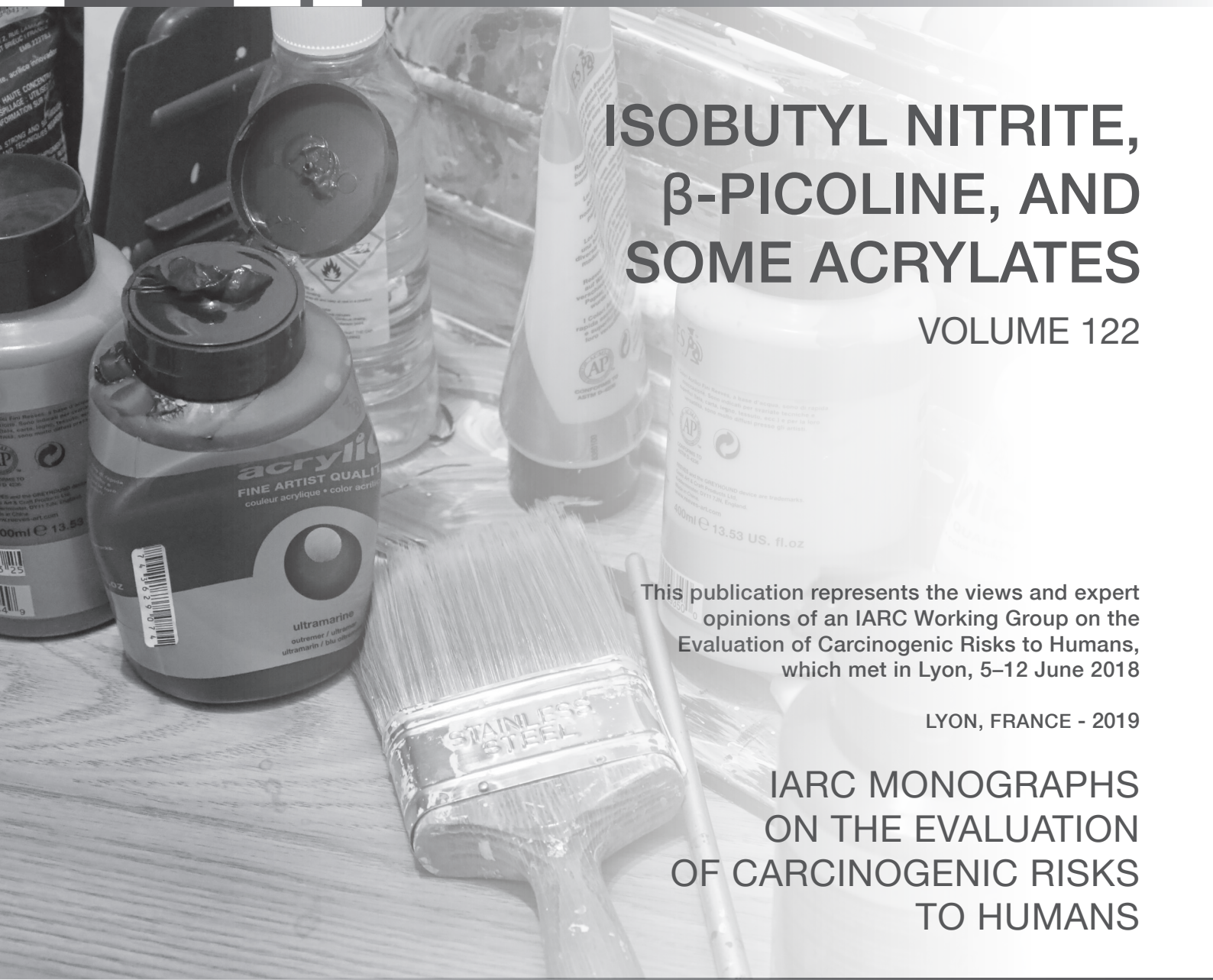
IARC MONOGRAPHS



ISOBUTYL NITRITE, β-PICOLINE, AND SOME ACRYLATES

VOLUME 122

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

2-ETHYLHEXYL ACRYLATE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 103-11-7

Deleted Chem. Abstr. Serv. Reg. Nos: 78733-32-1; 84948-57-2; 93460-77-6

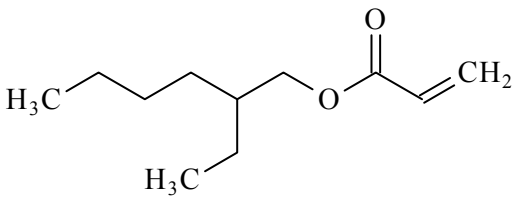
Chem. Abstr. Serv. name: 2-propenoic acid; 2-ethylhexyl ester

IUPAC systematic name: acrylic acid; 2-ethylhexyl ester

Synonyms: 2-ethylhexyl 2-propenoate; 2-ethyl hexyl acrylate; 2-ethyl-1-hexyl acrylate; 2-ethylhexanol acrylate; 2-ethylhexyl prop-2-enoate.

