NTP
National Toxicology Program

Draft NTP Technical Report TR576 on
Trimethylolpropane Triacrylate

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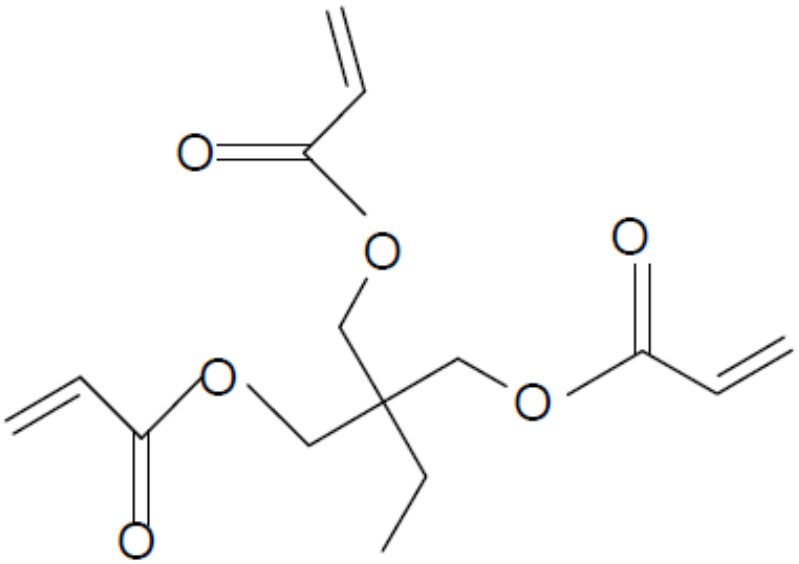
TMPTA



Use

- Cross-linking agent
- Production of ultraviolet curable inks
- Ingredient in acrylic glues, adhesives, and sealants
- Production volume of 10-50 million pounds

Nomination

- By the National Cancer Institute
- High and increasing production and use
- Potential for extensive human exposure
- Lack of adequate chronic toxicity and carcinogenicity data
- As one of the representative multifunctional acrylates

Studies Conducted by the NTP

Phase-1

- Genotoxicity study
- Contact hypersensitivity study
- ADME study
- 2-week and 3-month dermal studies in F344/N rats and B6C3F1/N mice
- 6-month dermal studies in FVB Tg.AC hemizygous mice

Phase-2

- 2-year dermal studies in F344/N rats and B6C3F1/N mice

Results

Phase - 1

Genetic Toxicology

- *In vitro*
  - Bacterial mutagenicity assays
    - Negative with and without S9
- *In vivo*
  - No increase in micronucleated erythrocytes
    - male or female 0.75 – 12 mg/kg TMPTA for 3 months (B6C3F1 mice)
    - male or female 0.75 – 12 mg/kg TMPTA for 6 months (Tg.AC mice)

GMM 3 (NTP, 2005)

Contact Hypersensitivity Test

- Irritant
  - Irritancy study
    - Maximal nonirritating dose – 0.1 % (w/v)
    - Minimal irritating dose – 0.25 % (w/v)
- Not a contact sensitizer
  - Negative mouse ear swelling test
  - Negative local lymph node assay

GMM 3 (NTP, 2005)

ADME Studies in Male Rats and Mice

- Moderately absorbed by dermal route
  - Rats - 55% at 1.7 mg/kg, 32.7% at 15.2 mg/kg, 18.7% at 130 mg/kg
  - Mice - 75% at 1.2 mg/kg
- Excretion – urine and as CO_2
- Tissue retention - < 1% at 72 h

GMM 3 (NTP, 2005)

2-Week Studies in Rats and Mice

- 0, 12.5, 25, 50, 100, 200 mg/kg in acetone
- No effect on survival
- No effect on rat body weight
- Decreased body weight gain in male mice (200 mg/kg)
- Increased final body weight in female mice (≥ 100 mg/kg)
- Irritation of skin (rats ≥ 50 mg/kg, all male mice, female mice ≥ 100 mg/kg)
- Skin lesions at the site of application
  - Epidermal hyperplasia, hyperkeratosis, sebaceous gland hyperplasia, chronic active inflammation, ulcer, degeneration
  - LOAEL - 12.5 mg/kg

GMM 3 (NTP, 2005)

3-Month Studies in Rats and Mice

- 0, 0.75, 1.5, 3, 6, 12 mg/kg in acetone
- No effect on survival or body weight
- Irritation of skin (12 mg/kg)

- Skin lesions at the site of application
  - Epidermal hyperplasia, sebaceous gland hyperplasia, degeneration, chronic active inflammation, hyperkeratosis
  - NOAEL - < 0.75 mg/kg (rats)
    0.75 mg/kg (mice)

