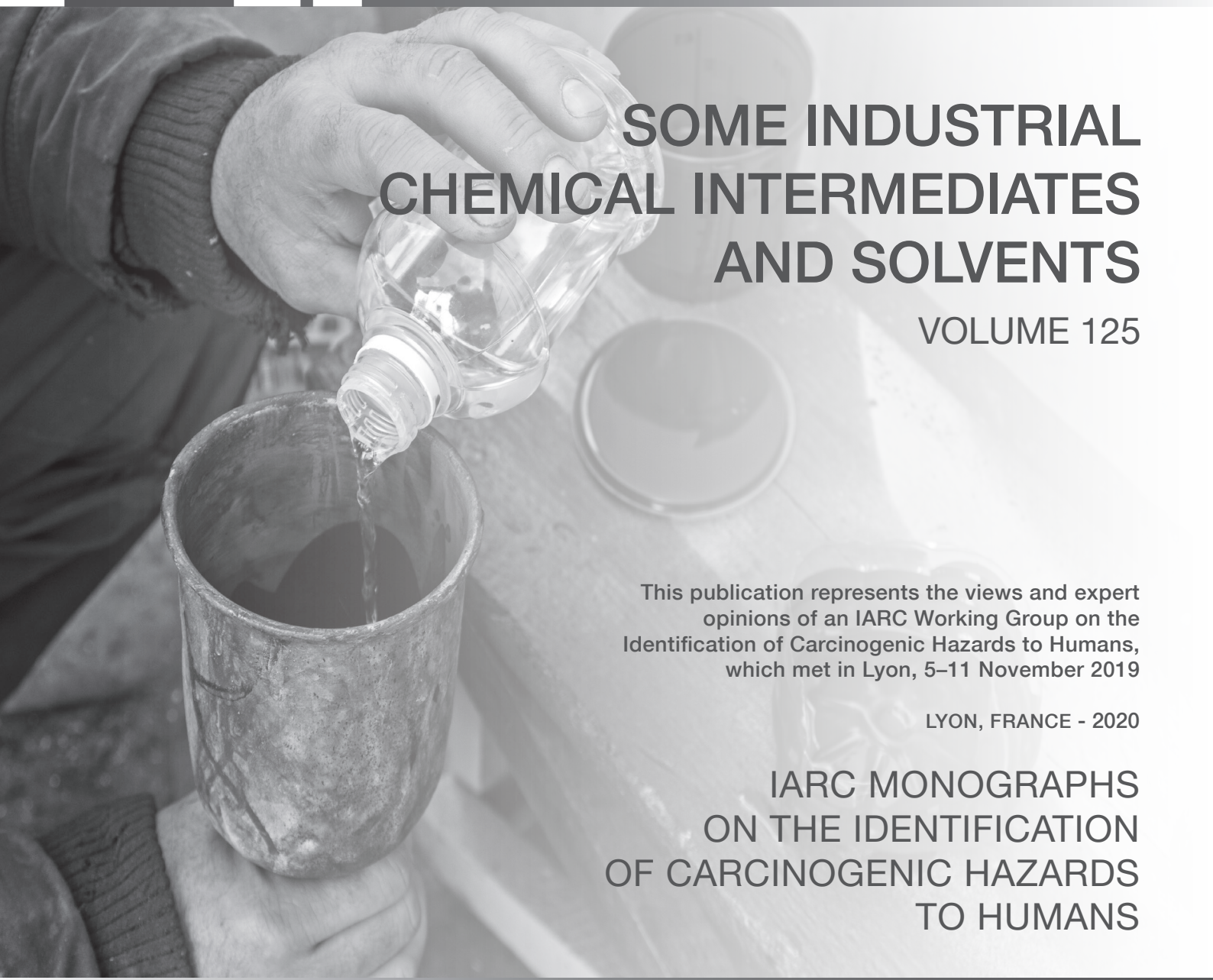
IARC MONOGRAPHS



SOME INDUSTRIAL CHEMICAL INTERMEDIATES AND SOLVENTS

VOLUME 125

This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, 5–11 November 2019

LYON, FRANCE - 2020

IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1-BUTYL GLYCIDYL ETHER

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 2426-08-6

Chem. Abstr. Serv. name: butyl 2,3-epoxypropyl ether

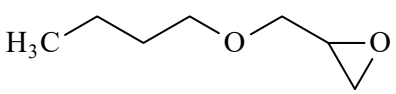
Preferred IUPAC name: 2-(butoxymethyl) oxirane

Synonyms: *n*-butyl glycidyl ether; butyl glycidyl ether; (butoxymethyl)oxirane; butyl 2,3-epoxypropyl ether; ether, butyl 2,3-epoxypropyl; oxirane, (butoxymethyl)-; 1-butoxy-2,3-epoxypropane; 3-butoxy-1,2-epoxypropane; glycidyl butyl ether; 2,3-epoxypropyl butyl ether.

1.1.2 Structural and molecular formulae, and relative molecular mass

Molecular formula: $C_7H_{14}O_2$

Relative molecular mass: 130.18 (NCBI, 2019).



1.1.3 Chemical and physical properties of the pure substance

Description: a clear, colourless to pale yellow liquid with a slightly unpleasant, irritating odour (Lewis, 2001; NTP, 2004)

Density (at 20 °C): 0.91 (NCBI, 2019)

Solubility: 20 g/L at 25 °C in water (Bingham et al., 2001)

Vapour pressure: 0.43 kPa at 25 °C (Lewis, 2001)

Vapour density: 3.78 (air = 1) (Wallace, 1979; Bingham et al., 2001)

Stability and reactivity: rapidly oxidized in air and reacts readily with acids, water and nucleophiles such as proteins and nucleic acids (Worksafe New Zealand, 2019)

*Octanol/water partition coefficient (*P):

log K_{ow} = 0.63 (Hansch et al., 1995)

Henry's law constant:

4.37×10^{-6} atm m^3 mol^{-1} [0.4 Pa m^3 mol^{-1}] at 25 °C (Environment Canada, 2010)

Melting point: 59 °C (NCBI, 2019)

Boiling point: 164 °C (Lewis, 2001)

Flash point: 64 °C (NTP, 2004)

Conversion factor: 1 ppm = 5.32 mg/m^3 at 25 °C and 101.3 kPa.

1.2 Production and uses

1.2.1 Production process

1-Butyl glycidyl ether is produced by the condensation of epichlorohydrin and *n*-butyl alcohol to form an intermediate chlorohydrin, which is then dehydrochlorinated to form an epoxide group (Bosch et al., 1985; NTP, 2004).

1.2.2 Production volume

1-Butyl glycidyl ether has been identified as a High Production Volume chemical by the Organisation for Economic Co-operation and Development (OECD) (OECD, 2009). Currently the majority of the registered manufacturing plants are located in Europe and the USA, whereas fewer sites are situated in Asia (Chem Sources, 2019). In the European Union, the total volume manufactured and/or imported is listed as between 100 and 1000 tonnes per year (ECHA, 2019). Between 1998 and 2006, aggregated production and/or import volumes in the USA were reported to be between 1 000 000 and 10 000 000 lbs [450–4500 tonnes] per year (HSDB, 2006; US EPA, 2008; OECD, 2009).

