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COMMENTS OF DR, MARVIN A. FRIEDMAN, PHD, DABT, DATS.

ON THE DRAFT EPA SAB REPORT REVIEW OF

EPA'S, "TOXICOLOGICAL REVIEW OF ACRYLAMIDE".

My name is Marvin Friedman. I am a Board certified toxicologist and Senior Advisor to SNF, the world's premier manufacturer of acrylamide. I have been studying acrylamide toxicology continuously for the past 28 years. I am presenting the oral comments of the North American Polyelectrolyte Producers Association (NAPPA).

1. We commend the SAB for recommending that EPA prepare a BMD for the Costas/Calleman study. This study represents the best source of information on acrylamide effects on human health. It is based on clinical monitoring of workers exposed to acrylamide in the workplace. It includes area monitoring for exposure and hemoglobin adducts for biomonitoring.
2. We are disappointed at the responses to Charge Questions 18, 19 and 20. SAB concludes that acrylamide is a genotoxic carcinogen based on the simplified rationale that acrylamide metabolizes to glycidamide, which produces DNA adducts and since acrylamide is mutagenic in mice, the tumors produced by acrylamide could only be induced by a genotoxic mode of action.
3. The charge that the hormonal mode of action is purely speculative dismisses most of the recent scientific analyses of acrylamide tumorigenicity. Further, it is no more speculative than the genotoxic mode action.
4. SAB has ignored the poor correlation between induction of DNA adducts and consequent mutagenicity. The best example of this is in the dominant lethal assay where the DNA adducts are observed throughout the spermatogenic cycle but only during a short period are

dominant lethal mutations observed. In the micronucleus test, this is also true. If one compares the incidence of micronuclei after a single administration (*e.g.*, Abramsson-Zeterburg, 2003) with that of multiple injections (5 days as in Witt *et al.*, 2003), the micronuclei incidence is the same. Except for the fact that both mutations and DNA adducts are observed, there are no conclusive data to prove that these adducts induce mispairing. There is information that acrylamide metabolism is required based upon both transgenic mice and using aminobenzotriazole to inhibit metabolism. Aminobenzotriazole, however, does not inhibit cell transformation *in vitro*.

5. Acrylamide is mutagenic in mice at high doses (the BMD₁₀ being about 40 mg/kg) but negative in somatic cells in rats, the species used for cancer assessment. When one analyzes strand breaks in the comet assay in both rats and mice, there is no temporal correlation between DNA adducts and positive comets. These inconsistencies can be explained through alternate modes of action for the mutagenicity. These include induction of oxidative stress and inhibition of kinesin, which together can explain virtually all of the findings. Acrylamide mutagenicity is very weak.
6. It is clear that adducts are formed and that acrylamide is mutagenic, at least in mice. The SAB makes the leap to cause and effect in several ways. First, they conclude that since it is mutagenic, the diagnosis of brain tumors by Dr. Stedham had to be incorrect and propose that his diagnosis be changed, without consulting him or any pathologist who has read the slides. In his written comments, Dr. McConnell has expressed strongly on this issue. Then, with brain tumors confirmed, the allegation is made that all compounds which induce gliomas and peritoneal mesotheliomas are mutagens. In fact, there are only 2 chemicals in this category: ethylene oxide and glycidol. Structural congeners such as epichlorohydrin, propylene oxide, etc., do not share this effect.
7. A Pathology Working Group (PWG), managed by the same organization that will conduct the PWG for the NCTR acrylamide chronic study, concluded that the peritoneal mesotheliomas were not a result of genotoxicity but were rather hormone related.

8. It should be noted in the report that there was no robust malignancy in these studies characteristic of genotoxic carcinogens. The SAB justifiably comments on the issue of the thyroid tumors. However, the pattern of response of all the tumors, including the thyroid, is the acceleration of background tumors. That physiological control mechanisms differ between elderly and younger rats is well established. In both chronic studies, rats appeared normal at 18 months and at 24 months benign tumors were observed. One would expect that life-threatening tumors would have been observed earlier if acrylamide were a genotoxic carcinogen.
9. SAB precludes consideration of mode of action by citing a lack of concordance between rodent and human cancer. However, it is widely accepted that because of the unique physiology of the rodent, some modes of tumor formation are not relevant to man. This is true of the fibroadenomas observed in female rats and the peritoneal mesotheliomas observed in males.
10. Reliance on mouse initiation/promoter studies is out of date science. These have been shown to be unreliable and not relevant to man (references are being submitted as an addendum to the hard copy of my presentation as an appendix). Furthermore, SAB did not point out that acrylamide was not a complete carcinogen in these studies as it always required TPA.
11. NAPPA believes that the evidence supports a non-genotoxic mode of action. SAB, at least, should have insisted that EPA conduct a risk assessment on the non-genotoxic mode action for completeness.
12. I would like to add that being allocated only 1 week to prepare comments and 2 weeks to organize and to prepare for oral testimony has resulted in the Industry response to the draft report being severely restricted both in scope and depth.