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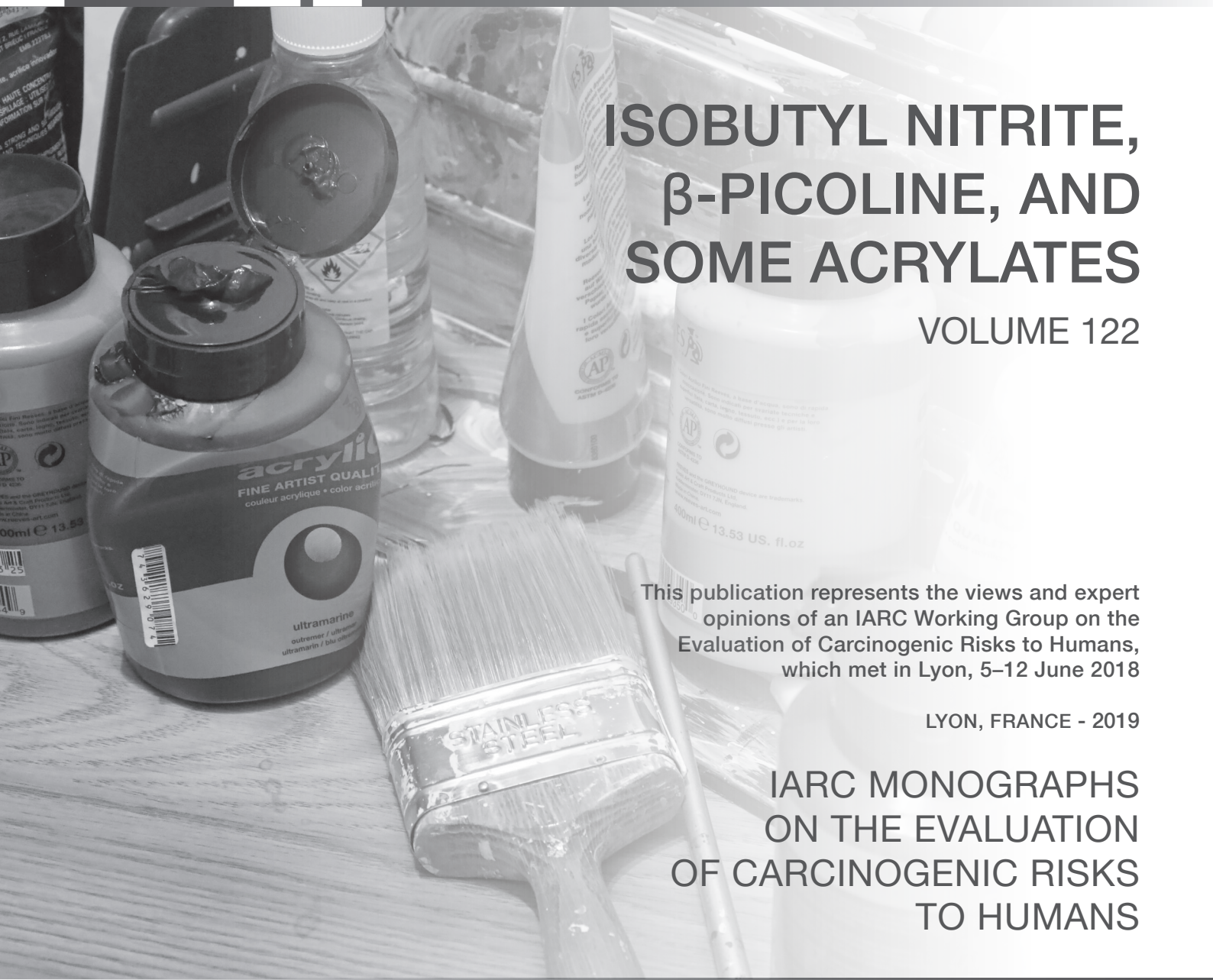

ISOBUTYL NITRITE, β-PICOLINE, AND SOME ACRYLATES

VOLUME 122

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International Agency for Research on Cancer

World Health Organization

TRIMETHYLOLPROPANE TRIACRYLATE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 15625-89-5

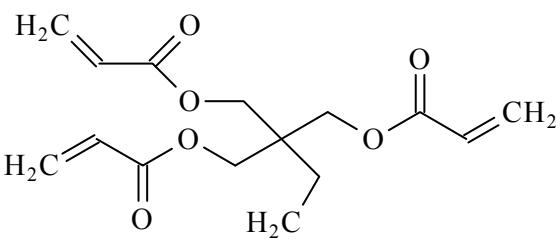
Chem. Abstr. Serv. name: trimethylolpropane triacrylate

IUPAC name: 2,2-bis(prop-2-enoyloxymethyl)butyl prop-2-enoate (NIH, 2018)

Synonyms: TMPTA; 1,1,1-trimethylolpropane triacrylate; 2,2-bis[(acryloyloxy)methyl]butyl prop-2-enoate; 2-propenoic acid; 2,2-bis[[(1-oxo-2-propen-1-yl)oxy]methyl] butyl ester; acrylic acid; triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol

1.1.2 Structural and molecular formula, and relative molecular mass

Molecular formula: $C_{15}H_{20}O_6$



Relative molecular mass: 296.3

1.1.3 Chemical and physical properties

Description: viscous, colourless to tan liquid (NTP, 2012)

Boiling point: higher than 200 °C at 1 mm Hg (NTP, 2012)

Vapour pressure: 5.9×10^4 mm Hg at 25 °C (HSDB, 2018)

Density: 1.11 g/cm^3 at 20 °C (HSDB, 2018)

Solubility: insoluble in water (NTP, 2012)

Stability: hygroscopic, light sensitive, and incompatible with strong oxidizing agents, acids, and bases; may undergo spontaneous polymerization when exposed to direct sunlight and heat, but may be stabilized with the monoethyl ester of hydroquinone (NTP, 2012)

Conversion factor: 1 ppm = 12.12 mg/m^3 at 1 atm, 25 °C

1.1.4 Technical products and impurities

Technical-grade trimethylolpropane triacrylate has a purity of more than 70%, and the major impurities are acrylic acid, trimethylolpropane diacrylate, trimethylolpropane-triacrylate–trimethylolpropane-monoacrylate adduct, trimeth-ylolpropane-triacrylate–trimethylolpropane-diacrylate adduct, and water (NTP, 2012). It also contains less than 1% hydroquinone or monomethyl ether hydroquinone as polymerization inhibitor (Merck index website). [The

Working Group noted that studies with the agent with analytical-grade purity (> 90%) were not available.]

