



Draft NTP Technical Report TR576 on Trimethylolpropane Triacrylate

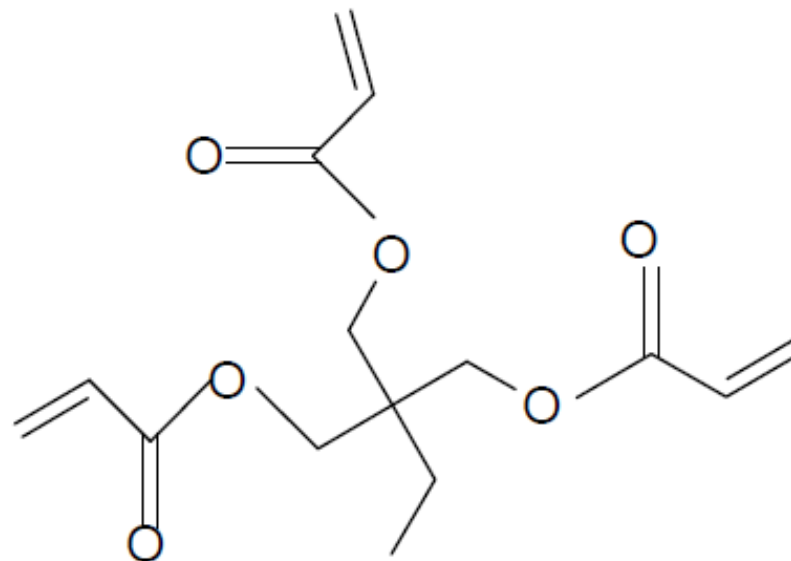
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TMPTA



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)



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



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 CO₂
- Tissue retention - < 1% at 72 h



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



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)



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



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

^aHistorical Incidence: dermal, all vehicle 2/250 (0-2%), all routes 4/1195 (0-2%)

^bHistorical Incidence: dermal, all vehicle 0/250, all routes 0/1195

^cHistorical Incidence: dermal, all vehicle 5/250 (0-6%), all routes 24/1198 (0-8%)

^dHistorical Incidence: dermal, all vehicle 0/250, all routes 2/1198 (0-2%)

^eHistorical 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 application) of male and female rats and mice