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January 25, 2012

Via Electronic Mail and US Mail

Danica Andrews, Designated Federal Official
Office of Liaison, Policy and Review
Division of the NTP, NIEHS
P.O. Box 12233
MD K2–03
Research Triangle Park, NC 27709

Re: NTP Draft Study Report No. 576; Request for Consideration by Peer Review Panel

Dear Ms. Andrews:

On behalf of RadTech North America International, Inc. (RadTech), the trade association for UV & EB curing technology, we are submitting the following comments on the Draft Technical Report 576 on trimethylolpropane triacrylate (TMPTA) in B6C3F1 mice and F344 rats conducted by the National Toxicology Program (NTP). Under the conditions of these 2-year dermal studies, Draft Report 576 proposes the following findings:

- No evidence of carcinogenic activity of trimethylolpropane triacrylate in female F344/N rats administered 0.3, 1.0, or 3.0 mg/kg and some evidence of carcinogenic activity of trimethylolpropane triacrylate in male F344/N rats based on increased incidences of malignant mesothelioma; and

- No evidence of carcinogenic activity of trimethylolpropane triacrylate in male B6C3F1/N mice administered 0.3, 1.0, or 3.0 mg/kg and some evidence of carcinogenic activity of trimethylolpropane triacrylate in female B6C3F1/N mice based on increased incidences of uncommon malignant hepatic neoplasms (hepatoblastoma and hepatocholangiocarcinoma) and benign stromal polyp or stromal sarcoma of the uterus.

RadTech supports the information that is being separately supplied by the Specialty Acrylate and Methacrylate (SAM) Panel for consideration by the Peer Review Panel. Prior to the February 8-9, 2012 meeting at which Draft Report 576 will be reviewed, RadTech is submitting the following comments for consideration by NTP and the Peer Review Panel.

Characterization of certain information on multifunctional acrylates and prior NTP testing in the Draft Report

RadTech would like to begin by offering comments on NTP's proposed study rationale on page 28 of the Draft Report, which is stated as follows:

> *Trimethylolpropane triacrylate was nominated by the National Cancer Institute for study due to its high production volume and use, the potential for human exposure, and the lack of adequate chronic toxicity and carcinogenicity data. It was also chosen as a representative of the multifunctional acrylate class. Trimethylolpropane triacrylate is a suspected carcinogen as a member of this class of compounds; some members of this class have been shown to be carcinogenic to mice in dermal studies. Trimethylolpropane triacrylate was studied in the Tg.AC hemizygous mouse model by the NTP and was found to be positive for carcinogenic activity, but the Tg.AC hemizygous mouse model was not accepted by the NTP Board of Scientific Counselors as an alternative test system for evaluation of potential carcinogenic activity (NTP, 2005a). Therefore, the NTP decided to perform the 2-year carcinogenicity studies in rats and mice that are reported here. (Emphasis added)*

The sentences underlined above could easily be misread to attribute suspected carcinogenic potential to the multifunctional acrylate class of compounds. This would be inappropriate for several reasons. Two long-term dermal studies conducted in cooperation with the USEPA showed no carcinogenic response in other acrylates/methacrylates in this class (triethylene glycol diacrylate (TREGDA) and triethylene glycol dimethacrylate (TREGDMA)).[1] In addition, TMPTA and several other acrylates were not found to elicit carcinogenic effects after 80-week dermal carcinogenicity studies as reported by Andrews and Clary.[2] TMPTA and numerous other acrylates are negative for mutagenicity *in vivo*.[3]

Moreover, the prominent weight given to test results for TMPTA using a transgenic mouse (the Tg.AC assay) is not appropriate for inclusion in this report. Through the NTP peer review process, a consensus was reached that results from this assay are not definitive of a carcinogenic response.[4] The way that the Draft Report characterizes these results was first rejected by the NTP Board of Scientific Counselors Subcommittee on Technical Reports in the spring of 2002.[5] Repeated peer review sessions

[1] van Miller et al., Regulatory Toxicol. Pharmacol. 37: 54-65, 2003.

[2] Andrews, L.S. and Clary, J.J., J. Toxicol. Environ. Health 19:149-164, 1986.