1.2 Production and use

1.2.1 Production process

Trimethylolpropane triacrylate is manufactured by esterification of trimethylolpropane (NTP, 2012).

1.2.2 Production volume

Trimethylolpropane triacrylate is a chemical with a high production volume (OECD, 2009). From 1986 to 2006, the United States Environmental Protection Agency (EPA) reported an annual national production volume of 10–50 million pounds [4500–23 000 metric tonnes] of trimethylolpropane triacrylate (HSDB, 2018). Recent production in Europe has been reported in the range of 10–100 thousand metric tonnes per year (ECHA, 2018). Production volumes in China were 3700, 4100, 8800, and 9300 metric tonnes per year for the years 2001, 2002, 2003, and 2004, respectively (Chinese Report, 2005).

1.2.3 Use

The major use of trimethylolpropane triacrylate is as a cross-linking agent in a wide range of industrial applications in adhesives and sealant chemicals, ultraviolet (UV)-curable inks, photosensitive chemicals, paint additives, coating additives, intermediates, and solvents (HSDB, 2018). Trimethylolpropane triacrylate is also used in paper and wood impregnates, wire and cable extrusion, polymer-impregnated concrete, and polymer concrete structural composites (NTP, 2012).

1.3 Analytical methods

The United States Occupational Safety and Health Administration (OSHA) has a sampling and analytical guide for trimethylolpropane triacrylate (unvalidated). Personal breathing zone air sampling is performed using XAD-7 sorbent sampling tubes, followed by solvent desorption with methanol, and analysis by high-performance liquid chromatography (HPLC) with UV spectrophotometric detection (OSHA, 2018).

A gas chromatography with mass spectrometry (MS) method has been described for the analysis of migration of trimethylolpropane triacrylate from UV ink systems (Papilloud & Baudraz, 2002). The limit of detection of this system was not reported. No methods for detection in biological media were available to the Working Group.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

Trimethylolpropane triacrylate does not occur naturally in the environment (HSDB, 2018). It readily degrades in the atmosphere by reacting with photochemically produced hydroxyl radicals; the half-life has been estimated as 11 hours. Total degradation of trimethylolpropane triacrylate in soil and water was 87% over a 4-week period with the formation of the diacrylate and monoacrylate esters plus trimethylolpropane (HSDB, 2018).

1.4.2 Exposure of the general population

Exposure in the general population may occur through dermal exposure when using products containing trimethylolpropane triacrylate, such as latex paints, and furniture and floor polishes (Voog & Jansson, 1992). No quantitative information on exposure was available to the Working Group.

1.4.3 Occupational exposure

Occupational exposure may occur through inhalation or dermal exposure in facilities manufacturing trimethylolpropane triacrylate or in industries using trimethylolpropane triacrylate. Occupational exposure to this compound has been reported primarily in printing plants, in the use of UV-curing inks, and in the adhesives and allied industries since the late 1970s. In the press area of a plastic tube department where UV-cured inks were used, air measurements of trimethylolpropane triacrylate were below the limit of detection (< 9 ppb [< 109 µg/m^3]) (NIOSH, 1994).

Studies of trimethylolpropane triacrylate have mainly investigated dermatitis and involved skin patch testing of workers or patients (Björkner et al., 1980; Dahlquist et al., 1983; Garabrant, 1985; Kanerva et al., 1998; Goon et al., 2002). Four cases of dermatitis were reported from a floor-manufacturing facility that used a varnish with an aziridine-based hardener containing 3–5% trimethylolpropane triacrylate; all four workers reacted to trimethylolpropane triacrylate in skin patch testing (Dahlquist et al., 1983). In a plant that manufactured plastic food containers, a printing process used seven acrylate oligomers, including trimethylolpropane triacrylate. One positive result of epicutaneous patch testing for trimethylolpropane triacrylate was reported among seven workers tested (Nethercott et al., 1983).

1.5 Regulations and guidelines

The American Industrial Hygiene Association derived a workplace environmental exposure level in the form of an 8-hour time-weighted average of 1 mg/m^3 for trimethylolpropane triacrylate. This limit comes with a skin notation (AIHA, 2011).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

Studies of carcinogenicity in mice and rats exposed to trimethylolpropane triacrylate were limited to skin application studies conducted by the United States National Toxicology Program (NTP, 2005, 2012) and reported by Andrews & Clary (1986). Results of these studies are summarized in Table 3.1 (see also Doi et al., 2005; Surh et al., 2014).

3.1 Mouse

3.1.1 Skin application

(a) B6C3F1/N and C3H/HeJ mice

In a study on 10 related acrylates and methacrylates (Andrews & Clary, 1986), 50 male C3H/HeJ mice [age, not reported] were exposed by skin application to trimethylolpropane triacrylate [purity, not reported] at a dose of 2.5 mg (~100 mg/kg body weight, bw, based on the assumption of a body weight of 25 g), twice per week for 80 weeks, at which point the experiment was terminated. Two groups of 50 mice each were used as negative controls; one group received no treatment and the other group was exposed to mineral oil only [whether this was a vehicle control was not stated]. The skin and body [peritoneal and thoracic] cavities were examined at necropsy and tissues were collected for histopathological examination [the specific tissues that were examined were not reported]. There were no skin tumours or systemic effects reported in treated animals. However, there were acanthoses and fibroses of the skin. [These were presumably at the site of application, although this was not stated. The specific incidence of

