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RE: Comments on the Draft Technical Report (No. 576) for Trimethylolpropane Triacrylate; 76 Fed. Reg. 77832 (Dec. 14, 2011)

Dear Ms. Andrews:

These comments are submitted on behalf of the Specialty Acrylates and Methacrylates (SAM) Panel of the American Chemistry Council (ACC). The ACC is the major trade association for the chemical producer industry and its members represent companies engaged in the business of chemistry. The ACC SAM Panel is comprised of member companies that produce a variety of acrylates and methacrylates, including members that produce Trimethylolpropane Triacrylate (TMPTA; CAS # 15625-89-5). The draft National Toxicology Program (NTP) Technical Report for TMPTA (No. 576) is currently scheduled for peer review and public oral comment at the February 8-9, 2012 meeting at the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina. Written comments related to the draft NTP Technical Report (No. 576) are due to NIEHS/NTP by January 25, 2012.

The SAM Panel has a long-term and positive relationship working with various agencies, including US EPA and National Institutes of Health/NTP on issues relating to potential health effects of specialty acrylates and methacrylates.

The SAM Panel supports the comments and information that are being separately submitted by RadTech International North America, the trade association for UV and EB curing technology which addresses, among other issues, liver tumor findings in the draft report.

As indicated in the introduction to the draft NTP technical report, the studies that are the subject of this report were conducted principally to address potential carcinogenic effects of TMPTA to skin based on historic reports of tumorigenesis in response to dermal application of other acrylates/methacrylates. Unfortunately, these earlier study results which suggested carcinogenic potential of some members of the specialty acrylate/methacrylate class were confounded due to design limitations, including but not limited to exposure concentrations which produced significant dermal ulceration and proliferative stress.

The SAM Panel notes that earlier published work[1] on specialty acrylates/methacrylates assisted NTP in establishing appropriate concentrations for the mouse and rat 2-year dermal studies presently under discussion. Moreover, the SAM Panel also recognizes that based on the findings presented in the NTP technical report, **even at dermally applied doses which produced significant irritation and dermal injury in F344/N rats** and **B6C3F1/N mice, there was no evidence of TMPTA-related dermal carcinogenesis.** However, based on histopathological findings in other tissues, the draft report concludes that there was "some evidence of carcinogenic activity." Each of the conclusions of "some evidence of carcinogenicity" is discussed briefly below.

Draft NTP Technical Report Conclusion: Some evidence of carcinogenic activity in male F344/N rats based on increased incidences of malignant mesothelioma.

As noted in the draft NTP technical report, findings of malignant mesothelioma were limited to the tunics around the testis in male F344/N rats, with dissemination into the peritoneal cavity. The incidence of this lesion in male rats in the control group was unexpectedly low, 0/50, given that the mean historical control incidence for 2-year dermal studies is 3.2% (8/250). The incidences of malignant mesothelioma in the 0.3 mg/kg and 1.0 mg/kg groups were 4% and 4%, respectively, which is very similar to the above referenced NTP mean historical control incidence (3.2%). Only the 3.0 mg/kg group was significantly elevated over the concurrent control, which, as noted previously, was lower than expected. The elevated incidence of malignant mesotheliomas in the 3.0 mg/kg group (10%, 5/50) does marginally exceed the NTP historical control range for dermal studies, all vehicles (0-8%). However, the interpretation of these (and other findings) in this report are limited by the fact that the NTP historical control database does not include any other dermal studies in which acetone was the vehicle, thereby precluding a direct and more meaningful comparison. The marginally elevated increased incidence in malignant mesotheliomas in male rats is the basis of the conclusion of "some evidence" of carcinogenicity in male F344/N rats. Based on an initial review of the published literature, the SAM Panel encourages the NTP and the Peer Review Panel to further consider relevant information on this specific lesion.