1.2.3 Uses

1-Butyl glycidyl ether is used as a viscosity-reducing agent, allowing easier handling of uncured resins (Bosch et al., 1985; Lee, 1989). It is also used as a reactive diluent for epoxy resins, as a chemical intermediate, and as an acid acceptor for stabilizing chlorinated solvents (Bingham et al., 2001; NTP, 2004; HSDB, 2006). Epoxy resins have applications as coatings, adhesives, binders, sealants, and fillers (Environment Canada, 2010). During curing, 1-butyl glycidyl ether participates in polymerization and cross-linking due to the presence of the epoxide functional group, allowing it to become covalently bound to the polymer (Bosch et al., 1985; Lee, 1989; Hamerton, 1996). Additionally, it is used as a dye-dispersing agent, a cotton or wool surface modifier, and a dye-enhancing agent (Azuma et al., 2016). 1-Butyl glycidyl ether has also been reported as an impurity in a material preservative for paint and pesticide products (Environment Canada, 2010).

1.3 Methods of measurement and analysis

1.3.1 Detection and quantification

1-Butyl glycidyl ether can be measured in air using coconut-shell charcoal solid sorbent tubes. The compound is analysed by gas chromatography (GC) with flame ionization detection (FID) using a stainless steel column, packed with 10% free fatty-acid phase (FFAP) on a 80/100 mesh Chromosorb W-AW DMCS column, the estimated limit of detection is 5 µg per sample (NIOSH Method 1616) (NIOSH, 1994, 2007). High-performance liquid chromatography (HPLC) coupled with a variable wavelength dual-beam ultraviolet-visible spectrophotometric detector can be used for the determination of 1-butyl glycidyl ether in air and other environmental media. Separation is achieved using a stainless-steel reversed-phase column. The absolute limit of detection can be as low as 1 ppb (Ramanujam et al., 1981).

1-Butyl glycidyl ether was measured in wastewater (Clark et al., 1991). The samples were extracted by liquid/liquid extraction and XAD-2 resin adsorption methodology. The extract was analysed by gas chromatography-mass spectrometry using a non-polar DB-1 fused silica column (Clark et al., 1991).

1.3.2 Biomarkers of exposure

No biomarkers of exposure in humans have been reported. [The Working Group noted that a method for the measurement of haemoglobin adducts of 1-butyl glycidyl ether has been

described in mice (Pérez et al., 1997) and concurs with the authors that this method could be useful for exposure assessment in humans.]

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

1-Butyl glycidyl ether is not known to occur naturally in the environment. Potential environmental emissions may occur from industrial facilities producing, handling, or using epoxy-based resins, coatings, and adhesives (Environment Canada, 2010).

(a) Air

In Canada, importers disclosed that 100–1000 kg were released into the air in 2006 (Environment Canada, 2010). If released to the atmosphere, 1-butyl glycidyl ether is not likely to degrade via direct photolysis. Its vapour pressure indicates that it will exist solely as a vapour in the ambient atmosphere (HSDB, 2006). The predicted atmospheric oxidation half-life for the compound is 0.54 days and it is not considered persistent in air (Environment Canada, 2010). The substance is not expected to react with photo-oxidative species such as ozone in the atmosphere (Environment Canada, 2010). Vapour-phase 1-butyl glycidyl ether will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 19 hours (HSDB, 2006; Environment Canada, 2010).

(b) Water

Clark et al. (1991) analysed semi-volatile pollutants in effluent streams from three wastewater treatment plants in the state of New Jersey, USA. Three sampling sets were performed at each facility; 1-butyl glycidyl ether was detected at an estimated concentration of 0.5 µg/L in samples from one facility.

If released into water, 1-butyl glycidyl ether is not expected to adsorb to suspended solids and sediment based upon the estimated soil absorption coefficient (K_{oc}) (HSDB, 2006). Volatilization from water surfaces is expected to be an important fate process based upon the estimated Henry's law constant for this agent (HSDB, 2006). Estimated volatilization half-lives in a model river and model lake are 1 and 16 days, respectively (HSDB, 2006). 1-Butyl glycidyl ether contains an epoxide group, which is susceptible to hydrolysis in water; however, the rate of this reaction is estimated to be very low (half-life of 60 years at pH 7). An estimated bioconcentration factor of 3 suggests that the potential for bioconcentration in aquatic organisms is low (HSDB, 2006).

(c) Soil

If released to soil, 1-butyl glycidyl ether is expected to have high mobility based upon an estimated K_{oc} of 52 (HSDB, 2006). Volatilization from moist soil surfaces is expected to be an important fate process based upon the estimated Henry's law constant (HSDB, 2006). 1-Butyl glycidyl ether from dry soil surfaces has the potential for volatilization, based upon its vapour pressure (HSDB, 2006).

1.4.2 Occupational exposure

Studies of occupational exposure have not been identified by the Working Group. Potential human exposure to 1-butyl glycidyl ether may occur via inhalation and dermal absorption at workplaces where 1-butyl glycidyl ether is produced or used (HSDB, 2006; Worksafe New Zealand, 2019). Potential exposure to 1-butyl glycidyl ether exists until the epoxy resin is completely cured (NTP, 2004).

In New Zealand, 52 590 workers were working in industries where there are potentially exposures to 1-butyl glycidyl ether (Statistics New Zealand, 2018). These industries included

Table 1.1 International limit values for 1-butyl glycidyl ether

Country	Limit value, 8 hours		Limit value, short-term	
	ppm	mg/m³	ppm	mg/m³
Australia	25	133		
Belgium	3	16.2		
Canada, Ontario	3			
Canada, Québec	25	133		
Denmark	6	30	12	60
Finland			25[a]	140[a]
France	25	135		
Japan, JSOH	0.25	1.33		
New Zealand	25	133		
People's Republic of China		60		
Republic of Korea	10	53		
Romania	19	100	38[a]	200[a]
Singapore	25	133		
Spain	25[b]	133 [b]		
Sweden	10	50	15[a]	80[a]
Switzerland	25	135	50	270
USA, NIOSH			5.6[c]	30[b]
USA, OSHA	50	270		
United Kingdom	[25][d]	[135][d]		

JSOH, Japan Society for Occupational Health; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration.

[a] 15-minute average value.

[b] Capable of causing occupational asthma (sensitization).

[c] Ceiling limit value, 15-minute.

[d] The United Kingdom Advisory Committee on Toxic Substances has expressed concern that, for the occupational exposure limits (OELs) shown in square brackets, health may not be adequately protected because of doubts that the limit was not soundly based. These OELs were included in the published United Kingdom 2002 list and its 2003 supplement, but are omitted from the published 2005 list.

From IFA (2019).

chemical manufacturing, basic polymer manufacturing, polymer product manufacturing, electrical equipment manufacturing, residential building construction, and non-residential building construction (Statistics New Zealand, 2018; Worksafe New Zealand, 2019). The National Institute for Occupational Safety and Health (NIOSH) has estimated that 60 217 workers (14 929 of these were female) were potentially exposed to 1-butyl glycidyl ether in the USA (NOES 1981–1983; NIOSH, 1990). The main occupations exposed were in machinery except electrical, electronic and electric equipment, transportation equipment, and instruments and related products (NIOSH, 1990). In 1978, NIOSH estimated that 13 000 workers in the USA were potentially exposed (NIOSH, 1978).

1.4.3 Exposure of the general population

Studies of exposure in the general population were not available to the Working Group. Due to the reactive, covalently bound inclusion of 1-butyl glycidyl ether in epoxy resins, potential exposure of the general population from consumer products is limited (NTP, 2004).

