DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Memorandum

Date: April 6, 2004

From: R. S. Chhabra, Study Scientist

Subject: Reconsideration of Triacrylate Studies (PETA and TMPTA)

To: The Record

A meeting was held on April 06, 2004, to reconsider the previously approved carcinogenicity studies on trimethylolpropane triacrylate (TMPTA) and pentaerythritol triacrylate (PETA). The participants in the meeting were: Drs. Bucher, Chhabra, Hailey, Melnick, Roycroft and Ms. Orzech.

Background Information: PETA and TMPTA were nominated to NTP by the NCI for multi-dose dermal carcinogenicity studies with a high priority. The nominations were as representatives of multifunctional acrylates used and produced in much smaller quantities than the basic acrylates. From the available data in the literature the critical effects of TMPTA and PETA are skin and eye irritation. Repeated dermal exposure to humans or animals leads to contact dermatitis and provokes corrosion to the skin. Both chemicals are moderate to strong sensitizers in experimental animals and humans. TMPTA and PETA are non-mutagenic in bacteria, but mutagenic in mammalian cells in vitro. The dermal carcinogenicity studies performed by Industry in mice were considered inadequate. NTP absorption and metabolism studies showed that ^{14}C TMPTA is absorbed from skin in rats and mice, parent chemical/metabolites are distributed throughout the body and excretion is mainly via urine. Following dermal application, the proportion of the dose absorbed increased as the dermal dose concentrations decreased. Quantitation of parent TMPTA in blood was not possible due to the chemical instability of TMPTA in blood.

The in vitro, 2- and 13-week dermal studies showed that both PETA and TMPTA affect the site of application (SOA) in F344 rats and B6C3F1 mice. The microscopic examination of the skin (SOA) showed hyperplasia, hyperkeratosis, parakeratosis and inflammation. No systemic toxicity was observed except some changes in organ weights, which were considered, unrelated to the treatment. In the Tg. AC dermal 26-Week studies, both PETA and TMPTA produced tumors at the site of application in a dose-related fashion. PETA was found to be a more potent dermal carcinogen than TMPTA. The results of transgenic mouse studies were presented to the NTP Board of Scientific Counselors Subcommittee on Technical Reports in the spring of 2002 as definitive studies for carcinogenicity. The Board did not accept the NTP recommendations and therefore, the reports were withdrawn and will be published as part of the new study report series on toxicity and carcinogenicity findings from genetically modified models.

In October 2002, the study scientist after consultation with a study design group recommended performance of two-year dermal toxicity and carcinogenicity studies on these chemicals using a traditional NTP bioassay protocol. The Project Review Committee (PRC) approved the recommendations. The dose levels selected for the TMPTA chronic dermal studies were 0, 0.75, 2.0 and 6.0/mg/kg in acetone for both rats and mice. The skin lesions at 12 mg/kg in TMPTA 90-day and transgenic mouse studies were severe enough to exclude that dose level. For the PETA chronic dermal studies the dose levels selected were 0, 0.75, 1.5, and 3.0 mg/kg in acetone for both rats and mice. The severity of the dermal toxicity observed at 6 mg /kg and above in the 90-day and transgenic mouse studies was considered prohibitive for the chronic bioassay. The contract was awarded in September 2003 to conduct the studies.

Group Deliberations: At the request of the American Chemistry Council's (ACC) Specialty Acrylate and Methacrylate (SAM) Panel the study design group listed above reconsidered the conduct of PETA and TMPTA studies. Another reason for this reconsideration was a changing in the Program emphasis on carrying out further studies leading to validation of transgenic mouse models. Based on the recommendations received by the Program at the March 10-11, 2004 meeting of the Scientific Advisory Committee for Alternative Toxicological Methods, Dr. Bucher informed the group that we should not consider validation of transgenic mouse models as a high priority rationale to do PETA and TMPTA chronic studies. At present the scientific community remains divided regarding the use of transgenic models as replacements for the traditional two-year bioassay to identify potential carcinogens. Taking into consideration this information, the group recommended that at present the NTP should perform studies on TMPTA only and retain an option to do studies on PETA later after the results of TMPTA suggested a need. The main reason for this recommendation was based on the fact that these chemicals are structurally related and had similar effects in the NTP toxicity and transgenic mouse studies, and most likely the chronic effects would be similar too. TMPTA was selected because it has less than 20% impurities compared to about 55% in PETA preparations. Also, the NTP has enough left over TMPTA from the previous studies and could thus perform the 2-year studies with the same material used in the prechronic and transgenic mouse studies.

In the 14-day and 90-day toxicity studies, the skin was the only target organ identified for these chemicals. Therefore, the dose levels for the TMPTA chronic studies were selected based on the severity of the skin lesions. Doses were selected as is routine for NTP dermal studies to avoid significant skin irritation, and to preclude adverse effects on survival and growth of animals. The dose levels selected for both male and female mice were 0, 0.75, 1.5, 3.0 and 6.0 mg/kg. Based upon the histological data from the 13-week studies, 3 mg/kg in mice was considered the likely MTD and an acceptable high dose. Because there is still some interest in genetically modified models, because a clear tumorigenic effect in the Tg.AC study occurred at 6 and not 3 mg/kg, and because lesions in animals exposed to 6 mg/kg were not markedly different from those at 3 mg/kg, a 4th group was added at 6 mg/kg. In male rats, 0, 0.75, 1.5, and 3.0 mg/kg and in female rats 0, 1.5, 3.0 and 6.0 mg/kg were selected. The higher dose levels for female rats were based on the fact that the incidence and severity of lesions in females exposed to 6.0 mg/kg in 90-day toxicity were almost identical to those in males exposed to 3.0 mg/kg. In both male and female mice the dose levels selected were 0, 0.75, 1.5, 3.0 and 6.0 mg/kg. Because the TMPTA studies would be performed using the same materials as used in the 90-day studies, the group did not consider it necessary to incorporate an interim sacrifice at 3 months or any of the additional studies suggested by the SAM panel to the TMPTA protocol.

Copy:

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