RADTECH
INTERNATIONAL
NORTH AMERICA

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THE ASSOCIATION
FOR THE
ADVANCEMENT
OF UV/EB PROCESSING
TECHNOLOGY

Dr. Kenneth Olden, Director
National Institute of Environmental Health Sciences, and
National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709-2233

Dear Dr. Olden:

I am writing on behalf of RadTech North America International, Inc. (RadTech) a nonprofit organization of more than 800 corporate and individual members. Our members are aware of the dermal carcinogenicity studies of trimethololpropane triacrylate (TMPTA) in B6C3F1 mice and F344 rats that the National Toxicology Program (NTP) is planning to initiate in the very near future. We are writing to request that two specific issues be addressed prior to the initiation of the in-life phases of these studies.

Specifically, RadTech understands that the current design of the planned TMPTA studies does not take into consideration certain aspects critical to the appropriate interpretation of their results. In particular, the selection of exposure levels proposed in the planned studies has apparently not utilized all of the available information about the type and degree of inflammatory response and cell proliferation that occurred in previous studies of TMPTA and related agents by NTP and others. To our knowledge, this factor does not appear to have been addressed at the necessary level of detail in the present study design. Secondly, the study design does not include specific monitoring of the inflammatory response and cell proliferation that are expected to occur.

We are sincerely concerned that the ability of NTP, of other agencies, and of our industry to objectively interpret the results of these studies may be confounded by the lack of inclusion of these key aspects in the studies. Prior work with TMPTA and representative acrylates teach that a central issue in the design and conduct of these studies is how to achieve an understanding of the relationship of any possible carcinogenicity findings to the inflammatory and associated cell proliferative activity known to be associated with poly-functional acrylates. Because the reactive molecules associated with inflammatory cell responses and the cell proliferation induced by irritating materials may contribute to carcinogenesis both independently of the carcinogenic activity of the test article (*e.g., via* cancer initiation by reactive oxygen species generated by inflammatory cells) and *via* strong promotional activity (*e.g.*, due to induced cellular proliferation), the failure to adequately measure and understand these

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responses would make it difficult to interpret the results and may compromise much of the value of the studies.

Following extensive interaction between industry and the U.S. Environmental Protection Agency (USEPA), it was jointly determined that careful monitoring of the irritation and cell proliferative responses associated with poly-functional acrylates was a critical factor in their evaluation (van Miller et al., Regulatory Toxicol. Pharmacol. 37: 54-65, 2003). The design of previous studies of model compounds in this class (trimethylene glycol diacrylate (TREGDA) and triethylene glycol dimethacrylate (TREGDMA)) that was agreed upon as a result of this government-industry interaction included careful monitoring of these factors. That cooperative interaction between government and industry to develop a sound scientific approach to studying acrylates and methacrylates as a class is considered an exemplary model by many of us of government and industry working together to achieve sound and reasonable regulatory controls. RadTech would like to work cooperatively with NTP to achieve a similar emphasis on these important factors in the presently planned studies of TMPTA.

We specifically request that two issues be addressed prior to initiation of the in-life phases of the currently-planned mouse and rat studies of TMPTA:

1. Conduct a comparative pathology review, using a panel of well-recognized expert pathologists identified by RadTech and by NTP, of the degree of inflammation, infiltration by specific classes of inflammatory cells, and cell proliferation in tissues from the two-week and three-month preliminary B6C3F1 mouse and F344 rat studies and the lifetime Tg.AC dermal carcinogenicity study conducted by NTP (NTP Technical Report 516, NIH Publication No. 02-4450) and the lifetime dermal carcinogenicity studies conducted by van Miller et al. (Regulatory Toxicol. Pharmacol. 37: 54-65, 2003). We consider this necessary to support the current dose selection, and also to assure that baseline data on the nature and magnitude of the induced inflammatory reactions are understood and are comparable across studies. RadTech understands that the doses presently planned to be used by NTP may exceed even the agency's own internal criteria for determining the Maximum Tolerated Dose (MTD) for dermal investigations. We hope this is not the case, and therefore we think it is necessary, before the in life stage begins, to have the prior pathology evaluated by an expert group of pathologists with experience in the field of dermal carcinogenesis. Following this review, the doses to be used should be re-evaluated based on the results of these findings, using as an upper test dose a level that induces minimal but demonstrable cell proliferation and irritant response.

2. Include a careful determination of cell proliferation, degree of inflammation, and specific inflammatory cell response during the course of the studies. At a minimum, this should include measurement of cell proliferation using BUDR-labeling and characterization of inflammatory cell infiltration using leukocyte-specific stains in satellite groups at two or three times during the course of the study. This information will be needed to interpret the study results appropriately,

may identify thresholds for key events that are necessary to understand in order to establish appropriate regulatory exposure standards, and is critical to allow comparison of results of the present studies with those previously reported in the literature.

These recommendations are based on our extensive discussions with toxicologists in our own organization and member companies, with the ACC SAM panel and other trade groups, and with an expert toxicologist, Dr. James MacGregor, who we have retained to evaluate the current study design in the context of previous studies.

RadTech is a committed stakeholder in the outcome of these studies because acrylates are used extensively in the range of industries that we represent. Specifically, TMPTA is used as a component in our ultraviolet and electron beam (UV/EB) coatings, adhesives, and inks. Our products have advantageous performance properties, are highly energy efficient, and are recognized by the USEPA for providing many businesses with the means to significantly lower their volatile air emissions. UV/EB is a fast growing technology for applications in graphic arts (packaging, labels, and metal and plastic containers for non-food and food applications), printing, wood furniture, electronics and photoresists, rapid prototype parts manufacture, automotive parts, and a host of other commercial products. Acrylate-based chemistry is the life blood of our business. Without it, our industry would not exist.

We share NTP's desire that your studies be of the best possible quality, and hope you will agree that these recommendations will assure that the results of these studies can adequately address the questions for which they have been designed. We are sincerely concerned that the ability of NTP, of other agencies, and of our industry to objectively interpret the results of these studies may be confounded by the lack of inclusion of these key aspects in the studies. We believe that these recommendations should be part of the studies to assure the overall scientific integrity of the study design, and hope that you agree and act favorably on these recommendations. We would be willing to discuss cost-sharing in relation to these initiatives with you if that is appropriate.

We understand that the initiation of the in-life phase of the NTP studies is imminent, and we respectfully request that you take immediate action on this request so that appropriate steps can be taken before this phase of the studies is initiated.

Sincerely yours,

David Diehl
President, RadTech