[3] Johannsen, F.R. et al., Regulatory Toxicol. Pharmacol. 50: 322-335, 2008; See also NTP's negative genotoxicity findings at http://ntp.niehs.nih.gov/index.cfm?objectid=BD8DA5DC-123F-7908-7B1846717AF01C32.

[4] NTP Workshop on Transgenics, Feb. 21, 2003.

[5] Chhabra, R.S., NTP, Memorandum to the Record, April 6, 2004.

continued to reject the characterization of these results in the Draft Report. Due to uncertainty over its utility, NTP's Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) did not move forward with validation of the Tg.AC model.[6]

Listed below are other references in the Draft Report that go beyond the scope of the studied chemical by attempting to characterize multifunctional acrylates as a class based on the results of this single study, or which are highly speculative on other grounds, such as through reliance on the results from the Tg.AC model:

- NTP's veiled and unsubstantiated reference to transgenic model results on other unnamed multifunctional acrylates on page 28;
- On page 62, the speculative statement that: "*Pentaerythritol triacrylate was not tested in 2-year studies because trimethylolpropane triacrylate and pentaerythritol triacrylate are structurally related and caused similar effects in the toxicity and transgenic mouse studies, and similar chronic effects were expected for both chemicals;*"and
- On page 65, the Draft Report again cites the Tg.AC model as support for the carcinogenic potential of TMPTA.

To maintain the integrity of NTP's Peer Review system, in which the NTP has been repeatedly advised not to infer that results from the Tg.AC model should be characterized as a carcinogenic response, RadTech respectfully asks that the Peer Review Panel:

- ✓ Recommend that the sentences noted above on pages 28, 62, and 65 be struck from the Draft Report.

2. ***Characterization of liver tumor incidence***

   a. ***Dose-response***

In Table 13 (page 57 of the Draft Report), the incidence of "hepatoblastoma (multiple)" in female mice is low. This effect is noted in one animal in the lowest dose group (0.3 mg/kg). In addition, incidences of "hepatoblastoma (includes multiple)" are separately noted and include 4 animals in the 0.3 mg/kg group, zero animals at the mid-range dose of 1.0 mg/kg, and 3 animals in the 3.0 mg/kg group. There is no dose-related response. This is similar to the results for "hepatocellular carcinomas" in Table 13, for which there is no associated dose response and NTP found these results not to be treatment related. With respect to these findings, NTP states on page 56:

[6] SACATM Meeting Summary Minutes, March 10-11 2004.

Female mice exposed to trimethylolpropane triacrylate showed positive trends in the incidences of hepatocellular carcinoma. However, increased incidences in treated groups were not significant and not dose related; therefore, this neoplasm is not treatment related.

RadTech respectfully requests that the Peer Review Panel consider:

- ✓ Whether NTP should re-evaluate its conclusion that low incidences of "hepatoblastoma, multiple" and "hepatoblastoma, (includes multiple)" are treatment related because the incidences are not dose-related;

- ✓ Whether these incidences could be sporadic incidences and not treatment related for other reasons in addition to lack of dose response;

- ✓ Whether NTP's characterization of these two categories hepatoblastoma (multiple) vs. hepatoblastoma (includes multiple) is appropriate; and

- ✓ Whether the hepatoblastoma findings should be re-evaluated to determine whether they should be re-classified, together with the hepatocholangiocarcinoma findings, as hepatocellular carcinomas. NTP has re-evaluated findings for these two liver tumor types for the tested species (B6C3F1 mice) in the past.[1] Their reclassification would not change the finding that incidences of hepatocellular carcinomas in the treated groups do not demonstrate a dose response.

The NTP Pathology Working Group (PWG) held a public review meeting on Oct. 1, 2009 to review the pathology for the rat findings. No liver effects were noted as treatment related in that study. However, to the best of RadTech's knowledge, no similar public meeting was held to review the mouse findings.

b. Incidence of hepatoblastoma and hepatocholangiocarcinoma in male mice

On page 56, NTP states:

Based on the rarity of these neoplasms in female mice and their absence in the concurrent vehicle controls, hepatoblastoma and hepatocholangiocarcinoma were considered to be treatment-related lesions.

