Toxicology Regulatory Services

Comments on the Draft Technical Report (No. 576) for Trimethylolpropane Triacrylate (TMPTA)

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Comments presented on behalf of the Specialty Acrylates and Methacrylates (SAM) Panel of the American Chemistry Council (ACC)

Overview

- TMPTA is a multifunctional monomer with numerous industrial applications
  - Nominated by National Cancer Institute (NCI) due to its high production volume and use, potential for human exposure and the lack of chronic toxicity and carcinogenicity data

- Test animals were dermally exposed to TMPTA (>78% pure) in acetone for up to 2 yrs: 0, 0.3, 1.0 or 3.0 mg/kg bw/day
  - F344/N male and female rats
  - B6C3F1/N male and female mice

- Dermally applied TMPTA produced significant dose-dependent skin irritation and dermal injury (e.g., hyperkeratosis, hyperplasia, chronic inflammation) in the exposed male and female mice and rats, but no evidence of TMPTA-related dermal carcinogenesis

Overview
(continued)

Study endpoints and recommendations discussed in subsequent slides:

- Male F344/N malignant mesotheliomas
- Female B6C3F1/N stromal polyp or sarcoma findings
- Female B6C3F1/N hepatic neoplasm findings
  - More detailed comments to be provided by RadTech International North America
- Requested considerations for NTP and the Peer Review Panel

Major Histopathological Findings

F344/N Rats – *Malignant Mesothelioma*

- F344/N male rats:
  - Positive trend in the incidences of malignant mesothelioma
    - Limited to tunics around testis with dissemination into the peritoneal cavity
    - Incidences in 0.3 and 1.0 mg/kg males within range of historical control animals
    - Incidence in 3.0 mg/kg bw/day males was significantly greater than concurrent control

Historical control incidence from 2-year dermal studies	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
8/250 (3.2%) Range (0-8%)	0/50 (0%)	2/50 (4%)	2/50 (4%)	5/50 (10%)*

*statistically significant ($p<0.05$) compared to concurrent control; adjusted for mortality

- F344/N female rats:
  - No reportable findings beyond site of application

Major Histopathological Findings F344/N Rats- *Malignant Mesothelioma* (continued)

- "Some evidence" of carcinogenicity in male F344/N rats:
  - Marginal increase in incidence in malignant mesotheliomas in male rats

- During the review process, the SAM Panel encourages NTP and the Peer Review Panel to consider the strain and species specificity of such tumors
  - *Maronpot *et al*. (2009) review:
    - Tunica vaginalis mesothelioma (TVM) responses are very specific to male F344 rats which brings into question their relevance for extrapolation to other species, especially humans
    - Similar tumors are not observed in females or mice in conventional cancer bioassays and have not been reported in other rat strains

*Maronpot *et al*. 2009. Critical Reviews in Toxicology.

Major Histopathological Findings
B6C3F1/N Mice – *Stromal Polyp or Sarcoma*

- B6C3F1/N male mice:
  - No reportable findings beyond site of application
- B6C3F1/N female mice:
  - Positive trend in the incidences of benign uterine stromal polyp
  - Incidences in 0.3 and 1.0 mg/kg females within range of historical control animals
  - Incidence in 3.0 mg/kg bw/day females was significantly greater than concurrent control

Historical control incidence from 2-year dermal studies (uterine stromal polyp)	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
5/250 (2%) (0-6%)	0/50 (0%)	1/50 (2%)	2/50 (4%)	5/50 (10%)*

*statistically significant ($p<0.05$) compared to concurrent control; adjusted for mortality

  - One uterine stromal sarcoma at 3.0 mg/kg bw/day (1/50, 2%)
    - Historical control incidence from all routes of administration (0-2%)

Major Histopathological Findings
B6C3F1/N Mice – *Stromal Polyp or Sarcoma* (continued)

- "Some evidence" of carcinogenicity in female B6C3F1/N mice:
  - Increased incidence of stromal polyp or stromal sarcoma of the uterus
- The incidence of stromal sarcoma was within the range of the historical control animals
- During the review process, the SAM Panel encourages NTP and the Peer Review Panel to consider the potential differences in stromal polyps from humans and rodents
  - *Davis (2012) review:
    - Different characteristics related to polyp formation in humans versus rodents (endometrial and stromal origin in humans versus only stromal origin in rodents)
    - Endometrial polyps are hormonally-sensitive in humans, but not in rodents
    - Incidence of benign stromal polyp has been increasing over time (up to 14.3%) in B6C3F1/N mice

*Davis, B. 2012. Toxicologic Pathology.

Major Histopathological Findings
B6C3F1/N Mice – *Hepatic Neoplasms*

- "Some evidence" of carcinogenicity in female B6C3F1/N mice:
  - Increased incidence of uncommon malignant hepatic neoplasms

- During the review process, the SAM Panel encourages NTP and the Peer Review Panel to consider the more detailed comments provided by RadTech International North America as well as the following information with respect to the observed hepatic neoplasms:
  - A dose-response relationship is absent
  - TMPTA and numerous additional acrylates have been shown to be non-genotoxic *in vivo* (*Johannsen *et al*., 2008)
  - Considering the lack of genotoxicity evidence or other convincing carcinogenic responses in B6C3F1/N mice, the biological relevance of these unusual liver tumors is doubtful

*Johannsen *et al*. 2008. Regulatory Toxicology and Pharmacology.

Requested Considerations for NTP and the Peer Review Panel

- Male F344/N Rats:
  - Consider expanding the technical report description and discussion of the TVM findings in male F344/N rats with reference to the published literature that these lesions are not relevant to humans

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

- Consider revising the conclusion from “some evidence” to “equivocal evidence” of carcinogenic activity for both male F344/N rats and female B6C3F1/N mice

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

Thank you for considering the comments presented on behalf of the Specialty Acrylates and Methacrylates (SAM) Panel of the American Chemistry Council (ACC)

Back-Up Slides

SAM Panel Members

- Arkema Inc.
- BASF Corporation
- IGM Resins Inc.
- Cytec Industries Inc.
- Rhodia Inc.
- Evonik Industries (Germany)
- EvonikRohMax (USA)
- San Ester
  - Mitsubishi Rayon is parent company in Japan
- Sartomer USA LLC