Table 3.1 Studies of carcinogenicity with technical-grade trimethylolpropane triacrylate in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$/N (M) 5–6 wk 105–106 wk NTP (2012)	Skin application TMPT, > 78% Acetone 0, 0.3, 1.0, 3.0 mg/kg bw, 1×/d, 5 d/wk 50, 50, 50, 50 30, 35, 29, 38	Any tumour type: no significant increase		Principal strengths: well-conducted GLP study
Full carcinogenicity Mouse, B6C3F$_1$/N (F) 5–6 wk 105–106 wk NTP (2012)	Skin application TMPT, > 78% Acetone 0, 0.3, 1.0, 3.0 mg/kg bw, 1×/d, 5 d/wk 50, 50, 50, 50 39, 31, 30, 30	*Liver* Hepatoblastoma (includes multiple) 0/50, 4/50, 0/50, 3/50 Hepatoblastoma (multiple) 0/50, 1/50, 0/50, 3/50 Hepatocholangiocarcinoma 0/50, 0/50, 1/50, 2/50 Hepatocellular carcinoma 12/50*, 13/50, 10/50, 19/50 *Uterus* Stromal polyp or stromal sarcoma (combined) 0/50*, 1/50, 2/50, 6/50** Stromal polyp 0/50*, 1/50, 2/50, 5/50** Stromal sarcoma 0/50, 0/50, 0/50, 1/50	 NS NS NS *P = 0.045 (trend), poly-3 test *P = 0.002 (trend), poly-3 test; **P = 0.014, poly-3 test *P = 0.008 (trend), poly-3 test; **P = 0.027, poly-3 test NS	Principal strengths: well-conducted GLP study See comment on purity in NTP (2012) male mouse experiment Hepatoblastoma and hepatocholangiocarcinoma are considered rare tumours in B6C3F$_1$/N female mice, with low historical control incidence Historical incidence for dermal studies (mean ± SD; range): hepatoblastoma, 2-yr, vehicle controls (all vehicles): 2/250 (0.8 ± 1.1%; 0–2%); all routes, 4/1195 (0.3 ± 0.8%; 0–2%); hepatocholangiocarcinoma: 0/250; all routes, 0/1195; hepatocellular carcinoma: 63/250 (25.2 ± 15.5%; 6–46%); all routes, 144/1195 (12.1 ± 10.8%; 0–46%); stromal polyp, vehicle controls (all vehicles): 5/250 (2.0 ± 2.5%; 0–6%); all routes, 24/1198 (2.0 ± 2.2%; 0–8%); stromal sarcoma: 0/250; all routes, 2/1198 (0.2 ± 0.6%; 0–2%); stromal polyp or stromal sarcoma (combined): 5/250 (2.0 ± 2.5%; 0–6%); all routes, 26/1198 (2.2 ± 2.2%; 0–8%)

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence (%) of tumours	Significance	Comments
Carcinogenicity with other modifying factor Mouse (transgenic), FVB/N-TgN (v-Ha-*ras*) (i.e. Tg.AC) hemizygous (M) 6 wk 28 wk NTP (2005)	Skin application TMPT, 80% Acetone 0, 0.75, 1.5, 3, 6, 12 mg/kg bw, 5×/wk 15, 15, 15, 15, 15, 15 14, 15, 12, 14, 13, 11	*Skin*: squamous cell papilloma 0/15*, 0/15, 0/15, 2/15, 12/15**, 13/15**	*$P < 0.001$ (trend), poly-3 test; **$P < 0.001$, poly-3 test	Principal strengths: well-conducted GLP study Purity: HPLC indicated a major peak and five impurities with a combined area of 22.2%. HPLC/MS indicated ten impurities including the five impurities found by HPLC, including four structurally related acrylates or adducts: trimethylolpropane diacrylate, trimethylolpropane-triacrylate–acrylic-acid adduct, trimethylolpropane-triacrylate–trimethylolpropane-monoacrylate adduct, and trimethylolpropane-triacrylate–trimethylolpropane-diacrylate adduct
Carcinogenicity with other modifying factor Mouse (transgenic), FVB/N-TgN (v-Ha-*ras*) (i.e. Tg.AC) hemizygous (F) 6 wk 28 wk NTP (2005)	Skin application TMPT, 80% Acetone 0, 0.75, 1.5, 3, 6, 12 mg/kg bw, 5×/wk 15, 15, 15, 15, 15, 15 15, 14, 12, 14, 14, 12	*Skin*: squamous cell papilloma 0/15*, 0/15, 0/15, 1/15, 11/15**, 15/15** Squamous cell carcinoma 0/15, 0/15, 1/15, 0/15, 1/15, 1/15 *Forestomach* Squamous cell papilloma 4/15*, 5/15, 4/15, 2/15, 5/15, 9/15** Squamous cell papilloma (multiple) 1/15, 1/15, 1/15, 1/15, 1/15, 3/15	*$P < 0.001$ (trend), poly-3 test; **$P < 0.001$, poly-3 test NS *$P = 0.014$ (trend), poly-3 test; **$P = 0.040$, poly-3 test NS	Principal strengths: well-conducted GLP study See comment on purity in NTP (2005) male Tg.AC mouse experiment

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence (%) of tumours	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 6 wk 104–105 wk NTP (2012)	Skin application TMPT, > 78% Acetone 0, 0.3, 1.0, 3.0 mg/kg bw, 1×/d, 5 d/wk 50, 50, 50, 50 23, 18, 28, 23	*Tunica vaginalis*: malignant mesothelioma 0/50*, 2/50, 2/50, 5/50**	*P = 0.024 (trend), poly-3 test; **P = 0.031, poly-3 test	Principal strengths: well-conducted GLP study See comment on purity in NTP (2012) male mouse experiment Historical incidence of malignant mesothelioma for 2-yr dermal study vehicle controls (all vehicles) (mean ± SD; range): 8/250 (3.2 ± 3.4%; 0–8%); all routes, 40/1249 (3.2 ± 2.8%; 0–8%)
Full carcinogenicity Rat, F344/N (F) 6 wk 104–105 wk NTP (2012)	Skin application TMPT, > 78% Acetone 0, 0.3, 1.0, 3.0 mg/kg bw, 1×/d, 5 d/wk 50, 50, 50, 50 27, 31, 24, 32	Any tumour type: no significant increase		Principal strengths: well-conducted GLP study See comment on purity in NTP (2012) male mouse experiment

bw, body weight; d, day; F, female; GLP, good laboratory practice; HPLC, high-performance liquid chromatography; M, male; MS, mass spectrometry; NS, not significant; SD, standard deviation; TMPT, trimethylolpropane triacrylate; UV, ultraviolet; wk, week; yr, year

these lesions was not provided either, though the authors stated these were "frequently present".] One mouse from each control group developed a papilloma of the skin. [The Working Group considered that this study was inadequate for evaluation as it was poorly described and provided no information regarding test article purity, vehicle used, site of application, method of application, or the specific incidence of non-neoplastic lesions. Survival and body-weight data were not provided. Additionally, only one dose of trimethylolpropane triacrylate and one sex were used in the study.]