1.5 Regulations and guidelines

Current threshold limit values by country are given in Table 1.1. The European Commission has classified 1-butyl glycidyl ether as a carcinogen (Category 2) and as a germ cell mutagen (Category 2) (ECHA, 2019). The German Research Foundation (DFG) and the Japan Society for Occupational Health (JSOH) categorized 1-butyl glycidyl ether in Group 3B and 2B of carcinogens, respectively (JSOH, 2016; DFG, 2017). The American Conference of Governmental Industrial Hygienists (ACGIH) recommended a threshold limit value–time-weighted average (TLV–TWA) of 3 ppm (16 mg/m^3) (ACGIH, 2014).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

Inhalation

In a study that complied with good laboratory practice (GLP), groups of 50 male and 50 female Crj:BDF1 [B6D2F$_1$/Crlj] mice (age, 6 weeks) were exposed by whole-body inhalation to 2,3-epoxypropyl ether [1-butyl glycidyl ether] (purity, > 99.7%) at a concentration of 0, 5, 15, or 45 ppm (v/v) in clean air for 6 hours per day, 5 days per week, for 2 years (JBRC, 2005a, b). Survival rates were unaffected in all groups of males exposed to 1-butyl glycidyl ether, and decreased in groups of females at 15 and 45 ppm. Survival to the end of 2 years for the groups at 0, 5, 15, and 45 ppm was 35/50, 35/49, 32/50, and 36/49 in males, and 33/50, 31/50, 27/50, and 22/50 in females, respectively. At cessation of treatment, body weights were significantly decreased at 45 ppm in males (–24%) and in females (–11%), relative to the respective control groups. All mice (except for one male at 5 ppm and one male at 45 ppm) underwent complete necropsy and histopathological examination.

Inhalation of 1-butyl glycidyl ether caused a significant dose-related increase ($P < 0.05$, Peto trend test) in the incidence of nasal cavity haemangioma in male mice. The incidence of nasal cavity haemangioma was significantly increased in male mice at 15 and 45 ppm ($P < 0.01$, Fisher exact test). Inhalation of 1-butyl glycidyl ether did not cause any dose-related increase in the incidence of nasal cavity schwannoma, nasal cavity squamous cell carcinoma, or nasal cavity histiocytic sarcoma in male mice. The incidence of nasal cavity schwannoma (controls, 0/50; 5 ppm, 0/49; 15 ppm, 0/50; and 45 ppm, 1/49), nasal cavity histiocytic sarcoma (controls, 0/50; 5 ppm, 2/49; 15 ppm, 0/50; and 45 ppm, 0/49) and nasal cavity squamous cell carcinoma (controls, 0/50; 5 ppm, 0/49; 15 ppm, 0/50; and 45 ppm, 2/49) were not significantly increased in any group of male mice exposed to 1-butyl glycidyl ether. [The incidence of nasal cavity squamous cell carcinoma in the group at 45 ppm exceeded the incidence observed in the historical control group (0/1596) and the incidence of nasal cavity schwannoma in the group at 45 ppm exceeded the incidence observed in the same historical control group (1/1596) of male Crj:BDF1 mice from 32 studies conducted in this laboratory.]

Inhalation of 1-butyl glycidyl ether caused a significant dose-related increase ($P < 0.01$, Peto trend test) in the incidence of nasal cavity haemangioma in female mice. The incidence of nasal cavity haemangioma was significantly increased in female mice exposed at 45 ppm ($P < 0.01$, Fisher exact test). One rare nasal cavity squamous cell carcinoma occurred in the group at the highest dose, and one rare nasal cavity

Table 3.1 Studies of carcinogenicity with 1-butyl glycidyl ether in mice and rats treated by inhalation (whole-body exposure)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, Crj: BDF1 (M) Age, 6 wk 104 wk JBRC (2005a, b)	Purity, > 99.7% 0, 5, 15, 45 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 35, 35, 32, 36	*Nasal cavity* Haemangioma 0/50, 2/49, 14/50**, 8/49**	Positive trend: $P < 0.05$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	Principal strengths: well-conducted GLP study; males and females used; study covered most of lifespan; multiple-dose study Other comments: no significant effect of treatment on survival; incidence in historical controls from 32 studies at laboratory: nasal cavity squamous cell carcinoma, 0/1596; nasal cavity schwannoma, 1/1596; and nasal cavity histiocytic sarcoma, NR
		Schwannoma 0/50, 0/49, 0/50, 1/49	NS	
		Squamous cell carcinoma 0/50, 0/49, 0/50, 2/49	NS	
		Histiocytic sarcoma 0/50, 2/49, 0/50, 0/49	NS	
Mouse, Crj: BDF1 (F) Age, 6 wk 104 wk JBRC (2005a, b)	Purity, > 99.7% 0, 5, 15, 45 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 33, 31, 27, 22	*Nasal cavity* Haemangioma 0/50, 0/50, 2/50, 7/50**	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); ** $P < 0.01$ (Fisher exact test)	Principal strengths: well-conducted GLP study; males and females used; study covered most of lifespan; multiple-dose study Other comments: significant decrease in survival in females at 15 ppm and 45 ppm; historical control incidence of nasal cavity squamous cell carcinoma, 0/1596 from 32 studies at laboratory; historical control incidence of histiocytic sarcoma of the uterus, 320/1595 (average, 20.1%; range, 10–32%)
		Squamous cell carcinoma 0/50, 0/50, 0/50, 1/50	NS	
		Histiocytic sarcoma 0/50, 0/50, 1/50, 0/50	NS	
		Uterus: histiocytic sarcoma 6/50, 10/50, 15/50*, 15/50*	Positive trend: $P < 0.01$ (Peto test); and NS (Cochran–Armitage test) *$P < 0.05$ (Fisher exact test)	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344/DuCrlj (M) Age, 6 wk 104 wk JBRC (2005c, d)	Purity, > 99.7% 0, 10, 30, 90 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 38, 38, 38, 11	*Nasal cavity* Squamous cell carcinoma 0/50, 0/50, 0/50, 35/50* Adenoma 0/50, 0/50, 5/50*, 0/50 Squamous cell papilloma 0/50, 0/50, 0/50, 1/50 Esthesioneuroepithelioma [neuroepithelial carcinoma] 0/50, 0/50, 0/50, 1/50 *Spleen*: mononuclear cell leukaemia 10/50, 16/50, 19/50*, 7/50	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); *$P < 0.01$ (Fisher exact test) *$P < 0.05$ (Fisher exact test) NS NS *$P < 0.05$ (Fisher exact test)	Principal strengths: study covered most of lifespan; males and females used; multiple-dose study; well-conducted GLP study Other comments: significant decrease in survival in high-dose males; historical control incidence: nasal cavity papilloma, squamous cell carcinoma or esthesioneuroepithelioma, 0/1849; nasal cavity adenoma, 2/1849 (average, 0.1%; range, 0–0.2%)
Rat, F344/DuCrlj (F) Age, 6 wk 104 wk JBRC (2005c, d)	Purity, > 99.7% 0, 10, 30, 90 ppm 6 h/day, 5 days/wk 50, 50, 50, 50 40, 45, 41, 15	*Nasal cavity* Squamous cell carcinoma 0/50, 0/50, 0/50, 28/50* Esthesioneuroepithelioma [neuroepithelial carcinoma] 0/50, 0/50, 0/50, 2/50 Sarcoma (NOS) 0/50, 0/50, 0/50, 1/50 Adenosquamous carcinoma 0/50, 0/50, 0/50, 1/50 *Spleen*: mononuclear cell leukaemia 7/50, 8/50, 5/50, 13/50	Positive trend: $P < 0.01$ (Peto test and Cochran–Armitage test); *$P < 0.01$ (Fisher exact test) NS NS NS Positive trend: $P < 0.01$ (Peto test)	Principal strengths: study covered most of lifespan; males and females used; multiple-dose study; well-conducted GLP study Other comments: significant decrease in survival in high-dose females; incidence in historical controls: nasal cavity squamous cell carcinoma, esthesioneuroepithelioma, sarcoma (NOS) or adenosquamous carcinoma, 0/1697

F, female; GLP, good laboratory practice; h, hour; M, male; NR, not reported; NOS, not otherwise specified; NS, not significant; ppm, parts per million; wk, week.

histiocytic sarcoma occurred in the group at the intermediate dose; none of these tumours occurred in female concurrent controls from the same laboratory.