[1] See, e.g., *"During the pathology review procedures several of the tumors diagnosed originally as hepatocholangiocarcinomas were considered more appropriately called hepatoblastomas."* Bucher J. (1990). Testimony at Board of Scientific Counselors, National Toxicology Program; Peer Review of Draft Technical Report of Long-Term Toxicology and Carcinogenesis Studies and Toxicity Study, Sodium Fluoride; Research Triangle Park, North Carolina, Thursday, April 26, 1990.

NTP's statement above appears to be based on the following factors: the control female mice in this test did not develop such tumors, the historical control ranges for female mice for hepatoblastoma are low, and hepatocholangiocarcinoma has not been seen in the historical control population of female mice.

However, Draft Report No. 576 reports the incidence of both hepatoblastoma and hepatocholangiocarcinoma in the control male mice (see Appendix C-8) as the same or higher than treated males. More specifically, 5 out of 50 of the control male mice developed hepatoblastoma in the liver and 2 out of 50 control males developed hepatocholangiocarcinoma in the liver. By comparison, the treated male groups either have lower or equal tumor incidences relative to the control group, except for one additional incidence in the 1.0 mg/kg treated group of hepatocholangiocarcinoma than in the control group. The historical control data for male mice is not provided in the NTP report.

A review of the published literature indicates supportive references for the rarity of these tumors, while at least one recent report has concluded that findings of hepatocholangiocarcinoma in B6C3F1 mice (males and females) have not been considered treatment-related in any NTP study.[8] Additionally, hepatoblastoma has been characterized in mice as "a poorly differentiated liver tumor that develops spontaneously or can be induced by a number of chemicals" and the authors note that mouse strains appear to differ in their susceptibility to this rare tumor, with B6C3F1 mice being among the susceptible strains.[9] The authors conclude:

> *Although a variety of chemicals caused an increased incidence of mice with hepatoblastoma, there was no apparent association between a specific chemical structure or a biological class of compounds and their capacity to induce hepatoblastomas.*

RadTech respectfully requests that the Peer Review Panel consider:

- ✓ The references provided in this section of our comments;
- ✓ The historical control data for the male mice for these tumor types; and
- ✓ On what basis, if any, would it be appropriate to characterize these neoplasms as treatment related given the incidences in control and treated male mice.

c. Statistical significance

In Table 13 on page 57, in female mice, hepatocholangiocarcinoma was observed in only one treated animal in the 1.0 mg/kg group. Also as previously noted, the incidence of "hepatoblastoma

[8] Moore, et al., Toxicol Pathol. 38:1 E7-E12, January 2010.

[9] Hepatoblastomas in Mice in the US National Toxicology Program (NTP) Studies. Toxicol. Pathol. 30: 580, 2002.

(multiple)" in female mice is noted in only one animal in the lowest dose group (0.3 mg/kg). RadTech respectfully requests that the Peer Review Panel consider:

- ✓ If the same tumor type is known to occur in male controls of the same species, does the lack of statistical significance of these findings in females support the finding that they are not-treatment related; and

- ✓ Whether these incidences should be considered for whether they are sporadic incidences and not treatment related for other reasons.

3. *Other comments*

RadTech respectfully asks the Peer Review Panel to address the following additional comments:

- ✓ Page 66 of the Draft Report includes commentary by NTP on whether or not TMPTA is a genotoxic or non-genotoxic carcinogen. However, NTP studies showed TMPTA is not genotoxic *in vivo*. The Draft Report should conclude that TMPTA is "not genotoxic" *in vivo*, based on NTP's results as well as other *in vivo* studies reported in the literature (Johanssen); and

- ✓ Appendix D-8, table D2, Liver: hepatocholangiocarcinoma is not included in the table and it should be.

* * *

In closing, we appreciate your consideration of our questions and areas for comment on these study results.

Sincerely yours,

[Redacted]

✓ Martha Marrapese, Esq. Karin Ke, Ph.D.

cc: Gary Cohen, Executive Director, RadTech