A recent published review by Maronpot and colleagues[2] examined the nature of tunica vaginalis mesothelioma (TVM) responses in 21 published rat cancer bioassays. Although this review is cited in the NTP technical report (pg. 63) when addressing the malignant mesothelioma findings, there is no additional discussion on the specificity of these tumors to F344 rats. Maronpot et al.[2] reported that TVM induction is a male F344 rat-specific (and possibly strain-specific) event, and in the absence of other chemical-induced tumorigenesis, is likely to be irrelevant in human risk assessment for the following reasons:

- In contrast to the rat, the tunica vaginalis in the adult human does not directly connect to the peritoneal cavity (as was noted in the TMPTA-treated rats). The TVM in humans are typically confined to the scrotal vaginal tunics, are locally invasive in about 50% of the cases, and when metastatic, typically spread via the lymphatic system;

- Examination of the literature indicates that a tunica vaginalis response to xenobiotic exposure is generally not seen in other strains and stocks of rats; the aging F344 rat has a more advanced development of testicular changes than other rat stocks and a greater background incidence of testicular mesotheliomas; the male F344 rat specificity of TVM tumorigenesis is not likely to be relevant to other rodent species, therefore, its applicability to human risk is highly questionable;
- Even in cases where xenobiotics produce robust TVM in male F344 rats, there are no mesotheliomas in female rats or in mice (such is the case with TMPTA), which highlights the unique sensitivity of the TVM response in male F344 rats;
- Considering the numerous delineated modes-of-action relevant to male F344 TVM induction involving Leydig-cell tumors and altered hormonal responses, none are considered to be relevant to humans.

In short, as outlined by Maronpot et al.[2], TVM are low-incidence spontaneous neoplasms in rats that can be increased by treatment. In their review of 21 chemicals, the mesothelioma responses to xenobiotic exposure by other than the peritoneal route are male F344 rat-specific. These tumors are never seen in female F344 rats or in either gender of mice in conventional cancer bioassays and have not been reported in other rat strains used for carcinogenicity testing. Because the TVM findings noted only in male F344/N rats from the 2-year TMPTA study are not able to be extrapolated to other rat strains or rodent species, then they are not likely to be relevant to human risk assessment. As a result, we strongly encourage NTP and the Peer Review Panel to consider expanding the discussion section of the report to better characterize the unique features of these lesions that render them unlikely to be considered in subsequent assessments that will address human risk. In addition, the SAM Panel requests that NTP and the Peer Review Panel consider revising the conclusion from "some evidence" of carcinogenic activity in male F344/N rats based on increased incidences of malignant mesothelioma to "equivocal evidence."

Draft NTP Technical Report Conclusion: Some evidence of carcinogenic activity in female B6C3F1/N mice based on increased incidences of stromal polyp or stromal sarcoma of the uterus.

The report cites positive trend tests for these lesions in female B6C3F1/N mice both for benign stromal polyps alone and when combined with a (one) stromal sarcoma. Only in the highest dose group, 3.0 mg/kg, was the increase in benign stromal polyps statistically significant compared with concurrent controls (5/50, 10% vs. 0/50, 0%) and slightly outside the range of the NTP historical control incidence for this finding from all 2-year dermal studies (0-8%). It is noteworthy that only a single stromal sarcoma was noted (1/50, 2%) at the high dose (3.0 mg/kg); therefore, the observed incidence of stromal sarcoma is within the NTP historical control range (0-2%) for this lesion from all 2-year NTP studies, for all routes of administration.

The SAM Panel notes that, as reviewed in a recent publication[3], there is evidence of "genetic drift" in B6C3F1/N mice, as the incidence of benign stromal polyp has been increasing over time. The range reported in this recent review[3] is 0-14.3%. It is recognized that interpretation of the findings presented in the current NTP technical report is hindered by the absence of directly

comparable historical control data from other studies in which acetone was employed as the vehicle. However, the incidence of benign stromal polyp in the present findings is well within the range of genetic drift seen in B6C3F1/N mice.

The draft NTP technical report concludes that there is "some evidence of carcinogenicity in female B6C3F1/N mice" based on the increased incidences of benign stromal polyp or stromal sarcoma of the uterus. The SAM Panel strongly encourages NTP and the Peer Review Panel to consider the significant body of evidence in the published literature that brings the relevance of this finding to humans into significant question for the reasons outlined below.