Inhalation of 1-butyl glycidyl ether caused a significant dose-related increase ($P < 0.01$, Peto test) in the incidence of histiocytic sarcoma of the uterus in female mice. The incidence of histiocytic sarcoma of the uterus was significantly increased in female mice at 15 and 45 ppm ($P < 0.05$, Fisher exact test).

Inhalation of 1-butyl glycidyl ether resulted in increased incidence and/or severity of non-neoplastic lesions in the nasal cavity of male mice (cuboidal change of the respiratory epithelium in the groups at 5, 15, and 45 ppm; angiectasis, respiratory metaplasia of glands, and respiratory metaplasia of the olfactory epithelium in the groups at 15 and 45 ppm; exudate, eosinophilic change of respiratory, and nodular hyperplasia of the transitional epithelium in the group at 45 ppm). Inhalation of 1-butyl glycidyl ether resulted in increased incidence and/or severity of non-neoplastic lesions in the nasal cavity of female mice (respiratory metaplasia of the olfactory epithelium in the groups at 5, 15, and 45 ppm; cuboidal change of the respiratory epithelium and respiratory metaplasia of glands in the groups at 15 and 45 ppm; angiectasis, and exudate and nodular hyperplasia of the transitional epithelium in the group at 45 ppm). [The strengths of this well-conducted GLP study included the use of multiple doses, the large number of animals per group, and testing in males and females.]

3.2 Rat

Inhalation

In a study that complied with GLP, groups of 50 male and 50 female F344/DuCrlj rats (age, 6 weeks) were exposed by whole-body inhalation to butyl 2,3-epoxypropylether [1-butyl glycidyl ether] (purity, > 99.7%) at a concentration of 0 (control), 10, 30, or 90 ppm (v/v) for 6 hours per day, 5 days per week, for 104 weeks (JBRC, 2005c, d). The survival rates of males and females at 90 ppm were significantly decreased compared with the respective controls; survival rates in males were 38/50 (control), 38/50 (10 ppm), 38/50 (30 ppm), and 11/50 (90 ppm); those in females were 40/50 (control), 45/50 (10 ppm), 41/50 (30 ppm), and 15/50 (90 ppm). The significantly decreased survival rates in males and females at 90 ppm were attributed to the increased number of deaths due primarily to nasal tumours. At 90 ppm, there was a significant decrease in the body weights of males (30%) and females (23%), compared with respective controls. All rats underwent complete necropsy and histopathological examination.

In the nasal cavity, there were significant increases in the incidence of squamous cell carcinoma at 90 ppm in males ($P < 0.01$, Fisher exact test) and females ($P < 0.01$, Fisher exact test), compared with respective controls, with a significant positive trend (Peto trend test, $P < 0.01$). Some cancers of the nasal cavity metastasized to the brain or Harderian gland (local invasion), and lung or lymph node. There was a significant increase in the incidence of nasal cavity adenoma in males at 30 ppm ($P < 0.05$, Fisher exact test). In the nasal cavity, there were also occurrences of esthesioneuroepithelioma [neuroepithelial carcinoma] in one male at the highest dose and two females at the highest dose, of squamous cell papilloma in one male at the highest dose, of sarcoma (not otherwise specified, NOS) in one female at the highest dose and of adenosquamous carcinoma in one female at the highest dose, which were not observed in the historical control database of the laboratory (males, 0/1849; females, 0/1697). The incidence of splenic mononuclear cell leukaemia was increased in exposed females as indicated by a significant positive trend (Peto trend test, $P < 0.01$); the incidence of splenic mononuclear cell leukaemia in males was

significantly increased only at 30 ppm ($P < 0.05$, Fisher exact test). Regarding non-neoplastic lesions, increased incidence or severity of lesions such as nasal respiratory epithelium squamous cell metaplasia, nasal squamous cell hyperplasia with atypia, nasal respiratory epithelium inflammation, olfactory epithelium atrophy, olfactory epithelium respiratory metaplasia and olfactory epithelium squamous cell metaplasia was noted in exposed males and females. [The strengths of this well-conducted GLP study included the use of multiple doses, the large number of animals per group, and testing in males and females.]

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

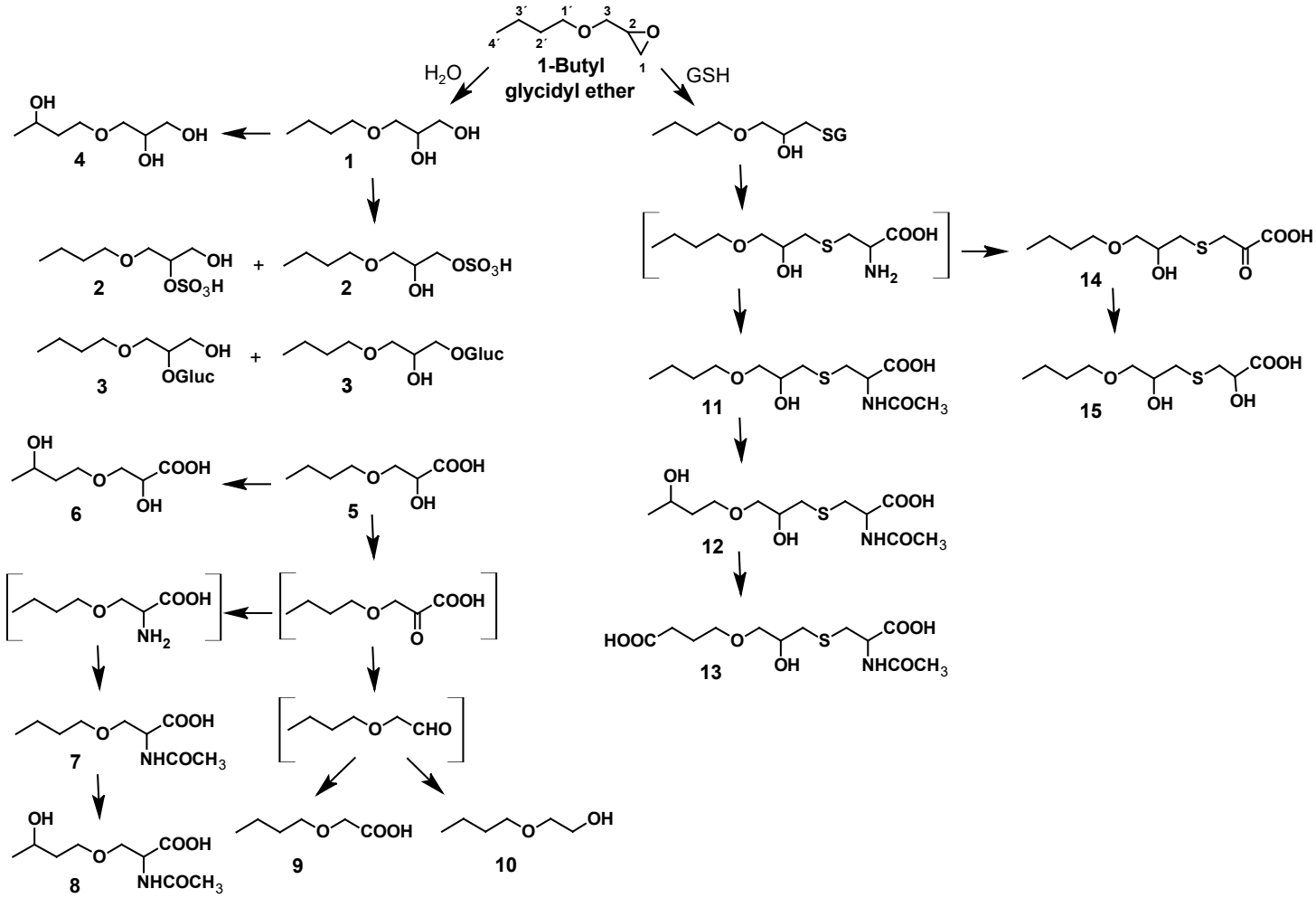
No direct data were available to the Working Group. Indirect evidence of absorption and distribution to the central nervous system was provided by Wallace (1979), who reported two clinical cases of poisoning by 1-butyl glycidyl ether.