Groups of 50 male and 50 female B6C3F$_1$/N mice (age, 5–6 weeks) were exposed to technical-grade trimethylolpropane triacrylate (purity, > 78%) in acetone by skin application at a dose of 0 (control), 0.3, 1.0, or 3.0 mg/kg bw once per day, 5 days per week for 105–106 weeks. HPLC with UV detection analysis of the test agent indicated one major peak (78.2%) and four impurities, each greater than 0.1% of the total peak area (7.1, 2.3, 10.8, and 1.5%). HPLC with MS analysis tentatively identified three of the four impurities as structurally related compounds: trimethylolpropane diacrylate (7.1%), trimethylolpropane-triacrylate–trimethylolpropane-monoacrylate adduct (2.3%), and trimethylolpropane-triacrylate–trimethylolpropane-diacrylate adduct (10.8%). The impurity present at 1.5% of the total peak area was not specifically identified; however, the fragment ions were consistent with those of a trimethylolpropane triacrylate adduct. The dose levels were selected to avoid significant skin irritation (based on the severity of skin lesions in a 3-month study) and to preclude adverse effects on survival and growth of the mice, and were applied to the interscapular region of the back after clipping the hair (NTP, 2012). There were slight decreases in survival in the exposed groups of females, but the decreases were not statistically significant. In males, survival in the groups exposed at 0.3 or 3.0 mg/kg bw was slightly higher than in controls, but these increases were not statistically significant. Body weights in the exposed groups did not differ significantly from those of controls. In females, there were treatment-related increases in the incidence of hepatoblastoma and hepatocholangiocarcinoma of the liver, and of stromal polyp or stromal sarcoma of the uterus. The incidence of hepatoblastoma was 0/50, 4/50 (8%), 0/50, and 3/50 (6%) in the groups exposed at 0, 0.3, 1.0, or 3.0 mg/kg bw, respectively; the incidence in the groups exposed at the lowest and highest doses was above the upper bound of the range (0–2%) for historical controls for this tumour in female mice (historical control incidence: dermal study, 2/250; all routes, 4/1195). The respective incidence of hepatocholangiocarcinoma was 0/50, 0/50, 1/50 (2%), and 2/50 (4%); hepatocholangiocarcinoma was not observed in 250 (skin application studies) or 1195 (all routes of exposure) historical controls in female mice. [The Working Group considered hepatoblastoma and hepatocholangiocarcinoma as rare neoplasms in female mice, and considered the increased incidence to be biologically significant.] The incidence of stromal polyp or stromal sarcoma (combined) of the uterus was significantly increased (0/50 (P for trend, 0.002), 1/50 (2%), 2/50 (4%), and 6/50 (12%, P = 0.014)) in all exposed groups; one female exposed at the highest dose developed a stromal sarcoma of the uterus. There was also a small but significant (P = 0.045) positive trend in the incidence of hepatocellular carcinoma (12/50, 13/50, 10/50, and 19/50 (38%)) in females. There were no treatment-related increases in neoplasms of the skin in females. There were no treatment-related neoplasms in males. In males and females, there were significant increases in the incidence of epidermal hyperplasia, melanocyte hyperplasia, and chronic inflammation of the skin at the site of application (NTP, 2012). [The Working Group noted this was a well-conducted study that complied with good laboratory practice (GLP).]

(b) Transgenic mouse

Groups of 15 male and 15 female FVB/N-TgN (v-Ha-*ras*) (i.e. Tg.AC) hemizygous mice were exposed to technical-grade trimethylolpropane triacrylate (purity, ~80%) in acetone by skin application at a dose of 0 (control), 0.75, 1.5, 3, 6, or 12 mg/kg bw once per day, 5 days per week for 28 weeks (NTP, 2005). The purity of the test agent (see Table 3.1 for details) was similar to that used in the 2-year studies in B6C3F$_1$/N mice and Fischer 344/N rats conducted by NTP (2012). The doses were applied to the interscapular region of the back after clipping the hair. In males and females, there were slight decreases in survival in all except one exposed group (all males exposed at 0.75 mg/kg bw survived), but the decreases were not statistically significant. Body weights in the treated groups did not differ significantly from those of controls. In males, there was a treatment-related increase in the incidence of squamous cell papilloma of the skin (0/15, 0/15, 0/15, 2/15, 12/15, and 13/15 in groups exposed at 0, 0.75, 1.5, 3, 6, or 12 mg/kg bw, respectively, including mice with multiple papillomas of the skin in the groups exposed at 6 and 12 mg/kg bw) at the site of application. The positive trend and the increase in the incidence in the groups exposed at 6 and 12 mg/kg bw (compared with concurrent controls) were statistically significant ($P < 0.001$). In females, there was a treatment-related increase in the incidence of squamous cell papilloma of the skin at the site of application (0/15, 0/15, 0/15, 1/15, 11/15, and 15/15, including mice with multiple papillomas of the skin in the groups exposed at 6 and 12 mg/kg bw); this increased incidence in the females exposed at 6 and 12 mg/kg bw, and the positive trend, were statistically significant ($P < 0.001$). Squamous cell carcinomas of the skin (0/15, 0/15, 1/15, 0/15, 1/15, and 1/15) were also observed in some exposed groups. In females, there was also a statistically significant increase in the incidence of squamous cell papilloma of the forestomach (4/15, 5/15, 4/15, 2/15, 5/15, and 9/15) in the group exposed at 12 mg/kg bw ($P = 0.040$), with a significant positive trend ($P = 0.014$). Three females in the group exposed at 12 mg/kg bw and one female in each of the other groups (including controls) had multiple squamous cell papillomas of the forestomach. In male and female mice, there were significant increases in the incidence of epidermal hyperplasia, hyperkeratosis, and chronic inflammation of the skin at the site of application (NTP, 2005). [The Working Group noted that this was a well-conducted study that complied with GLP.]