1.1.2 Structural and molecular formulae, and relative molecular mass

Molecular formula: $C_{11}H_{20}O_2$



(Royal Society of Chemistry, 2018)

Relative molecular mass: 184.28

1.1.3 Chemical and physical properties

Description: colourless liquid (HSDB, 2018)

Boiling point: 214–218 °C (HSDB, 2018)

Melting point: –90 °C (HSDB, 2018)

Density: specific gravity, 0.880 g/cm^3 at 25 °C (HSDB, 2018)

Solubility: slightly soluble in water (< 0.01% by weight, wt%, at 20 °C); soluble in alcohols, ethers, and many organic solvents (acetone, benzene, ethyl ether, heptane, methanol, and carbon tetrachloride) (Union Carbide Corp., 1982)

Vapour pressure: 0.14 mm Hg [19 Pa] at 20 °C

Relative vapour density (air = 1): 6.4 at 20 °C (Hoechst Celanese Corp., 1992)

Flash point: 92 °C (open cup); rapid, uncontrolled polymerization can cause explosion (Tyler, 1993)

Conversion factor: 1 ppm = 7.54 mg/m^3 at 1 atm, 25 °C.

1.1.4 Technical products and impurities

2-Ethylhexyl acrylate is available as a commercial product with a purity of 99% or greater. Impurities include: water, 0.05–0.10 wt% maximum; acidity (as acrylic acid), 0.009 wt% maximum; hydroquinone (polymerization inhibitor), 90–120 ppm; and monomethyl ether of hydroquinone (polymerization inhibitor), 13–120 ppm (Union Carbide Corp., 1982;

Hoechst Celanese Corp., 1988; ECHA, 2005; HSDB, 2018).

1.2 Production and use

1.2.1 Production process

Direct, acid-catalysed esterification of acrylic acid with 2-ethylhexanol is the principal method for the manufacture of 2-ethylhexyl acrylate. The most common catalysts are sulfuric and *para*-toluenesulfonic acid, and sulfonic acid functional cation-exchange resins. The monomethyl ether of hydroquinone is added as a polymerization inhibitor, and the esters are used in this form in most industrial applications (ECHA, 2005).

1.2.2 Production volume

2-Ethylhexyl acrylate has been listed as a chemical with a high production volume (OECD, 2009). The estimated production volume of 2-ethylhexyl acrylate in the USA in 1991 was 48 thousand metric tonnes (United States International Trade Commission, 1993). By 1999, the total European Union production volume was estimated to be 70 thousand metric tonnes per year (ECHA, 2005). Accounting for imports and exports, in 1999 a total amount of 90 thousand metric tonnes per year was estimated to be available on the European market, 32 thousand metric tonnes used as internal intermediate, and 58 thousand metric tonnes sold to external processing sites (ECHA, 2005). Production volume in China was 43 thousand metric tonnes in 2008 (Chinese Report, 2008), and doubled to 85 thousand metric tonnes in 2010 (Chinese Report, 2010).

1.2.3 Use

Acrylic esters are used in the production of polymers and copolymers with a wide range of applications. Polymers containing 2-ethylhexyl acrylate are used in different types of food-packaging materials (Tyler, 1993). As a plasticizing co-monomer, 2-ethylhexyl acrylate is used in the production of resins for pressure-sensitive adhesives, latex paints, reactive diluents and/or cross-linking agents, textile and leather finishes, and coatings for paper (HSDB, 2018). 2-Ethylhexyl acrylate can also be used as a co-monomer in solution polymers for industrial metal finishing (Mannsville Chemical Products Corp., 1984; Tyler, 1993). A common use of 2-ethylhexyl acrylate is as a major component in acrylic pressure-sensitive adhesives. The typical composition of an adhesive for general-purpose tape is 75% 2-ethylhexyl acrylate (Temin, 1990).

2-Ethylhexyl acrylate is also used in ultraviolet-curable coatings without solvents, which provide a glossy, abrasion-resistant finish on book covers, for example. A typical ultraviolet-cured formulation might include 10% 2-ethylhexyl acrylate diluent monomer and small amounts of photoinitiator (Mannsville Chemical Products Corp., 1984).

More recent uses of 2-ethylhexyl acrylate include in the manufacture of plastics for transdermal drug delivery systems applied in the fields of estrogen replacement therapy, and in the delivery of anti-inflammatory drugs in eye surgery (Kotiyan & Vavia, 2001; Duarte et al., 2008).

1.3 Analytical methods

Methods for sampling and analysing air have been developed for vapours of acrylate monomers, including 2-ethylhexyl acrylate (Bosserman & Ketcham, 1980; Samimi & Falbo, 1982). The most common method used is United States Occupational Safety and Health Administration PV2026, in which the acrylate monomer vapour is adsorbed on activated silica gel or charcoal, desorbed in carbon disulfide, and analysed by gas chromatography with flame ionization detection (OSHA, 2010). The limit of quantitation is 0.01 ppm (0.08 mg/m^3).