Endometrial stromal polyps in rodents appear as age-related lesions. Based on a review of more than 400 compounds tested by NTP[3], no structure activity relationship or common mechanism of action is apparent with substances that have been associated with benign stromal polpys. More importantly, endometrial polyps that occur in women and the uterine endometrial stromal polyps that occur in rodents have distinctly different characteristics. Human endometrial polyps develop from both endometrial and stromal components whereas rodent stromal polyps develop from stromal components only. Endometrial polyps in women are clearly hormone sensitive, while in rodents, these lesions do not appear to be hormonally sensitive. Based on these key differences, endometrial stromal polyps observed in rodent bioassays, including the benign stromal polyps in the present studies with TMPTA, appear to have limited or more likely, no relevance to humans[3]. As such, we strongly encourage NTP and the Peer Review Panel to consider expanding the discussion section of the draft report to better characterize the unique features of these lesions that bring into question their relevance in subsequent assessments that will address human risk. In addition, the SAM Panel requests that NTP and the Peer Review Panel consider revising the conclusion from "some evidence" of carcinogenic activity in female B6C3F1/N mice based on increased incidences of stromal polyp or stromal sarcoma of the uterus to "equivocal evidence."

Draft NTP Technical Report Conclusion: Some evidence of carcinogenic activity in female B6C3F1/N mice based on increases of uncommon malignant hepatic neoplasms (hepatoblastoma and hepatocholangiocarcinoma).

There is little evidence to support the conclusion of carcinogenic activity in female B6C3F1/N mice based on increases of uncommon malignant hepatic neoplasms. Although the noted tumor types are indeed rare, a dose-response relationship is clearly absent. Moreover, TMPTA and numerous additional acrylates (60+) have been demonstrated to be non-genotoxic *in vivo*[4]. Thus, the absence of evidence of genotoxicity of TMPTA, and the lack of any other clear and compelling carcinogenic response in B6C3F1/N mice (or F344/N rats) in other tissues, renders the biological significance of these unusual liver tumors reported in female B6C3F1/N mice from the present study uncertain. As a result of the aforementioned concerns, and considering the more detailed comments on this issue provided by RadTech International North America, the SAM Panel urges NTP and the Peer Review Panel to consider revising the conclusion of "some evidence" of carcinogenic activity in female B6C3F1/N mice based on increases of uncommon malignant hepatic neoplasms to "equivocal evidence."

In agreement with the more comprehensive comments submitted separately by RadTech International North America, the SAM Panel also believes that reference to the previously conducted dermal studies in transgenic mice are inappropriate, potentially misleading, and should be deleted from the report.

Requested Considerations for NTP and the Peer Review Panel Regarding Potential Changes to the Draft NTP Technical Report on TMPTA

In summary, the SAM Panel urges NTP and the Peer Review Panel to:

- Consider expanding the report description and discussion of the unusual nature of tunica vaginalis mesothelioma (TVM) in male F344/N rats with reference to the compelling evidence in the published literature that these lesions are not relevant to humans;

- Consider revising the conclusion from "some evidence" of carcinogenic activity in male F344/N rats based on increased incidences of malignant mesothelioma to "equivocal evidence;"

- Consider expanding the report description and discussion of the unusual nature of benign stromal polyps in female B6C3F1/N mice with reference to the compelling evidence in the published literature that these lesions are not relevant to humans;

- Consider revising the conclusion from "some evidence" of carcinogenic activity in female B6C3F1/N mice based on increased incidences of stromal polyp or stromal sarcoma of the uterus, to "equivocal evidence;"

- Consider revising the conclusion from "some evidence" of malignant hepatic neoplasms in female B6C3F1/N mice to "equivocal evidence" based on the well-documented absence of *in vivo* genotoxicity of TMPTA and acrylates as a class and the absence of a dose-dependent increase in these lesions;

- Consider omitting references to the NTP studies conducted with transgenic mouse strains.

Should there be any questions regarding these comments from the ACC SAM Panel, I can be contacted as follows:

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Sincerely,

[Redacted]

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References

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