3.2 Rat

3.2.1 Skin application

Groups of 50 male and 50 female Fischer 344/N rats (age, 6 weeks) were exposed to technical-grade trimethylolpropane triacrylate (purity, > 78%) in acetone by skin application at a dose of 0 (control), 0.3, 1.0, or 3.0 mg/kg bw once per day, 5 days per week for 104–105 weeks. The test agent was from the same batch as that used in the 2-year NTP (2012) study in mice; the types and quantities of impurities were therefore identical (see Section 3.1.1). The dose levels were selected to avoid significant skin irritation (based on the severity of skin lesions in a 3-month study) and to preclude adverse effects on survival and growth. The doses were applied to the interscapular region of the back after clipping the hair (NTP, 2012). Survival in treated groups was similar to that of controls. There were no differences in body weights in the treated groups compared with controls. There was a significant increase in the incidence of malignant mesothelioma of the tunica vaginalis in male rats (0/50, 2/50 (4%), 2/50 (4%), and 5/50 (10%) in the groups exposed at 0, 0.3, 1.0, or 3.0 mg/kg bw, respectively) in the group exposed at the highest dose ($P = 0.031$), with a significant positive trend ($P = 0.024$). The incidence in the group exposed

at the highest dose was above the upper bound of the historical control range (0–8%). There were no treatment-related neoplasms of the skin at the site of application in males or females, and no treatment-related neoplasms in other organs in females. In males and females, there were significant increases in the incidence of epidermal hyperplasia and hyperkeratosis of the skin at the site of application (NTP, 2012). [The Working Group noted that this was a well-conducted GLP study.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

Data on absorption, distribution, metabolism, and excretion of the trimethylolpropane triacrylate in humans were not available to the Working Group.

4.1.2 Experimental systems

The absorption, distribution, and excretion of [^{14}C]-trimethylolpropane triacrylate were investigated in male Fischer 344/N rats and B6C3F$_1$ mice after dermal exposure, and in male Fischer 344/N rats after exposure by intravenous injection (NTP, 2005).

In rats, the percentage of trimethylolpropane triacrylate absorbed after a single dermal exposure decreased with increasing dose (55, 33, and 19% for exposure at 1.7, 15.2, and 130 mg/kg bw, respectively) after 72 hours. At 72 hours, the total radioactivity recovered in the excreta was approximately 45, 19, and 5% of the applied respective doses. The cumulative excreted radiolabel was partitioned approximately 63% in the urine, 4–6% in the faeces, and 26–30% in exhaled carbon dioxide, regardless of the dose administered. Most of the radiolabel remaining in the rats 72 hours after dermal exposure was associated with the skin at the application site (~9% of the absorbed compound, primarily intact [^{14}C]-trimethylolpropane triacrylate). After a single dermal exposure at 124 mg/kg bw, HPLC analysis of acetone extracts from the stripped skin indicated that trimethylolpropane triacrylate (73%) was the major compound entering the systemic circulation; two additional peaks (not identified) accounted for 14% and 10% of the radiolabel. At all doses, the total radiolabel associated with collected tissues at 72 hours did not exceed 1%. Compared with other tissues, the kidney had higher tissue:blood ratios of trimethylolpropane triacrylate equivalents, which were not due to covalent binding to kidney proteins but were probably associated with the urine (NTP, 2005).

In male rats exposed to [^{14}C]-trimethylolpropane triacrylate at 9.4 mg/kg bw by intravenous bolus injection, a total of approximately 77% of the radiolabelled compound was excreted in the urine (48%), faeces (9%), and exhaled carbon dioxide (20%) 72 hours later, and the average total recovery of radiolabel was 90%. The highest concentration of radiolabel found in tissues collected 72 hours after exposure was in the blood (~5%), with other tissues (combined) accounting for approximately 2%. Contrary to that observed after dermal exposure, the tissue:-blood ratio of radiolabel in the kidney was not elevated compared with other tissues; however, the systemically available radiolabelled material resulted in covalent binding to kidney macromolecules (NTP, 2005).

In male mice, the total absorbed dose 72 hours after a single dermal exposure to [^{14}C]-trimethylolpropane triacrylate at 1.2 mg/kg bw was approximately 1.4-fold the amount absorbed by rats exposed at a similar dose. The percentage of the absorbed dose remaining in the skin at the site of application (31%) was much higher in mice

than in rats. Approximately 42% of the administered dose was excreted by the mice in the urine, faeces, and exhaled carbon dioxide, which was similar to the percentage excreted by rats exposed at 1.7 mg/kg bw. However, the radiolabel in the excreta of mice at 72 hours was partitioned 39% in the urine, 13% in the faeces, and 43% in exhaled carbon dioxide, a much lower excretion in the urine and a higher excretion in the faeces and exhaled carbon dioxide compared with rats. Similarly to rats, very little radiolabel (~0.2%) was associated with mouse tissues 72 hours after exposure; compared with other tissues, the unexposed skin had a higher tissue:blood ratio of trimethylolpropane triacrylate equivalents (NTP, 2005).

No data on the specific metabolites of trimethylolpropane triacrylate were available to the Working Group. Although stability studies indicated that [^{14}C]-trimethylolpropane triacrylate is not chemically stable in the whole blood of male rats, the extent of metabolism and the identity of the metabolites have not been reported (NTP, 2005).