No biological markers are reported for exposure to 2-ethylhexyl acrylate.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

2-Ethylhexyl acrylate is readily biodegradable in air, water, and soil (ECHA, 2005). The atmospheric half-life is approximately 19 hours (ECHA, 2005). 2-Ethylhexyl acrylate has moderate mobility in soil (HSDB, 2018). In the effluent of an onsite waste-treatment facility, 2-ethylhexyl acrylate was detected at concentrations ranging from 0.6 to 11 ppb (μg/L) (mean, 4 ppb). The treatment facility received water from a large petrochemical plant where the influent untreated wastewater contained 2-ethylhexyl acrylate at 0.55–5.60 ppm (mg/L) (mean, 2.0 ppm) (Berglund & Whipple, 1987).

1.4.2 Exposure in the general population

2-Ethylhexyl acrylate is not known to occur as a natural product. Exposure in the general population may occur through the use of consumer products (e.g. adhesives, furniture coatings, or paints) or through inadvertent release by industry in the local environment (HSDB, 2018). No quantitative information on exposure was available to the Working Group.

1.4.3 Occupational exposure

Occupational exposure occurs in both the manufacture and use of 2-ethylhexyl acrylate. As a result of its low vapour pressure, exposure by inhalation is expected to be low. Dermal exposure may occur during spills or leaks (Björkner et al., 1980).

The exposure of workers to styrene and several acrylates (including 2-ethylhexyl acrylate) and area concentrations were monitored in a United States facility where acrylic ester-styrene copolymers were produced (Samimi & Falbo, 1982). The personal concentrations of 2-ethylhexyl acrylate at a process reactor (Reactor A) that had an opening hatch for the addition of starting products ranged from not detectable to 2 ppb [20 μg/m^3] (mean, 0.4 ppb [3 μg/m^3]); nine personal samples taken at a similar reactor contained no detectable concentrations. A further 13 personal samples collected from workers tending a completely closed reactor ranged from not detectable to 5 ppb [40 μg/m^3] (mean, 1 ppb [8 μg/m^3]). No detectable concentrations were found in six personal samples taken from workers at a closed polymer flake continuous reactor. In 11 personal samples collected at the unloading docks, concentrations ranged from not detectable to 5 ppb [40 μg/m^3] (mean, 2 ppb [20 μg/m^3]). Eight area samples taken at Reactor A had concentrations ranging from not detectable to 161 ppb [1.21 mg/m^3] (mean, 30 ppb [230 μg/m^3]); the remaining 41 area samples had no detectable concentrations (Samimi & Falbo, 1982).

Detailed data on the exposure of workers during the manufacture of 2-ethylhexyl acrylate in four plants in the USA were summarized by Tyler (1993). Workers were exposed to mean concentrations ranging from 30 to 500 ppb [0.23–3.77 mg/m^3], depending upon manufacturing plant location (Tyler, 1993).

In a study from spring/summer 2016 among 13 road workers from three companies using paint containing 2-ethylhexyl acrylate, exposure to organic solvents and acrylates was measured over a 5-day working period (de Poot, 2016); 8-hour time-weighted average (TWA) concentrations of methyl methacrylate, butyl acrylate, and 2-ethylhexyl acrylate were measured. Although the highest concentrations of methyl methacrylate were measured during manual sputtering, mechanical extruding, and paint spraying, all three measurements of 2-ethylhexyl acrylate were below the limit of detection (0.4 mg/m^3). For short-term task-based measurements, the highest concentrations of methyl methacrylate

resulted from filling spraying reservoirs with paint. One task-based measurement was below the limit of detection for 2-ethylhexyl acrylate (7 mg/m^3) (de Poot, 2016).

1.5 Regulations and guidelines

A small number of countries have occupational exposure limits for 2-ethylhexyl acrylate. In Germany, Poland, and Switzerland the 8-hour TWA and short-term occupational exposure limit is 38 mg/m^3, and in Austria it is 82 mg/m^3. In Latvia and the Russian Federation, there is a much lower 8-hour TWA occupational exposure limit of 1 mg/m^3 (IFA, 2018).

The United States Food and Drug Administration has established regulations for the use of monomers, polymers, and copolymers, including 2-ethylhexyl acrylate, in food-contact materials. The quantity of the monomers should not exceed 5 wt% of total polymer units (CFR, 2017).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

2-Ethylhexyl acrylate was reviewed by the Working Group in *IARC Monographs* Volume 60 (IARC, 1994). The Working Group concluded that there is *limited evidence* in experimental animals for the carcinogenicity of 2-ethylhexyl acrylate. This section provides an evaluation of the studies of carcinogenicity in experimental animals reviewed in the previous monograph.