4.1.2 Experimental systems

Radiolabelled 1-butyl glycidyl ether was administered orally to rats and mice (Chen et al., 2007). Male rats and female mice received a single dose of 2, 20, or 200 mg/kg bw by gavage, while female rats and male mice were dosed only at 200 mg/kg bw. The disposition of [1-^{14}C]butyl glycidyl ether was evaluated 24 hours after dosing. The majority of the administered dose was excreted in the urine (rats, 84–92%; mice, 64–73%), while the remainder was excreted in the faeces (rats, 2.6–7.7%; mice, 5.3–12.2%) and in expired air as carbon dioxide ($^{14}CO_2$) (rats, ≤ 1.5%; mice, 10–18%), or remained in the tissues (rats, 1.8–4.4%; mice, 1.5–1.7%). No parent compound was excreted. Detailed analysis of rat and mouse urine identified 15 metabolites in total, produced by two major metabolic pathways: (a) hydration to give a diol; and (b) conjugation with glutathione (Fig. 4.1). Hydration pathway metabolites, accounting in total for 61–76% of the administered dose, included 3-butoxy-2-hydroxypropanol (1) and its monosulfate (2) and monoglucuronic (3) conjugates and its 3′-hydroxy derivative (4), 3-butoxy-2-hydroxypropionic acid (5) and its 3′-hydroxy derivative (6), 3-butoxy-2-acetylaminopropionic acid (also known as *O*-butyl-*N*-acetylserine) (7) and its 3′-hydroxy derivative (8), butoxyacetic acid (9), and 2-butoxyethanol (10). Glutathione conjugation pathway metabolites accounted in total for 22–38% of the administered dose. Of these, 3-butoxy-1-(*N*-acetylcystein-*S*-yl)-2-propanol (also known as 3-butoxy-2-hydroxypropyl mercapturic acid) (11), its 3′-hydroxy derivative (12) and a carboxylic acid obtained by ω-oxidation of the 3-butoxy group (13) were detected both in rats and mice. Additional related products, detected in mouse urine only, were derived from the intermediate *S*-cysteine conjugate of 1-butyl glycidyl ether (3-butoxy-1-(cystein-*S*-yl)-2-propanol). Oxidative deamination of this conjugate resulted in the formation of the corresponding α-keto acid (14), followed by its reduction to the α-hydroxy acid (15).

Oral administration of [1-^{14}C]butyl glycidyl ether (20 mg/kg bw) to male Wistar rats (by gavage) or New Zealand White rabbits (by double-gelatine capsule) resulted in the rapid absorption, metabolism, and excretion of the compound (Eadsforth et al., 1985). Most of the administered [1-^{14}C]butyl glycidyl ether was eliminated within 24 hours (87% in rats, 78% in rabbit, respectively), while total elimination during 4 days accounted for 91% and 80% of the administered dose in rats and rabbits, respectively. In both species, a major route of biotransformation was via hydrolytic opening of the epoxide

Fig. 4.1 Metabolic pathways of 1-butyl glycidyl ether in rats and mice



Compounds identified in the urine: 3-butoxy-2-hydroxypropanol (1) and its monosulfate (2) and monoglucuronic (3) conjugates and a 3′-hydroxy derivative (4), 3-butoxy-2-hydroxypropionic acid (5) and its 3′-hydroxy derivative (6), 3-butoxy-2-acetylaminopropionic acid (7) and its 3′-hydroxy derivative (8), butoxyacetic acid (9), 2-butoxyethanol (10), 3-butoxy-2-hydroxypropylmercapturic acid (11) and its 3′-hydroxy derivative (12), 3-(3′-carboxy)propoxy-2-hydroxypropylmercapturic acid (13), 3-(3-butoxy-2-hydroxypropyl)thio-2-oxopropionic acid (14) and 3-(3-butoxy-2-hydroxypropyl)thio-2-hydroxypropionic acid (15).
GSH, glutathione.
Adapted with permission from Chen et al. (2007). Chen L-J, Lebetkin EH, Nwakpuda EI, Burka LT (2007). Metabolism and disposition of *n*-butyl glycidyl ether in F344 rats and B6C3F$_1$ mice. *Drug Metab Dispos*. 35(12):2218–24.

ring followed by oxidation of the resulting diol to 3-butoxy-2-hydroxypropionic acid (5) (9% in rats, 35% in rabbits) and subsequent oxidative decarboxylation to yield free butoxyacetic acid (9) (10% in rats, 5% in rabbits). In rabbit urine, another 5% of butoxyacetic acid (9) was present in a conjugated form. Additionally, 23% of the dose administered to rats was excreted in the urine as 3-butoxy-2-acetylaminopropionic acid (7), while this metabolite amounted to only 2% in rabbits. Two possible metabolic routes of the formation of 3-butoxy-2-acetylaminopropionic acid (7) from 3-butoxy-2-hydroxypropionic acid (5) were proposed of which the first one appears to be more likely: (a) dehydrogenation of the latter followed by transamination; and (b) cleavage of the epoxide ring by ammonia followed by oxidation of the terminal hydroxymethyl group and *N*-acetylation.

1-Butyl glycidyl ether is likely to be absorbed through the skin given that the median lethal dose (LD_{50}) for dermal exposures in rabbits (0.79–4.93 g/kg bw) is of similar magnitude to the LD_{50} values for oral (1.53–2.26 g/kg bw) or intraperitoneal (0.70–1.14 g/kg bw) administration in mice and rats (NTP, 2004).

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether 1-butyl glycidyl ether is electrophilic or can be metabolically activated to an electrophile; is genotoxic; alters cell proliferation, cell death, or nutrient supply; or is immunosuppressive. Insufficient data were available for the evaluation of other key characteristics of carcinogens.

4.2.1 Is electrophilic or can be metabolically activated to an electrophile

1-Butyl glycidyl ether was a direct-acting mutagen in *Escherichia coli* WP2 *uvrA* and alkylated 4-(*p*-nitrobenzyl)-pyridine and deoxyguanosine (Hemminki et al., 1980) (see Section 4.2.2 (b)(iii) and Table 4.4). 1-Butyl glycidyl ether formed haemoglobin adducts when administered to male C3H/Hej mice in vivo (4 mg/mouse, intraperitoneal dose) (Pérez et al., 1997).

4.2.2 Is genotoxic

Table 4.1, Table 4.2, Table 4.3, and Table 4.4 summarize the studies evaluated that report genetic and related effects of 1-butyl glycidyl ether.

(a) Humans

(i) Human cells in vitro

See Table 4.1.