[The Working Group noted that the structure of trimethylolpropane triacrylate suggests susceptibility to blood esterases that may catalyse hydrolysis to acrylic acid, along with trimethylolpropane diacrylate, trimethylolpropane monoacrylate, and/or trimethylolpropane. The excretion of [^{14}C]O_2 after exposure to trimethylolpropane triacrylate by dermal application and intravenous injection in rodents (NTP, 2005) is consistent with the release of acrylic acid (IARC, 1999). Likewise, urinary metabolites of acrylic acid, including cysteine conjugates (IARC, 1999), might explain the elevated tissue:blood radiolabel ratio in the kidney found after dermal exposure of rats to radiolabelled trimethylolpropane triacrylate in the NTP study (NTP, 2005).]

4.2 Mechanisms of carcinogenesis

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016) in the following order: is genotoxic; induces chronic inflammation. Insufficient data were available for evaluation of the other key characteristics of carcinogens.

4.2.1 Genetic and related effects

Trimethylolpropane triacrylate has been evaluated for genetic and related effects in a variety of assays. Table 4.1, Table 4.2, and Table 4.3 summarize the studies that have been reported in non-human mammals in vivo, in non-human mammalian cells in vitro, and in non-mammalian experimental systems, respectively, in the primary peer-reviewed literature.

Genetic and related effects of trimethylolpropane triacrylate in human cells in vitro, and in experimental systems in vivo, were reviewed in Kirkland & Fowler (2018). [The Working Group was unable to evaluate this study independently because the data were not publicly available.]

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.1

In male and female Sprague-Dawley rats exposed to a single dose of a slurry of the trimethylolpropane triacrylate cross-linked polymer (up to 16 mL/kg bw; 5:10:25 weight proportions of polymer:ethanol:water) by oral gavage, no increase in the incidence of chromosomal aberrations in the bone marrow was observed (Thompson et al., 1991).

Technical-grade trimethylolpropane triacrylate did not induce an increase in the frequency of micronucleated normochromatic erythrocytes (NCEs) in male and female B6C3F$_1$

Table 4.1 Genetic and related effects of trimethylolpropane triacrylate in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Chromosomal aberrations	Rat, Sprague-Dawley (M, F)	Bone marrow	–	Cross-linked polymer 16 mL/kg bw (slurry: 5 g test material, 10 g ethanol, 25 g distilled water)	Oral gavage; single dose	Purity, NR Average relative molecular mass, > 1 000 000	Thompson et al. (1991)
Micronucleus formation	Mouse, $B6C3F_1$ (M, F)	Peripheral blood; normochromatic and polychromatic erythrocytes	–	12 mg/kg bw	Dermal; 0.75, 1.5, 3, 6, 12 mg/kg bw, 3 mo	Purity, > 78%	NTP (2005)
Micronucleus formation	Mouse, Tg.AC hemizygous (M, F)	Peripheral blood; normochromatic and polychromatic erythrocytes	–	12 mg/kg bw	Dermal; 0.75, 1.5, 3, 6, 12 mg/kg bw, 6 mo	Purity, > 78%	NTP (2005)

bw, body weight; F, female; HID, highest ineffective dose; LED, lowest effective dose; M, male; mo, month; NR, not reported

[a] –, negative; the level of significance was set at $P < 0.05$ for all cases

Table 4.2 Genetic and related effects of trimethylolpropane triacrylate in non-human mammalian cells in vitro

End-point	Species, tissue/cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Unscheduled DNA synthesis	Rat primary hepatocytes	–	NT	Cross-linked polymer, 1500 µg/mL	Purity, NR Average relative molecular mass, > 1 000 000	Thompson et al. (1991)
Mutation, *Tk*	Mouse L5178Y lymphoma	+	NT	0.65 µg/mL	Purity, NR	Dearfield et al. (1989)
Mutation, *Tk*	Mouse L5178Y lymphoma	–	–	Cross-linked polymer, 3300 µg/mL	Purity, NR Average relative molecular mass, > 1 000 000	Thompson et al. (1991)
Mutation, *Tk*	Mouse L5178Y lymphoma	+	–	2.5 µM	Purity, 79%	Cameron et al. (1991)
Mutation, *Hprt*	Chinese hamster ovary K1-BH4	–	NT	0.7 µg/mL	Purity, NR	Moore et al. (1989)
Mutation, *Hprt*	Chinese hamster ovary K1-BH4	–	NT	0.5 µg/mL	Purity, NR	Moore et al. (1991)
Mutation, *Hprt*	Chinese hamster ovary K1-BH4	–	NT	1.0 µg/mL	Purity, NR	Moore et al. (1991)
Chromosomal aberrations	Mouse L5178Y lymphoma	+	NT	0.7 µg/mL	Purity, NR	Dearfield et al. (1989)
Chromosomal aberrations	Chinese hamster ovary K1-BH4	+	NT	0.2 µg/mL	Purity, NR	Moore et al. (1989)
Micronuclei	Mouse L5178Y lymphoma	(+)	NT	0.7 µg/mL	Purity, NR	Dearfield et al. (1989)

HIC, highest ineffective concentration; LEC, lowest effective concentration, NR, not reported; NT, not tested

[a] +, positive; –, negative; (+), positive in a study of limited quality; the level of significance was set at $P < 0.05$ for all cases

Table 4.3 Genetic and related effects of trimethylolpropane triacrylate in non-mammalian experimental systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Salmonella typhimurium TA98, TA100, TA1537	Reverse mutation	–	–	10 000 µg/plate	Purity, 79%	Cameron et al. (1991)
Salmonella typhimurium TA1535	Reverse mutation	–	+/–	3333 µg/plate	Purity, 79%	Cameron et al. (1991)
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	Cross-linked polymer 6666 µg/plate	Purity, NR; average relative molecular mass, > 1 000 000	Thompson et al. (1991)
Salmonella typhimurium TA98, TA100	Reverse mutation	–	–	10 000 µg/plate	Purity, ~80%	NTP (2012)
Escherichia coli WP2uvrA/pKM101	Reverse mutation	–	–	10 000 µg/plate	Purity, ~80%	NTP (2012)

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported

[a] –, negative; +/–, equivocal (variable response in several experiments within an adequate study); the level of significance was set at $P < 0.05$ for all cases

mice exposed dermally at 0.75–12 mg/kg bw for 3 months. The treatment did not affect the ratios of micronucleated polychromatic erythrocytes to NCEs in the peripheral blood, indicating that trimethylolpropane triacrylate did not induce bone marrow toxicity (NTP, 2005).