See Table 3.1

3.1 Mouse

3.1.1 Skin application

A group of 40 male C3H/HeJ mice (age, 7–10 weeks) was exposed to a 75% (by volume) solution of 2-ethylhexyl acrylate (purity, 99%) in acetone three times per week for their lifetime (DePass, 1982; DePass et al., 1985). The fur was clipped from the back of each mouse once per week. Treated mice received "one brushful" of the dosing solution per application, a dose of approximately 20 mg per application estimated by weighing the sample bottle before and after dosing each group of 40 mice. Two groups of 40 mice were given acetone only and served as vehicle controls. Survival of the treated group at 18 months was 15/40 (38%) compared with 35/80 (44%) in the combined acetone control groups. All mice exposed to 2-ethylhexyl acrylate were dead 2 years after the start of the experiment. No information on body weights or other clinical observations were reported. A statistically significant increase in the incidence of squamous cell papilloma of the skin (4/40 (10%) vs 0/80 controls [P = 0.0111, Fisher exact test]) and of squamous cell papilloma or carcinoma (combined) of the skin (6/40 (15%) vs 0/80 controls [P = 0.0011, Fisher exact test]) was observed.

A recent publication by Murphy et al. (2018a) provided no new data on the carcinogenicity of 2-ethylhexyl acrylate, but critically evaluated the study of carcinogenicity in mice exposed dermally to 2-ethylhexyl acrylate by DePass et al. (1985). Murphy et al. (2018a) indicated that the application of contemporary evaluation criteria to the dataset on dermal carcinogenicity from DePass et al. (1985), demonstrates that 2-ethylhexyl acrylate induced skin tumours only at concentrations exceeding the maximum tolerated dose (MTD) and only in the immune-dysregulated C3H/HeJ mouse model. [The Working Group noted that the study by DePass et al. (1985) used the C3H/HeJ mouse and was designed to determine

Table 3.1 Studies of carcinogenicity with 2-ethylhexyl acrylate 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, C3H/HeJ (M) 7–10 wk Lifetime DePass et al. (1985)	Skin application 2-Ethylhexyl acrylate, 99% Acetone 0, 0, ~20 mg, 3×/wk 40, 40, 40 7, 5, 0	*Skin* Squamous cell papilloma 0/40, 0/40, 4/40* (10%) Squamous cell carcinoma 0/40, 0/40, 2/40 (5%) Squamous cell papilloma or carcinoma (combined) 0/40, 0/40, 6/40* (15%)	 *[P = 0.0111 compared with combined control groups, Fisher exact test] [NS] *[P = 0.0011 compared with combined control groups; Fisher exact test]	Principal limitations: poor dosing method of using "one brushful" of dosing solution (75% 2-ethylhexyl acrylate in acetone), and calculating approximate dose by weighing the sample bottle before and after dosing each group of 40 mice; use of only one sex and only one dose; data and discussion of pathology findings for the skin only; limited dosing of only 3 d/wk The number of surviving mice given is at 2 yr
Full carcinogenicity Mouse, C3H/HeJ (M) 6 wk Lifetime Wenzel-Hartung et al. (1989)	Skin application 2-Ethylhexyl acrylate, ≥ 99.5% Acetone 0 (untreated), 0 (vehicle control), 2.5, 21, 43 (stop-exposure group; treatment stopped at 24 wk), 86.5% (w/w); 25 µL 3×/wk 80, 80, 80, 80, 80, 80 NR	*Skin* Papilloma 0/80, 0/80, 0/80, 4/80 (5%), 0/80, 8/80* (10%) Cornified squamous cell carcinoma 0/80, 0/80, 0/80, 20/80* (25%), 0/80, 16/80* (20%) Malignant melanoma 0/80, 0/80, 0/80, 7/80* (9%), 0/80, 9/80** (11%) Fibrosarcoma 0/80, 0/80, 0/80, 5/80* (6%), 0/80, 0/80 Haemangioma 0/80, 0/80, 0/80, 0/80, 0/80, 1/80 (1%) Basal cell carcinoma 0/80, 0/80, 0/80, 1/80 (1%), 0/80, 0/80	 *[P < 0.007, Fisher exact test] *[P < 0.0001, Fisher exact test] *[P = 0.0136, Fisher exact test]; **[P = 0.0031, Fisher exact test] *[P = 0.03, one-tail Fisher exact test] [NS] [NS]	Principal limitations: use of only one sex and limited dosing of only 3 d/wk

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 Mouse, NMRI BR (M) 48–50 d 2 yr Mellert et al. (1994)	Skin application 2-Ethylhexyl acrylate, ≥ 99.7% Acetone 0, 21.5, 43.0, 85.0% (w/w); 25 µL 3×/wk 41, 40, 39, 39 NR	*Skin* Squamous cell papilloma or squamous cell carcinoma 0/41, 0/40, 0/39, 0/39 Keratoacanthoma 0/41, 0/40, 0/39, 0/39		Principal limitations: use of only one sex and limited dosing of only 3 d/wk; data and discussion of pathology findings for the skin only; no detailed information on survival and body weight Number of mice given at start is the effective number of mice; there were ~40 mice/group at the beginning of the experiment
Initiation–promotion (tested as initiator) Mouse, NMRI BR (M) 48–50 d 2 yr Mellert et al. (1994)	Skin application 2-Ethylhexyl acrylate, ≥ 99.7% Acetone 0, 21.5, 43.0, 85.0% (w/w), treated 3×/wk with 25 µL 2-ethylhexyl acrylate for 7 mo, then no treatment for 2 mo, and finally TPA (5 µg in 0.1 mL) 2×/wk for 20 wk 37, 30, 39, 36 NR	*Skin* Squamous cell papilloma 0/37, 1/30, 1/39, 1/36 Squamous cell carcinoma 0/37, 0/30, 0/39, 0/36 Keratoacanthoma 0/37, 0/30, 0/39, 0/36	[NS]	Principal limitations: use of only one sex and limited dosing of only 3 d/wk; data and discussion of pathology findings for the skin only; no detailed information on survival and body weight Number of mice given at start is the effective number of mice; there were ~40 mice/group at the beginning of the experiment