Several studies examined effects of 1-butyl glycidyl ether on induction of DNA repair through unscheduled DNA synthesis (UDS) assay. A linear dose–response relationship was seen in the UDS assay for 1-butyl glycidyl ether (l, 10, and 100 ppm), with significant effects at 10 and 100 ppm, in human leukocytes (US EPA, 1977). Cell viability was significantly affected at 500 ppm. Positive results were obtained in the UDS assay in human peripheral blood lymphocytes isolated from two female donors and exposed to 1-butyl glycidyl ether in vitro (Frost & Legator, 1982). Concentrations varied depending on the donor (10–1000 µg/mL and 4–1000 µg/mL), with cell viability comparable to those of control experiments, except for the highest concentration tested. [The Working Group noted that no statistical analysis was performed by the authors and insufficient information was provided to conduct statistical tests.]

Positive results in the UDS assay were also reported for 1-butyl glycidyl ether in WI38

Table 4.1 Genetic and related effects of 1-butyl glycidyl ether in human cells in vitro

End-point	Tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Unscheduled DNA synthesis	Leukocytes	+	NT	10 ppm [1300 µg/mL]	Donor information unspecified	US EPA (1977)
Unscheduled DNA synthesis	Peripheral blood lymphocytes	+	NT	100 µg/mL		Frost & Legator (1982)
Unscheduled DNA synthesis	Lung fibroblast cell line (WI38)	(–)	+	4 µg/mL	No effect at 8 µg/mL; experiments –S9 were only carried out at up to 1.2 µg/mL	Thompson et al. (1981)

HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested; S9, 9000 × *g* supernatant.

[a] –, negative; (–), see study quality comments.

Table 4.2 Genetic and related effects of 1-butyl glycidyl ether in non-human mammals in vivo

End-point	Species, strain, (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Micronucleus formation	Mouse, B6D2F$_1$ (F)	Bone marrow	–	200 mg/kg bw	Oral; 5 days; 1×/day	Only one dose tested	US EPA (1977)
Micronucleus formation	Mouse, BDF (F)	Bone marrow	–	200 mg/kg bw	Oral, 5 days, 1×/day	Only one dose tested	Connor et al. (1980)
Micronucleus formation	Mouse, BDF (F)	Bone marrow	+	675 mg/kg bw	Intraperitoneal, 1 or 2 days, 1×/day		Connor et al. (1980)
Chromosomal aberrations	Rat, Sprague-Dawley CR-1 (M, F)	Bone marrow	+	104 mg/kg bw	Intraperitoneal, 5 days, 1×/day	Dose of 313 mg/kg and positive controls were without effect	US EPA (1979)
Dominant lethal mutations	Mouse, B6D2F$_1$ (M)	Fetal implants	+	1500 mg/kg bw	Skin, 8 wk, 3×/wk		US EPA (1977)
Dominant lethal mutations	Mouse, B6D2F$_1$ (M)	Fetal implants	+	1500 mg/kg bw	Skin, 16 wk, 3×/wk		Pullin (1978)
Dominant lethal mutations	Mouse, BDF (M)	Fetal implants	+	1500 mg/kg bw	Skin, 8 wk, 3×/wk		Whorton et al. (1983)
Mutagenicity of urine	Mouse, B6D2F$_1$ (F) and ICR (F)	Host-mediated assay; Ames test in *Salmonella typhimurium* strains TA1535, +/– β-glucuronidase	–	200 mg/kg bw	Oral, 4 days, 1×/day		US EPA (1977)
Mutagenicity of urine	Mice, ICR (F)	Host-mediated assay; Ames test in *S. typhimurium* strains TA1535, +/– β-glucuronidase	–	200 mg/kg bw	Oral, 4 days, 1×/day		Connor et al. (1980)
Mutagenicity of urine	Mice, BDF (M)	Host-mediated assay; Ames test in *S. typhimurium* strains TA1535 and TA98, +/– β-glucuronidase	– –	1500 mg/kg bw 3000 mg/kg bw	Dermal, 8 wk, 3×/wk Dermal, 16 wk, 3×/wk		Connor et al. (1980)

F, female; HID, highest ineffective dose; LED, lowest effective dose (units as reported); M, male; wk, week.

[a] +, positive; –, negative.

Table 4.3 Genetic and related effects of 1-butyl glycidyl ether in non-human mammals in vitro

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Reference
		Without metabolic activation	With metabolic activation		
Gene mutation, *Tk* locus	L5178Y mouse, lymphoma cells	+	+	100 µg/mL	Thompson et al. (1981)
Sister-chromatid exchange	Chinese hamster V79	+	NT	2.5 mM [325.5 µg/mL]	von der Hude et al. (1991)

HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested; *Tk*, thymidine kinase.

[a] +, positive.

Table 4.4 Genetic and related effects of 1-butyl glycidyl ether in non-mammalian systems

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Reference
		Without metabolic activation	With metabolic activation		
Salmonella typhimurium TA1535	Reverse mutation	+	–/+	0.5 µmol/plate [65 µg/plate]	US EPA (1977)
Salmonella typhimurium TA1535	Reverse mutation	+	+	260 µg/plate	Connor et al. (1980)
Salmonella typhimurium TA1535	Reverse mutation	+	+	8.2 µg/plate (–S9); 24.7 µg/plate (+S9)	Thompson et al. (1981)
Salmonella typhimurium TA1535	Reverse mutation	+	+	333 µg/plate (–S9 and + hamster S9); 1000 µg/plate (+ rat S9)	Canter et al. (1986)
Salmonella typhimurium TA100	Reverse mutation	+	+	10 000 µg/plate	Wade et al. (1979)
Salmonella typhimurium TA100	Reverse mutation	+	NT	260 µg/plate	Connor et al. (1980)
Salmonella typhimurium TA100	Reverse mutation	+	+	222.2 µg/plate	Thompson et al. (1981)
Salmonella typhimurium TA100	Reverse mutation	+	+	100 µg/plate (–S9); 333 µg/plate (+S9)	Canter et al. (1986)
Salmonella typhimurium TA98	Reverse mutation	–	–	2.0 µmol/plate [260 µg/plate]	US EPA (1977)
Salmonella typhimurium TA98	Reverse mutation	–	–	10 000 µg/plate	Wade et al. (1979)
Salmonella typhimurium TA98, TA1537, TA1538	Reverse mutation	–	NT	260 µg/plate	Connor et al. (1980)
Salmonella typhimurium TA98, TA1537, TA1538	Reverse mutation	–	–	2000 µg/plate	Thompson et al. (1981)
Escherichia coli WP2 *uvrA*	Reverse mutation	+	NT	Doses tested: 10–10 000 µM [1.3–1300 µg/mL]; LEC was not reported	Hemminki et al. (1980)
Escherichia coli PQ37	DNA damage	+	NT	1 mM [130 µg/mL]	von der Hude et al. (1990)

HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested; S9, 9000 × *g* supernatant.

[a] +, positive; –, negative; –/+, equivocal.

human lung fibroblast cells (Thompson et al., 1981). [The Working Group noted that this study provided no statistical analysis of the data and only qualitative comparisons are possible.]

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.2.

The potential for 1-butyl glycidyl ether to induce micronucleus formation in bone marrow cells was tested in two studies. When administered orally to B6D2F$_1$ female mice, 1-butyl glycidyl ether (200 mg/kg bw, 5 daily doses) had no significant effect on micronucleus formation in the bone marrow (US EPA, 1977). In female BDF mice, intraperitoneal (but not oral) administration of 1-butyl glycidyl ether significantly increased micronucleus formation in bone marrow (Connor et al., 1980).

