Meeting with the SAM Panel

October 29, 2003

ACC Representatives
Dr. Gary Ceska, Sartomer Corporation
Dr. Fred Johannsen, UCB Chemicals
Dr. John Van Miller, TRS Inc.
Dr. Anne LeHuray, American Chemistry Council (SAM Panel Manager)

NIEHS Representatives
Dr. John Bucher
Dr. Rajendra Chhabra
Dr. Rick Hailey
Dr. Cynthia Smith

Dr. Mary Wolfe

Dr. Bucher welcomed everyone. The attendees introduced themselves.

Introduction to the SAM Panel

Dr. LeHuray provided general comments about the SAM Panel.

- It is an industry group, founded 1987 to conduct research addressing questions about carcinogenicity of acrylates and methacrylates.
- There are 12 Membership companies.
- The major, current activity is HPV/ICCA Program (HPV >/= $1x10^6$ lb/yr).

She gave a chronology of the SAM research program. Dr. LeHuray distributed a list of SAM Panel final research reports and related documents and noted that SAM Panel reports are in the public domain.

Chemistry

Dr. Ceska's comments for PETA and TMPTA centered on what they are and how they're used.

- PETA and TMPTA are low volume acrylates that form highly cross-linked polymers.
- Workplace exposure is minimal and no consumer exposure is anticipated.
- Both PETA and TMPTA currently have very limited use per se. Over the past 20 years, the primary use is the alkoxylated forms because this derivitization reduces/eliminates skin irritation and enhances reactivity. .
- SAM Panel survey: commercial PETA is primarily triester (average 31%) and tetraester (average 45%).
- SAM Panel survey: commercial TMPTA is primarily triester (average 81%).
- Curing routes are UV/Electron Beam or heat.

Toxicology and Carcinogenicity Studies

Dr. Van Miller showed tables listing historical bioassays on multifunctional acrylates, both positive and negative, information on other bioassays with monofunctional acrylates, and details about four TREGDA range finding and chronic bioassays reported by Van Miller *et al.* (*Regulatory Toxicology* 37:54-65, 2003). A copy of this paper was provided. His slides and comments also addressed dose selection issues for the planned NTP chronic studies of PETA and TMPTA based upon his evaluation of the completed NTP 3-month studies and the TREGDA studies.

Dr. Chhabra distributed a handout summarizing information on outcomes of the NTP pre-chronic studies, the studies conducted in Tg.AC and on the dose levels proposed for the chronic bioassay. He said the contract for the chronic bioassay would be awarded soon.

Dr. Bucher briefly highlighted the view of regulatory agencies regarding transgenics: p53 is most accepted, rasH2 from Japan is generally accepted, and FDA accepts Tg.AC for registration of dermally applied drugs. He noted that the NIEHS was involved in development of the Tg.AC model. The NTP is conducting the 2-year studies for carcinogenicity of PETA and TMPTA in standard rodent models to confirm the findings in the Tg.AC.

There was discussion about skin irritation, its signs and diagnosis, and its potential relationship to tumor outcome. The NTP acknowledged that its historical database only includes 26 completed and reported cancer studies where the chemical was applied dermally. Only four of those studies were positive for dermal carcinogenicity. Dr. Van Miller raised questions about dose setting in the NTP chronic studies and indicated that the SAM Panel feels that the proposed high and mid doses, 3 and 1.5 mg/kg/day for PETA and 6 and 2 mg/kg/day for TMPTA, would produce excessive irritation in both rats and mice and are, therefore, too high. He also suggested a dose below 0.75 mg/kg be included. The NTP participants responded that based on their experience and information in the literature, the minimal to mild chemically induced dermal lesions and cell proliferations are not always triggers for formation of tumors. The SAM Panel-sponsored studies on TREGDA also supports this point, where no tumors were observed even though there were significant skin lesions and cell proliferation observed at various time points in the studies. The review of the Van Miller paper suggests the criteria used for selection of dose levels for the PETA and TMPTA chronic studies by the NTP are generally similar to the ones used for studies on TREGDA. The NTP believes its low dose at 0.75 mg/kg is low enough. However, the NTP said it would review again the prechronic data from PETA and TMPTA studies to make sure the selection of dose levels is appropriate for the planned chronic studies. The NTP traditionally includes a dose that reaches the MTD. If there is any adjustment in the dose selection, the SAM will be informed.

The NTP invited comments from the ACC on the protocol for the chronic studies. The ACC requested that pathological response be evaluated at early time points during the study and proposed that cell proliferation studies be included to see if cell acanthosis correlates with BrdU labeling.

Chemistry of PETA and TMPTA Used in NTP Studies

Dr. Smith presented information about the PETA and TMPTA used in the previous NTP studies (3-month and Tg.AC).

- TMPTA from Aldrich - 80-85 % pure
    - 14-day, 90-day and Tg.AC studies all done with the same lot
    - Samples were reanalyzed for purity after 30-days of the study, periodically during the studies, and at the end; no changes were observed.
    - NTP has sufficient TMPTA to do the chronic study
- PETA

- The product used in the 90-day and Tg.AC studies was 40% pure and 10% pure for the 14-day study.
- NTP is now doing characterization of material for a study and having problem because of impurity of the available PETA from commercial sources.

Dr. Ceska cautioned the NTP to look for the presence of inhibitors (HQ or MeHQ) in the samples. Dr. Smith asked the SAM Panel's assistance in getting PETA to study.

Summary

Dr. Bucher said the NTP would consider adding animals to the chronic study so skin histopathological evaluations could be conducted. The program would consider evaluations at 14-days and 90-days to enable comparisons to the previous 14-day and 90-day NTP studies, especially since the material being tested is different from that used previously.

The ACC asked if it might provide monetary support for the additional histopathology studies. The NTP declined this offer, but added that the ACC could make a contribution to the NIEHS gift fund.

Dr. Bucher asked the ACC to provide written input about what elements they would like to see changed or added to the protocols for the chronic studies, but added that the NTP would have sole responsibility for their design, conduct and analysis. The NTP asked that any comments on the protocols be sent in a timely manner, because the program is continuing to move forward with initiation of the chronic studies.

The NTP asked the ACC for help in identifying lots of PETA for use in the NTP study. The NTP would like PETA of similar composition to that tested in the Tg.AC.