d, day; M, male; mo, month; NR, not reported; NS, not significant; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week; w/w, weight for weight; yr, year

the carcinogenic potency of 2-ethylhexyl acrylate in rodent skin. Although this study may have used higher concentrations than recommended by current guidelines, it was conducted according to the contemporary standards of that time and in a widely used and accepted strain of mouse for skin application studies. Although the study by DePass et al. (1985) was limited because of the use of only one sex and a single dose, and a limited dosing for only 3 days per week, the Working Group considered it was still performed adequately according to the standards of that time for skin application studies for an evaluation of the carcinogenicity of 2-ethylhexyl acrylate.]

Five groups of 80 male C3H/HeJ mice (age, 6 weeks) were exposed to a 25-µL solution of 2-ethylhexyl acrylate (purity, ≥ 99.5%) in acetone at either 0% (vehicle control), 2.5% (w/w; lowest dose), 21% (intermediate dose), 43% (stop-exposure dose), or 86.5% (highest dose) three times per week for their lifetime (Wenzel-Hartung et al., 1989). The fur was clipped from the back of each mouse once per week. Treatment of the group at 43% was stopped after 24 weeks, and the mice in this group were kept for their lifetime (stop-exposure test) to determine the reversibility or persistency of the lesions. An untreated group of 80 mice served as an additional control group. There was a slight, but statistically significant, increase in body weight in all four groups of exposed mice compared with controls. Survival was similar between exposed and control mice. Scaling and scabbing were observed in all exposed groups and persisted throughout the treatment period. Regression of these skin lesions was observed within 7 weeks after stopping treatment in the stop-exposure group. Exposure to 2-ethylhexyl acrylate for life caused a statistically significant increase in the incidence of papilloma of the skin in the group exposed at the highest dose; incidences for the untreated and vehicle controls, and groups exposed at 2.5%, 21%, and 86.5%, were 0/80, 0/80, 0/80, 4/80, and 8/80 ($P < 0.007$, Fisher exact test), respectively. A statistically significant increase in the incidence of cornified squamous cell carcinoma of the skin (0/80, 0/80, 0/80, 20/80; $P < 0.0001$, Fisher exact test), and 16/80 ($P < 0.0001$, Fisher exact test)) and of malignant melanoma (0/80, 0/80, 0/80, 7/80; $P = 0.0136$, Fisher exact test), and 9/80 ($P = 0.0031$, Fisher exact test)) was observed for groups exposed at the intermediate and highest doses. Five mice developed fibrosarcoma of the skin [significantly increased; $P = 0.03$, one-tail Fisher exact test] and one mouse developed a basal cell carcinoma of the skin in the group exposed at the intermediate dose, and one haemangioma of the skin was observed in the group exposed at the highest dose. No skin tumours were reported in the control (untreated or vehicle) groups, the group exposed at the lowest dose, or the stop-exposure group.

A recent publication by Murphy et al. (2018a) provided no new data on the carcinogenicity of 2-ethylhexyl acrylate, but critically evaluated the study of the carcinogenicity in mice exposed dermally to 2-ethylhexyl acrylate by Wenzel-Hartung et al. (1989). Murphy et al. (2018a) indicated that the application of contemporary evaluation criteria to the dataset on dermal carcinogenicity from Wenzel-Hartung et al. (1989), demonstrates that 2-ethylhexyl acrylate induced skin tumours only at concentrations exceeding the MTD and only in the immune-dysregulated C3H/HeJ mouse model. [The Working Group noted that the study by Wenzel-Hartung et al. (1989) was conducted in the C3H/HeJ mouse and was designed to determine the carcinogenic potency of 2-ethylhexyl acrylate in rodent skin. Although this study may have used higher concentrations than recommended by current guidelines, it was conducted according to the contemporary standards of that time and in a widely used and accepted strain of mouse for skin application studies. Although the study by Wenzel-Hartung et al. (1989) was limited because of the use of only one sex and limited dosing for only

3 days per week, the Working Group considered it was still performed adequately according to the standards of that time for skin application studies for an evaluation of the carcinogenicity of 2-ethylhexyl acrylate. Indeed, there exists a relationship between wound healing and cancer that has long been recognized in the literature. Chronic inflammation has been associated with malignant transformation in numerous tissues, and the biological mechanisms that regulate wound healing have been shown to promote transformation and growth of malignant cells. The Tlr4 mouse model (C3H/HeJ) reviewed by Murphy et al. (2018a) spontaneously develops tumours of the liver in males and tumours of the mammary glands in females, and not tumours of the skin. 2-Ethylhexyl acrylate induced tumours of the skin only at concentrations exceeding the MTD and in the immune-dysregulated C3H/HeJ mouse model. However, melanoma and fibrosarcoma of the skin, as well as cornified squamous cell carcinoma of the skin, are not characteristic of the immune-dysregulated C3H/HeJ mouse model in the scientific literature.]