The potential for 1-butyl glycidyl ether to induce chromosomal aberrations in bone marrow cells was tested in one study in Sprague-Dawley CR-1 male and female rats given 1-butyl glycidyl ether (31, 104, or 313 mg/kg bw per day) by intraperitoneal administration for five consecutive days (US EPA, 1979). Chromosomal aberrations examined included chromatid breaks, chromosome breaks, markers (dicentric, exchanges, rings or translocation), and severely damaged cells. Chromosomal aberrations were significantly elevated only in the group at the intermediate dose, but no effect was observed in the groups receiving the lowest or highest dose or the positive control. The percentage of severely damaged cells was significantly increased in the groups receiving the lowest and highest dose and in the positive controls, but not in the group receiving the intermediate dose. The percentage of aberrant cells was significantly increased in all groups. [The Working Group noted that this report did not analyse sex-specific effects, or distinguish between the types of chromosomal aberrations, and that the positive control experiments did not yield the expected results.]

Three studies investigated 1-butyl glycidyl ether for its ability to induce dominant lethal mutations in mice. In the first study in male B6D2F$_1$ mice, 1-butyl glycidyl ether (1500 mg/kg bw on the skin) significantly decreased pregnancy rates and increased the number of fetal deaths per pregnancy after mating to virgin females (US EPA, 1977). In a second study of the same design but examining 16 weeks of exposure and with an expanded dose range (750, 1500, and 3000 mg/kg bw) (Pullin, 1978), fetal deaths were increased at 3000 mg/kg bw, significant reductions in pregnancy rates were observed at 1500 and 3000 mg/kg bw, and reductions in the mean number of implants per pregnancy were also observed at 1500 and 3000 mg/kg bw. [The Working Group noted that the study by Pullin (1978) was reported as an abstract and only in summary form.] In a third study, Whorton et al. (1983) applied 1-butyl glycidyl ether (375, 750, and 1500 mg/kg bw) to the skin of male BDF hybrid mice, three times per week for 8 weeks. Each study group included 36–44 males, 96–120 pregnant females, and counted 757–1001 implants. No significant dose-related changes in pregnancy rates or in average number of implants per pregnant female were found; however, there was evidence of a significant increase in fetal death rates by the end of the first week at a dose of 1500 mg/kg bw.

Two reports did not find a mutagenic effect of urine from mice treated with 1-butyl glycidyl ether in vivo. No effects were observed when urine samples from treated female B6D2F$_1$ or female ICR mice were tested in *Salmonella typhimurium* strain TA1535 with or without the addition of β-glucuronidase (US EPA, 1977). Similarly, no effect of 1-butyl glycidyl ether was seen when urine was collected from female ICR mice treated by gavage, or from male BDF mice exposed by dermal application, and tested with *S. typhimurium* strains TA1535 and TA98 with

or without the addition of β-glucuronidase (Connor et al., 1980).

(ii) Non-human mammalian cells in vitro

See Table 4.3.

1-Butyl glycidyl ether was mutagenic but not cytotoxic in L5178Y *Tk*$^{+/-}$ mouse lymphoma cells (Thompson et al., 1981). Addition of control or Aroclor-induced rat liver S9 fraction reduced the mutagenicity of 1-butyl glycidyl ether. [The Working Group noted that no statistical analysis was performed by the authors and data included in the study were insufficient to conduct a statistical test.]

1-Butyl glycidyl ether induced a concentration-dependent increase in the frequency of sister-chromatid exchanges in Chinese hamster V79 cells in the absence of metabolic activation (von der Hude et al., 1991).

(iii) Non-mammalian experimental systems

See Table 4.4.

The potential for 1-butyl glycidyl ether to cause mutations was examined in several studies in bacterial test systems. 1-Butyl glycidyl ether was mutagenic in *S. typhimurium* TA1535 strain at all concentrations tested without metabolic activation (US EPA, 1977). Addition of either phenobarbital- or Aroclor-induced rat liver S9 fraction reduced 1-butyl glycidyl ether mutagenicity. In the same study, 1-butyl glycidyl ether was not mutagenic in *S. typhimurium* TA98 strain, with or without metabolic activation. 1-Butyl glycidyl ether was mutagenic in *S. typhimurium* strain TA100, but not in strain TA98, and addition of rat liver S9 fraction was without effect (Wade et al., 1979). 1-Butyl glycidyl ether gave positive results in *S. typhimurium* strains TA1535 and TA100, but not in strains TA1537, TA1538, or TA98 (Connor et al., 1980). 1-Butyl glycidyl ether produced a dose-dependent response (1–4 µmoles/plate), and addition of Aroclor- or phenobarbital-induced rat liver S9 slightly decreased the net frequency of revertants, with Aroclor-induced S9 producing the greatest decrease. [The Working Group noted that no significance testing was performed by the authors.] Similarly, 1-butyl glycidyl ether was mutagenic in *S. typhimurium* strains TA1535 and TA100, but not in strains TA1537, TA1538, or TA98 (Thompson et al., 1981). [The Working Group noted that no statistical significance testing was performed by the authors.] Similar results were reported by Canter et al. (1986), who found linear increases in the frequency of revertants in the TA100 strain at or above 100 µg per plate without S9, and above 333 µg/plate with either hamster or rat liver microsomes, and in the TA1535 strain at or above 333 µg/plate without S9 or with hamster S9, and at or above 1000 µg/plate with rat liver S9. [The Working Group noted that positive results in strains TA100 and TA1535 are indicative of base-pair substitution, and negative results in TA98, TA1537, and TA1538 are indicative of lack of frameshift mutations.]

In the *E. coli* WP2 *uvrA* reverse mutation assay, 1-butyl glycidyl ether was mutagenic in the absence of an exogenous metabolic system (Hemminki et al., 1980). 1-Butyl glycidyl ether induced DNA damage in the SOS chromotest with *E. coli* PQ37 (von der Hude et al., 1990).

4.2.3 Alters cell proliferation, cell death, or nutrient supply

No effect of 1-butyl glycidyl ether on the mitotic index in bone marrow was found in Sprague-Dawley CR-1 male and female rats given 1-butyl glycidyl ether (up to 313 mg/kg bw per day) by intraperitoneal administration for five consecutive days (US EPA, 1979).

In a 13-week study in mice (Crj:BDF1), there were lesions in the respiratory epithelium and olfactory epithelium of the nasal cavity attributable to treatment with 1-butyl glycidyl ether (JBRC, 2003b). These lesions included squamous metaplasia in respiratory epithelium (at 200 ppm), as well as respiratory metaplasia (at 25 ppm or greater) and atrophy (at 50 ppm or

greater) in olfactory epithelium. In F344/DuCrj rats, there were lesions in the respiratory epithelium and olfactory epithelium of the nasal cavity attributable to treatment with 1-butyl glycidyl ether (JBRC, 2003a). In respiratory epithelium, these lesions included hyperplasia (at 50 ppm or greater), inflammation and necrosis (both lesions at 100 ppm or greater), and squamous metaplasia (at 200 ppm). In olfactory epithelium, these lesions included atrophy (at 100 ppm or greater) and inflammation, respiratory metaplasia, and necrosis (all three lesions at 200 ppm).

In Crj:BDF1 mice treated with 1-butyl glycidyl ether by inhalation for 2 years (JBRC, 2005a, b), exposures resulted in increased incidence and/or severity of the following non-neoplastic lesions in the nasal cavity in both males and females (see Section 3.1 for greater detail): cuboidal change of the respiratory epithelium, respiratory metaplasia of glands, and respiratory metaplasia of the olfactory epithelium; and nodular hyperplasia of the transitional epithelium. In male mice, eosinophilic change in the respiratory epithelium was also observed.