Similarly, there was no increase in the frequency of micronucleated NCEs in peripheral blood samples from male and female Tg.AC hemizygous mice exposed dermally to trimethylolpropane triacrylate at 0.75–12 mg/kg bw for 6 months. In this experiment, the percentage of circulating NCEs (in the total erythrocytes) decreased in male and female mice exposed at 12 mg/kg bw, which was an indication of erythropoiesis stimulation, with increased numbers of immature erythrocytes present in the blood (NTP, 2005).

(ii) Non-human mammalian cells in vitro

See Table 4.2

Exposure to the trimethylolpropane triacrylate cross-linked polymer at up to 1500 µg/mL did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes (Thompson et al., 1991). The trimethylolpropane triacrylate cross-linked polymer was also tested for the induction of *Tk* mutations in the L5178Y mouse lymphoma assay, both in the absence (at up to 1392 µg/mL) and presence (at up to 3300 µg/mL) of rat liver S9; the results were negative (Thompson et al., 1991).

Trimethylolpropane triacrylate at concentrations of up to 0.7 µg/mL [purity, not reported] was tested in L5178Y mouse lymphoma cells, without exogenous metabolic activation, for the induction of chromosomal aberrations, micronuclei, and forward mutations at the *Tk* locus. Concentration-related positive responses were observed for all three end-points; some cytotoxicity was observed at all concentrations. The trifluorothymidine-resistant mutants were primarily small in size (Dearfield et al., 1989). A later study confirmed the induction of a mutagenic response by trimethylolpropane triacrylate (stated purity, 79%) in the mouse lymphoma assay in the absence of metabolic activation but, again, some cytotoxicity was observed; the addition of S9 decreased both the toxicity and the mutagenic response (Cameron et al., 1991). By contrast, an earlier review (Andrews & Clary, 1986) reported an equivocal result for trimethylolpropane triacrylate in the mouse lymphoma assay, but no details were provided regarding the experimental conditions.

When tested in K1-BH4 Chinese hamster ovary (CHO) cells using the standard monolayer protocol, trimethylolpropane triacrylate at concentrations of up to 0.5 µg/mL [purity, not reported] did not induce an increase in mutant frequency at the *Hgprt* locus of the target cells. Similarly, no mutagenicity was observed at concentrations of up to 1 µg/mL in an adapted CHO suspension assay that used cell numbers comparable to those of the L5178Y mouse lymphoma assay (Moore et al., 1991). However, the same group reported that trimethylolpropane triacrylate at concentrations of up to 0.2 µg/mL induced concentration-related increases in the frequency of chromosomal aberrations in the suspension CHO assay (Moore et al., 1989).

(iii) Non-mammalian experimental systems

See Table 4.3

Trimethylolpropane triacrylate was reported to give negative results in the Ames test, with and without exogenous metabolic activation, and in the yeast D4 assay; however, no experimental details were provided (Andrews & Clary, 1986). In a later study, trimethylolpropane triacrylate (stated purity, 79%) at up to 10 000 µg/plate was found to be weakly mutagenic in *Salmonella typhimurium* strain TA1535 in the presence of hamster (but not rat) liver S9 activation; negative results were obtained in the same strain in the absence of exogenous metabolic activation, as well as in *S. typhimurium* strains TA98, TA100, and TA1537, with and without rat or hamster

liver S9 fractions (Cameron et al., 1991). The negative results in *S. typhimurium* strains TA98 and TA100, with and without rat liver S9 mix, were confirmed in a more recent study (NTP, 2012) that used trimethylolpropane triacrylate at a concentration of up to 10 000 µg/plate (stated purity, ~80%). Negative results were similarly obtained in *Escherichia coli* strain WP2 uvrA/pKM101, considered analogous to *S. typhimurium* strain TA102 (NTP, 2012).

When tested in multiple strains of *S. typhimurium*, the trimethylolpropane cross-linked polymer was not mutagenic at concentrations of up to 6666 µg/plate, either in the absence or presence of induced rat liver S9 mix (Thompson et al., 1991).

4.2.2 Chronic inflammation

(a) Humans

No data were available to the Working Group, except for that on conjunctivitis discussed below (see Section 4.3.1).

(b) Experimental systems

Non-neoplastic inflammatory skin lesions were observed at the site of application in 14-week, 3-month, and 2-year studies of trimethylolpropane triacrylate (Doi et al., 2005; NTP, 2012). Non-neoplastic skin lesions were observed at the site of application in the 3-month studies in male and female rats and mice exposed to trimethylolpropane triacrylate at or above concentrations of 3 mg/kg bw, 5 days per week, and characterized as epidermal hyperplasia and hyperkeratosis. There was a significant increase in the incidence of non-neoplastic lesions in male and female Fischer 344/N rats after topical exposure to trimethylolpropane triacrylate at 1.0 or 3.0 mg/kg bw, 5 days per week, for 2 years. Hyperkeratosis was also increased in female rats exposed to trimethylolpropane triacrylate at 0.3 mg/kg bw. In the same studies, male and female B6C3F$_1$ mice exposed to trimethylolpropane triacrylate at 3.0 mg/kg bw had a significantly increased incidence of epidermal hyperplasia, melanocyte hyperplasia, and chronic inflammation at the site of application. Epidermal hyperplasia was increased in female mice only after exposure to trimethylolpropane triacrylate at 1.0 mg/kg bw, although chronic inflammation was significantly increased in male mice only at the same dose (NTP, 2012). In Tg.AC mice, similar non-neoplastic lesions were observed at the site of trimethylolpropane triacrylate application and included epidermal hyperplasia, hyperkeratosis, and chronic active inflammation, which were consistently present in both males and females at doses of more than 3 mg/kg bw, 5 days per week, for 6 months (Doi et al., 2005).

4.3 Other adverse effects

4.3.1 Humans

Although much of the toxicity observed in humans exposed to trimethylolpropane triacrylate appears to be allergic in nature, there are reports of skin irritation and inflammation in the absence of sensitization (Nethercott, 1978; Cofield et al., 1985). Nethercott (1978) also reported conjunctivitis in workers exposed to a mixture of acrylic monomers in cured inks.