Four groups of approximately 40 male NMRI BR mice (age, 48–50 days) were exposed to a 25-µL solution of 2-ethylhexyl acrylate (purity, ≥ 99.7%) in acetone at either 0 (vehicle control), 21.5% (w/w; lowest dose), 43.0% (intermediate dose), or 85.0% (highest dose) on their clipped dorsal skin three times per week for 2 years (Mellert et al., 1994). Body weights and survival were similar between exposed and control animals. No squamous cell papillomas, squamous cell carcinomas, or keratoacanthomas of the skin were reported in the groups exposed to 2-ethylhexyl acrylate or in the vehicle controls. A positive control group of mice exposed to benzo[*a*]pyrene developed squamous cell carcinomas of the skin. [The Working Group noted that the study was limited by the use of only one sex, the limited dosing of only 3 days per week, the provision of data and discussion of histopathology for the skin only, and the lack of detailed information on survival and body weight.]

3.1.2 Initiation–promotion

Four groups of approximately 40 male NMRI BR mice (age, 48–50 days) were exposed to a 25-µL solution of 2-ethylhexyl acrylate (purity, ≥ 99.7%) in acetone at either 0% (vehicle control), 21.5% (lower dose), 43.0% (intermediate dose), or 85.0% (higher dose) on their clipped dorsal skin three times per week for 7 months (Mellert et al., 1994). Exposure to 2-ethylhexyl acrylate was discontinued at 7 months, and after 2 months mice were exposed to a solution of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in 0.1 mL acetone, at a dose of 5 µg per mouse twice per week for 20 weeks, and observed for up to an additional 10 months. Body weights and survival were similar between exposed and control animals. One squamous cell papilloma of the skin was seen at the application site in the groups exposed to 2-ethylhexyl acrylate (lower, intermediate, and higher doses) plus TPA; no squamous cell carcinomas or keratoacanthomas of the skin were reported in these groups. No tumours of the skin were observed in the acetone plus TPA control group. A positive control group of mice exposed to benzo[*a*]pyrene plus TPA developed squamous cell carcinomas or keratoacanthomas of the skin. [The Working Group noted that the study was limited by the use of only one sex, the limited dosing of only 3 days per week, the provision of data and discussion of histopathology for the skin only, and the lack of detailed information on survival and body weight.]

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 2-ethylhexyl acrylate in humans were not available to the Working Group.

4.1.2 Experimental systems

2-Ethylhexyl acrylate has been shown to be readily absorbed in rats exposed via intravenous and intraperitoneal injection (Sapota, 1988); after exposure, radiolabelled 2-ethylhexyl acrylate was distributed to all major tissues in rats. One hour after exposure, the tissues with the highest percentages of 2-ethylhexyl acrylate radioactivity were kidney and liver; smaller amounts were found in brain, thymus, spleen, and blood (Gut et al., 1988; Sapota, 1988).

After the exposure of rats to 2-ethylhexyl acrylate by intraperitoneal injection, the major route of excretion was through expiration (as CO_2; > 75% within 24 hours); excretion in urine and faeces was only observed in smaller quantities (Sapota, 1988). However, after oral exposure, both expiration (50% within 24 hours) and urine (38% within 24 hours) were major routes for the elimination of radiolabel (Sapota, 1988). The total radiolabel excreted within 72 hours of the exposure of rats to radiolabelled 2-ethylhexyl acrylate, either orally or via intraperitoneal injection, was approximately 90% and 93% of the administered dose, respectively (Sapota, 1988). In another study in rats, less than 0.01% of the administered dose was excreted in the faeces. In urine, 13.5% of an intravenous dose and 7.2% of an intraperitoneal dose were excreted within 24 hours. For both routes of administration, more than 50% of the administered dose was expired, mostly as carbon dioxide (Gut et al., 1988).

2-Ethylhexyl acrylate is believed to undergo carboxylesterase-catalysed metabolism (Kopecký et al., 1985; see Fig. 4.1). After the exposure of rats to 2-ethylhexyl acrylate by intraperitoneal injection, thioether excretion in the urine was observed (Gut et al., 1988). In rats exposed by inhalation, there was a dose-related increase in the amount of excreted urinary thioethers. In addition, a decrease in the number of non-protein glutathione groups was also observed in the blood and liver of these rats (Vodička et al., 1990). In the same study, 2-ethylhexyl acrylate also showed reactivity with glutathione, with a half-life of 36.4 minutes (Vodička et al., 1990).