GMM 3 (NTP, 2005)

Tg.AC Mouse Model

- FVB background
- Inducible zeta-globin promoter
- Mutant v-Ha-*ras* transgene
- Genetically initiated model

26-Week Studies in FVB Tg.AC Hemizygous Mice

- 0, 0.75, 1.5, 3, 6, 12 mg/kg in acetone
- No effect on survival or body weight

- Skin lesions at the site of application
  - Epidermal hyperplasia, chronic active inflammation, hyperkeratosis

GMM 3 (NTP, 2005)

26-Week Studies in FVB Tg.AC Hemizygous Mice

Dose (mg/kg)	0	0.75	1.5	3	6	12
Male						
Skin						
Papilloma	0**	0	0	2	12**	13**
Female						
Skin						
Papilloma	0**	0	0	1	11**	15**
Carcinoma	0	0	1	0	1	1
Forestomach						
Papilloma	4*	5	4	2	5	9*

N=15
* P<0.05, Poly-3 test
** P<0.01, Poly-3 test

GMM 3 (NTP, 2005)

Tg.AC Mouse Model

- Not considered as an alternative to traditional 2-year bioassay for carcinogenicity testing by the Technical Reports Review subcommittee (2004)

- Same comments from the Scientific Advisory Committee on Alternative Toxicological Methods (2004)

Results

Phase - 2

2-Year Studies in F344/N Rats and B6C3F1/N Mice

- 0, 0.3, 1.0, 3.0 mg/kg in acetone
- 50 males and females per group
- No effect on survival or body weight

Neoplastic Lesions in F344/N Rats (Male)

Dose (mg/kg)	0	0.3	1.0	3.0
Malignant Mesothelioma	0*	2	2	5*

N = 50
* P < 0.05, Poly-3 test
Historical Incidence: dermal, all vehicle 8/250 (0-8%)
all routes 40/1249 (0-8%)

Nonneoplastic Skin Lesions (site of application) in F344/N Rats

Dose (mg/kg)	0	0.3	1.0	3.0
Male				
Epidermal Hyperplasia	1	0	12**	28**
Hyperkeratosis	2	4	33**	49**
Female				
Epidermal Hyperplasia	0	4	11**	25**
Hyperkeratosis	0	11**	42**	50**

N = 49 or 50
** P < 0.01, Poly-3 test

Neoplastic Lesions in B6C3F1/N Mice (Female)

Dose (mg/kg)	0	0.3	1.0	3.0
Liver				
Hepatoblastoma[a]	0	4	0	3
Hepatocholangiocarcinoma[b]	0	0	1	2
Uterus				
Stromal Polyp[c]	0**	1	2	5*
Stromal Sarcoma[d]	0	0	0	1
Stromal Polyp or Stromal Sarcoma[e]	0**	1	2	6*

N = 50

*P<0.05, **P<0.01, Poly-3 test

[a]Historical Incidence: dermal, all vehicle 2/250 (0-2%), all routes 4/1195 (0-2%)

[b]Historical Incidence: dermal, all vehicle 0/250, all routes 0/1195

[c]Historical Incidence: dermal, all vehicle 5/250 (0-6%), all routes 24/1198 (0-8%)

[d]Historical Incidence: dermal, all vehicle 0/250, all routes 2/1198 (0-2%)

[e]Historical Incidence: dermal, all vehicle 5/250 (0-6%), all routes 26/1198 (0-8%)

Nonneoplastic Skin Lesions (site of application) in B6C3F1/N Mice

Dose (mg/kg)	0	0.3	1.0	3.0
Male				
Epidermal Hyperplasia	10	7	15	44**
Melanocyte Hyperplasia	0	0	0	19**
Chronic Inflammation	13	17	26**	43**
Female				
Epidermal Hyperplasia	7	7	15*	34**
Melanocyte Hyperplasia	1	1	3	33**
Chronic Inflammation	37	36	43	48**
Ulcer	0	0	3	3
Acute Inflammation	1	1	2	4

N = 50

** P < 0.01, Poly-3 test

Conclusions

- Male F344/N rats
  - *Some evidence of carcinogenic activity*
    - Malignant mesothelioma
- Female F344/N rats and Male B6C3F1/N mice
  - *No evidence of carcinogenic activity*
- Female B6C3F1/N mice
  - *Some evidence of carcinogenic activity*
    - Uncommon malignant hepatic neoplasms
      - Hepatoblastoma and hepatocholangiocarcinoma
    - Stromal polyp or stromal sarcoma
- Increased incidences of nonneoplastic lesions
  - Skin (site of appication) of male and female rats and mice