There are numerous case reports and studies describing the development of allergic contact dermatitis after exposure to industrial mixtures of acrylates containing trimethylolpropane triacrylate (Emmett & Kominsky, 1977; Nethercott, 1978; Björkner et al., 1980; Dahlquist et al., 1983; Nethercott et al., 1983; Garabrant, 1985; Le et al., 2015). Case reports of allergic conjunctivitis (Kanerva et al., 1998; Mancuso & Berdondini, 2008) and asthma (Kanerva et al., 1995; Sánchez-Garcia et al., 2009) have been noted for exposed individuals working with UV-cured paints and inks, with positive reactivity to trimethylolpropane triacrylate in patch tests. When patch testing was conducted, individuals frequently displayed

positive reactions to two or more acrylates (Emmett & Kominsky, 1977; Nethercott, 1978).

4.3.2 Experimental systems

Trimethylolpropane triacrylate applied directly to the skin gave positive results at non-sensitizing concentrations in a dermal irritancy study using female BALB/c mice (NTP, 1995). In a similar study using $B6C3F_1$ mice, trimethylolpropane triacrylate concentrations of 1–30% resulted in significant irritation (Hayes & Meade, 1999).

There are numerous studies in rodents describing sensitization after exposure to trimethyl-olpropane triacrylate (Nethercott et al., 1983; Parker & Turk, 1983; Hayes & Meade, 1999). Cross-reactivity to multiple acrylates has also been demonstrated in animal models (Björkner, 1984; Clemmensen, 1984; Parker et al., 1985; Hayes & Meade, 1999).

Bull et al. (1987) examined the direct immunogenicity of trimethylolpropane triacrylate after footpad injection in female Hartley guinea-pigs. Anti-trimethylolpropane triacrylate antibody levels were elevated in animals immunized with trimethylolpropane triacrylate conjugated to bovine gamma globulin in the presence of Freund's complete adjuvant, but were not detected when unconjugated trimethylolpropane triacrylate was used. The antibodies produced were cross-reactive with methyl acrylate, but not 4-vinyl pyridine (Bull et al., 1987).

4.4 Data relevant to comparisons across agents and end-points

See the monograph on isobutyl nitrite in the present volume.

5. Summary of Data Reported

5.1 Exposure data

Trimethylolpropane triacrylate is only available in technical-grade form, of purity 70–90%, and includes incomplete reaction products, inhibitors, and catalysts. Trimethylolpropane triacrylate is a high production volume chemical that is produced worldwide. It is used in ultraviolet-curable inks, photosensitive chemicals, paint additives, coating additives, and adhesive and sealant chemicals, intermediates, and solvents. Occupational exposure primarily occurs in manufacturing facilities. The concentrations of exposure to trimethylolpropane triacrylate in workers using ultraviolet inks were below the limit of detection. Dermal exposure of the general population may occur through the use of consumer products, such as latex paints and furniture and floor polishes, containing trimethylolpropane triacrylate. No quantitative information was available on environmental concentrations and exposure in the general population.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

In one 2-year good laboratory practice (GLP) skin application study in male and female mice, technical-grade trimethylolpropane triacrylate caused an increase in the incidence of hepatoblastoma and hepatocholangiocarcinoma in females; the Working Group considered hepatoblastoma and hepatocholangiocarcinoma to be rare neoplasms in female mice, and concluded that the increased incidence of these tumours was biologically significant. There was a significant increase in the incidence (with a significant

positive trend) of stromal polyp and stromal polyp or stromal sarcoma (combined) of the uterus in female mice. There was also a significant positive trend in the incidence of hepatocellular carcinoma in female mice. There was no significant increase in tumour incidence in male mice.

In one 2-year GLP skin application study in male and female rats, technical-grade trimethylolpropane triacrylate caused a significant increase in the incidence (with a significant positive trend) of malignant mesothelioma of the tunica vaginalis in males. There was no significant increase in tumour incidence in female rats.

In a 28-week GLP skin application study in male and female Tg.AC hemizygous mice, exposure to technical-grade trimethylolpropane triacrylate significantly increased the incidence (with a significant positive trend) of squamous cell papilloma of the skin at the site of application in male and female mice, and of squamous cell papilloma of the forestomach in female mice.

5.4 Mechanistic and other relevant data

No data on the absorption, distribution, and excretion of trimethylolpropane triacrylate in exposed humans were available to the Working Group. In rats, the percentage of trimethylolpropane triacrylate absorbed is inversely related to dose after dermal exposure. Regardless of the route of exposure (dermal or intravenous injection), urinary excretion is the primary elimination pathway, followed by carbon dioxide exhalation. Excretion pathways are similar in dermally exposed mice.

No data on the specific metabolites of trimethylolpropane triacrylate were available in either humans or experimental animals, although the excretion of carbon dioxide suggests the occurrence of hydrolysis to acrylic acid.

Regarding the key characteristics of carcinogens, there is *weak* evidence that trimethylolpropane triacrylate is genotoxic. No data were available in humans or in human cells in vitro. After dermal exposure, trimethylolpropane triacrylate gave negative results in the mouse peripheral blood micronucleus test. Trimethylolpropane triacrylate gave dose-dependently positive results in rodent cells in vitro, inducing chromosomal aberrations, micronucleus formation, and forward mutations at the *Tk* locus in mouse cells, and chromosomal aberrations, but not *Hgprt* mutations, in hamster cells, although some cytotoxicity was observed. Trimethylolpropane triacrylate also gave negative results in the Ames test.

There is *moderate* evidence that trimethylolpropane triacrylate induces chronic inflammation, based on observations of dermal hyperplasia in multiple cell types in chronically exposed rodents.

Irritant and allergic types of contact dermatitis were reported in humans, with similar results in studies in rodents.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of technical-grade trimethylolpropane triacrylate.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of technical-grade trimethylolpropane triacrylate.

6.3 Overall evaluation

Technical-grade trimethylolpropane triacrylate is *possibly carcinogenic to humans (Group 2B)*.

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