Two mercapturic acid metabolites have been identified in rat urine: *N*-acetyl-(2-carboxyethyl)cysteine and *N*-acetyl-2-(2-ethyl-hexyloxycarbonyl)ethylcysteine (Kopecký et al., 1985). Two unidentified metabolites were detected in the bile of rats (Cikrt et al., 1986).

4.2 Mechanisms of carcinogenesis

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016). Data were available only for the key characteristic "is genotoxic".

4.2.1 Genetic and related effects

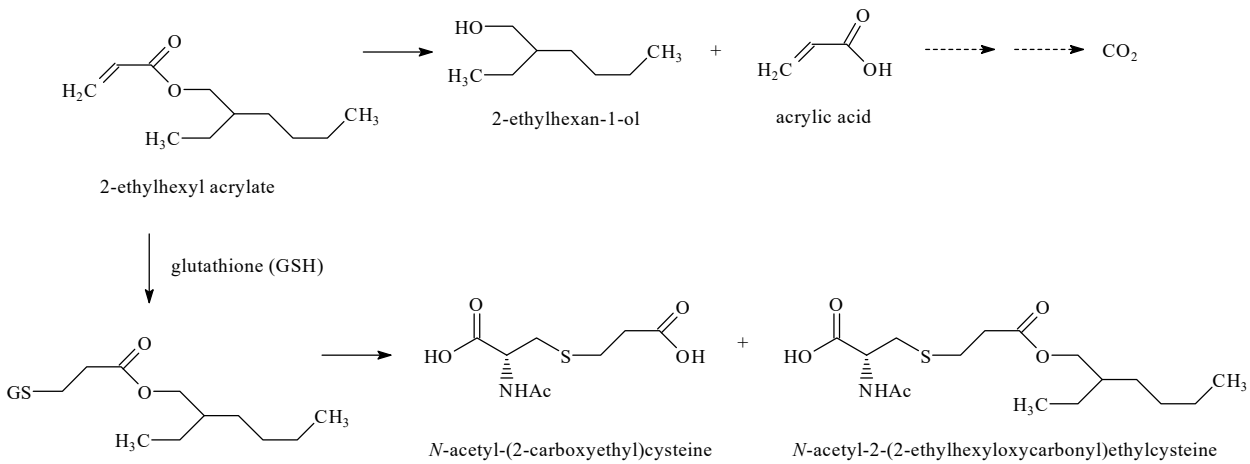
(a) Humans

See Table 4.1

No data from exposed humans were available to the Working Group.

In human lymphocytes, 2-ethylhexyl acrylate did not increase the number of micronucleated cells after 4 hours of exposure followed by 16 hours of recovery in the absence and presence of S9, or after 20 hours of continuous exposure in the absence of S9. A statistically significant increase in the number of micronucleated cells compared with corresponding control values

Fig. 4.1 Proposed metabolic pathways for 2-ethylhexyl acrylate



The two cysteine conjugates have been identified in rat urine. The *N*-acetyl-(2-carboxyethyl)cysteine conjugate may also stem from glutathione addition to acrylic acid
Compiled by the Working Group

was observed in the 4-hour exposure experiment in the absence of S9; however, the numbers were within the range of the 95% limit of the historical control data (Murphy et al., 2018b).

(b) Experimental systems

See Table 4.2

(i) Non-human mammalian cells in vitro

2-Ethylhexyl acrylate yielded equivocal results at the thymidine kinase *(Tk)* locus of mouse lymphoma cells without metabolic activation. The mutant frequency was increased at some test doses; however, the mutant frequency was not increased at higher concentrations and was not consistent across trials. In addition, cell survival was lower than 50% (Dearfield et al., 1989). After exposure to 2-ethylhexyl acrylate, no mutagenic effect was reported in the hypoxanthine-guanine phosphoribosyl transferase (*Hprt*) assay in Chinese hamster ovary cells without metabolic activation, and in Chinese hamster V79 cells in the absence or presence of S9 (Moore et al., 1991, Murphy et al., 2018b).

Equivocal results were reported for the induction of chromosomal aberrations in L5178Y mouse lymphoma cells after exposure to 2-ethylhexyl acrylate; there was no clear dose–response relationship and cell survival was less than 50%. In the same cell line, 2-ethylhexyl acrylate did not increase the number of micronucleated cells (Dearfield et al., 1989).

(ii) Non-mammalian experimental systems

In *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, 2-ethylhexyl acrylate was not mutagenic in the assay for reverse mutation in the presence or absence of metabolic activation (Zeiger et al., 1985).

