associated with non-genotoxic compounds. Acrylamide is among the non-robust responses for mesothelioma.

Since non-genotoxic chemicals are associated with tunica vaginalis mesothelioma induction, a plausible non-genotoxic mechanism seems apparent. In 18 of the 21 studies the route of xenobiotic administration was oral, inhalation, or subcutaneous (vs. intraperitoneal injection) and these 18 studies were conducted in F344 rats. F344 males have a greater than 90% incidence of spontaneous Leydig cell tumors secondary to dramatic age-associated perturbation of the hormonal milieu. The altered hormonal balance within the testes results in a hormonally rich transudate that bathes the mesothelial cells of the scrotal sac and stimulates an autocrine mitogenic response. The pressure on the mesothelial cells from the enlarged testes also stimulates the same autocrine mitogenesis. The enhanced mesothelial cell mitogenesis results in increased frequency of tunica vaginalis mesotheliomas in male F344 rats. Neither female F344 rats nor mice of either gender in the same studies developed mesothelioma. Based upon my pathology experience, the tunica vaginalis mesothelioma response is specific to the male F344 rat, can be exacerbated by treatment, and is not a relevant predictor of human carcinogenic risk (See Table 31). Furthermore, the F344 rat tunica vaginalis mesothelioma is less aggressive, less pleomorphic, and less anaplastic with only a minimal stromal component in contrast to asbestos-associated human mesotheliomas.

Prompted by a statement regarding malignant reticulosis on page 38 of the SAB draft report, I want to make the point that (a) the major references related to diagnostic criteria and classification and (b) the prevailing opinion of toxicologic pathologists who evaluate rodent cancer studies is that malignant reticulosis is a

lymphoreticular neoplasm with a pronounced perivascular and subarachnoid infiltrative growth pattern and is not of astrocytic/glial origin.