Table 4.1 Genetic and related effects of 2-ethylhexyl acrylate in human cells in vitro

End-point	Tissue, cell line	Results[a]		Concentration (μg/mL) (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Micronucleus formation	Lymphocytes	–	NT	44.9	4 h exposure followed by 16 h recovery	Murphy et al. (2018b)
Micronucleus formation	Lymphocytes	NT	–	286	4 h exposure followed by 16 h recovery	Murphy et al. (2018b)
Micronucleus formation	Lymphocytes	–	NT	71.4	20 h continuous exposure	Murphy et al. (2018b)

h, hour; HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested

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

Table 4.2 Genetic and related effects of 2-ethylhexyl acrylate in experimental systems

End-point	Species, cell line	Results[a]		Concentration (μg/mL) (LEC or HIC)	Reference
		Without metabolic activation	With metabolic activation		
Mutation, *Tk*	Mouse L5178Y lymphoma	+/–	NT	37	Dearfield et al. (1989)
Mutation, *Hprt*	Chinese hamster ovary	–	NT	26	Moore et al. (1991)
Mutation, *Hprt*	Chinese hamster ovary	–	NT	80	Moore et al. (1991)
Mutation, *Hprt*	Chinese hamster V79	NT	–	230.4	Murphy et al. (2018b)
Mutation, *Hprt*	Chinese hamster V79	–	NT	115.2	Murphy et al. (2018b)
Chromosomal aberration	Mouse L5178Y lymphoma	+/–	NT	34	Dearfield et al. (1989)
Micronucleus formation	Mouse L5178Y lymphoma	–	NT	34	Dearfield et al. (1989)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	–	–	10 000 μg/plate	Zeiger et al. (1985)

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

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

4.3 Other adverse effects

4.3.1 Irritancy and sensitization

(a) Humans

In Finland, 5 cases (all women) of occupational contact urticaria and protein contact dermatitis caused by 2-ethylhexyl acrylate were reported for the period 1990 to 1994 (Kanerva et al., 1996).

(b) Experimental systems

2-Ethylhexyl acrylate showed low potency for skin irritation in a primary irritation test in rabbits. In addition, 2-ethylhexyl acrylate showed low potency for cytotoxicity in a cultured dermis model (Tokumura et al., 2010). In male C3H/HeJ mice, dermal exposure to 2-ethylhexyl acrylate three times per week for their lifetime caused skin irritation such as scaling, scabbing, hyperkeratosis, and hyperplasia at all concentrations. In a similar study of dermal exposure to 2-ethylhexyl acrylate for 24 weeks, skin irritation was observed in all treatment groups; however, the skin damage was reversible for the two lowest doses (Wenzel-Hartung et al., 1989). The results of a 2-year study of dermal exposure to 2-ethylhexyl acrylate provide further evidence that 2-ethylhexyl acrylate is a skin irritant (Mellert et al., 1994).

2-Ethylhexyl acrylate was demonstrated to be a sensitizer in rodents (Waegemaekers & van der Walle, 1983; Dearman et al., 2007).

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

2-Ethylhexyl acrylate is a high production volume chemical that is produced worldwide. It is used as a plasticizing co-monomer in the production of resins for pressure-sensitive adhesives, latex paints, reactive diluents and/or cross-linking agents, textile and leather finishes, and coatings for paper. It is moderately volatile and has moderate mobility in soil. It is unlikely to persist in the environment. No quantitative data on exposure of the general population were identified. Workers involved in the manufacture of 2-ethylhexyl acrylate had personal concentrations well below the occupational exposure limit. Recent exposure measurements of road workers using paint containing 2-ethylhexyl acrylate were below the limit of detection.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

2-Ethylhexyl acrylate was tested for carcinogenicity in three skin application studies in male mice.

In two studies in C3H/HeJ mice, 2-ethylhexyl acrylate caused a significant increase in the incidence of squamous cell papilloma and of squamous cell papilloma or carcinoma (combined) of the skin in one study, and a significant increase in the incidence of papilloma, cornified squamous cell carcinoma, malignant melanoma, and of fibrosarcoma of the skin in the second study. In the third study, which used a different strain of mice, 2-ethylhexyl acrylate did not significantly increase the incidence of tumours of the skin either with or without subsequent application of 12-*O*-tetradecanoylphorbol-13-acetate.

5.4 Mechanistic and other relevant data

No data on the absorption, distribution, metabolism, or excretion of 2-ethylhexyl acrylate in exposed humans were available. In rats, 2-ethylhexyl acrylate is readily absorbed, distributed to all major tissues, and mainly excreted as carbon dioxide in expired air and as mercapturic acid conjugates in the urine. 2-Ethylhexyl acrylate undergoes carboxylesterase-catalysed metabolism and conjugation with glutathione.

With respect to the key characteristics of human carcinogens, there is *weak* evidence that 2-ethylhexyl acrylate is genotoxic. No data were available in exposed humans or in non-human mammals in vivo. In human cells in vitro, 2-ethylhexyl acrylate gave negative results for micronucleus formation. In a small number of studies in rodent cells in vitro, equivocal or negative results were reported for the induction of mutations, micronucleus formation, and chromosomal aberrations. Further, 2-ethylhexyl acrylate gave negative results in the Ames test, both with and without metabolic activation.

Irritant and allergic contact dermatitis have been reported in humans, with similar results in some studies in rodents.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of 2-ethylhexyl acrylate.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-ethylhexyl acrylate.

6.3 Overall evaluation

2-Ethylhexyl acrylate is *possibly carcinogenic to humans (Group 2B).*

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