In F344/DuCrlj rats treated with 1-butyl glycidyl ether by inhalation for 104 weeks (JBRC, 2005c, d), exposures resulted in increased incidence and/or severity of the following non-neoplastic lesions in the nasal cavity in both males and females (see Section 3.2 for greater detail): nasal respiratory epithelium squamous cell metaplasia, nasal squamous cell hyperplasia with atypia, olfactory epithelium atrophy, olfactory respiratory epithelium metaplasia and olfactory epithelium squamous cell metaplasia.

4.2.4 Is immunosuppressive

1-Butyl glycidyl ether decreased relative thymus weight in males at doses above 100 ppm and in females at a dose of 200 ppm in a 13-week study in F344/DuCrj rats treated by inhalation (JBRC, 2003a). A reduction in thymus weight and T-cell count in the peripheral blood was observed in mice (strain unspecified) exposed to 1-butyl glycidyl ether by gavage (at 450 but not at 225 mg/kg bw for 14 days) (Xue & Lei, 1988). Concavalin A-stimulated lymphocyte proliferation was reduced in both dose groups; however, no effect of 1-butyl glycidyl ether was observed in the plaque-forming cell assay. [The Working Group noted that these results were reported as an abstract and only in summary form.]

4.2.5 Evidence on other key characteristics of carcinogens

In F344/DuCrlj rats treated with 1-butyl glycidyl ether by inhalation for 104 weeks (JBRC, 2005c, d), exposures resulted in increased incidence and/or severity of nasal respiratory epithelium inflammation in both males and females (see Section 3.2 for greater detail).

One study investigated the ability of 1-butyl glycidyl ether to transform Balb/3T3 mouse embryo fibroblast cells in vitro (Connor et al., 1980). 1-Butyl glycidyl ether at non-cytotoxic concentrations (between 10 and 670 µg/mL) had no effect on cell transformation.

No significant lesions were seen in a study of dermal exposure to 1-butyl glycidyl ether (0.75, 1.5 and 3 g/kg bw) for 16 weeks in B6D2F_1 male and female mice (Pullin, 1978) that examined histopathological changes in the lung, liver, and testes. [The Working Group noted that these results were reported as an abstract and only in summary form.]

4.3 Data relevant to comparisons across agents and end-points

The analysis of the bioactivity in vitro of the agents reviewed in *IARC Monographs* Volume 125 was informed by data from high-throughput screening assays generated by the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the Government of the USA (Thomas et al., 2018).

1-Butyl glycidyl ether was one of thousands of chemicals tested across the large assay battery of the Tox21 and ToxCast research programmes as of 1 September 2019 (US EPA, 2019). Detailed information about the chemicals tested, assays used, and associated procedures for data analysis is also publicly available (US EPA, 2019). [The Working Group noted that the metabolic capacity of the cell-based assays is variable, and generally limited, as acknowledged in Kavlock et al. (2012).]

Among the 432 assays in which 1-butyl glycidyl ether (at concentrations up to 100 µM) was tested, it was found to be inactive in almost all assays. Active responses were observed in several assays for nuclear receptor activity and cell viability (US EPA, 2019). For nuclear receptors, borderline activity (potency of less than 50% or non-monotone dose–response fits) was found for only three assays: nuclear receptor subfamily 1, group I, member 2 (pregnane X receptor, PXR); thyrotropin-releasing hormone receptor; and nuclear factor, erythroid 2-like 2 (antioxidant response element). For cell viability, 1-butyl glycidyl ether was shown to be cytotoxic in human embryonic kidney HEK 293 cells at a half-maximal activity concentration (AC_{50}) of 22.9–24.3 µM, and in human hepatoma HEPG2 cells at an AC_{50} of 29.9–32.3 µM.

5. Summary of Data Reported

5.1 Exposure characterization

1-Butyl glycidyl ether is a High Production Volume chemical that is used as a reactive intermediate and viscosity-reducing solvent in the manufacture of epoxy resins. Additionally, it is used for stabilizing chlorinated compounds and as a surface modifier in the dyeing of cotton and wool. Potential occupational exposure may occur at workplaces where 1-butyl glycidyl ether is produced or used, whereas exposure of the general population is likely to be limited due to its participation in the polymerizing process. However, published studies documenting actual exposure levels were not identified.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

In one well-conducted study that complied with good laboratory practice (GLP) in male and female mice exposed by whole-body inhalation, 1-butyl glycidyl ether caused a significant increase, with a significant positive trend, in the incidence of haemangioma of the nasal cavity in males and females, and histiocytic sarcoma of the uterus in females. In the same study, inhalation of 1-butyl glycidyl ether caused occurrence of squamous cell carcinoma of the nasal cavity in males and females that was never reported in a large number of historical controls of similar sex and strain in the same laboratory.

In one well-conducted study that complied with GLP in male and female rats exposed by whole-body inhalation, 1-butyl glycidyl ether significantly increased the incidence of nasal cavity squamous cell carcinoma in males and females with a significant positive trend, and nasal cavity adenoma in males. Other rare tumours of the nasal cavity such as esthesioneuroepithelioma [neuroepithelial carcinoma], adenosquamous carcinoma, sarcoma (not otherwise specified), or squamous cell papilloma were also found in the treated groups of male and female rats. In males, there was a significant increase in the incidence of splenic mononuclear cell leukaemia. In females, there was a significant positive trend in the incidence of splenic mononuclear cell leukaemia.

5.4 Mechanistic evidence

No direct data on absorption, distribution, metabolism, or excretion in humans were available; however, two clinical cases of poisoning by inhalation of 1-butyl glycidyl ether provide indirect evidence of absorption and distribution to the central nervous system in humans. Studies of oral administration of 1-butyl glycidyl ether in rats, mice, and rabbits showed nearly complete absorption and rapid (within 24 hours of dosing) elimination, primarily in the urine. Skin absorption of 1-butyl glycidyl ether is likely to be as efficient as oral absorption on the basis of the similarity in median lethal dose (LD_{50}) between these routes of exposure and species. There are two metabolic pathways for 1-butyl glycidyl ether: hydration to the diol intermediates (accounting for about 75% of metabolites produced) and conjugation with glutathione.

Overall, there is consistent and coherent evidence in experimental systems that 1-butyl glycidyl ether exhibits key characteristics of carcinogens (alters cell proliferation, cell death, or nutrient supply). There is consistent evidence for increases in the incidence of various proliferative non-neoplastic lesions in the respiratory system of rodents exposed chronically by inhalation. Effects included respiratory and olfactory epithelium metaplasia in both species, squamous epithelium hyperplasia with atypia in male and female rats, and nodular hyperplasia of the transitional epithelium in male and female mice. There is suggestive evidence that 1-butyl glycidyl ether is electrophilic. 1-Butyl glycidyl ether is an epoxide that forms haemoglobin adducts in mice, and is a direct-acting mutagen and an alkylating compound in studies in bacteria and with deoxyguanosine, but adducts have not been characterized. There is suggestive evidence that 1-butyl glycidyl ether is genotoxic, as the studies cover a narrow range of experiments. In primary human cells, 1-butyl glycidyl ether induced unscheduled DNA synthesis in the few available studies. 1-Butyl glycidyl ether caused micronucleus formation in mice and chromosomal aberrations in rats when administered intraperitoneally, but not orally. 1-Butyl glycidyl ether induced dominant lethal mutations after repeated dermal exposure in mice. 1-Butyl glycidyl ether was mutagenic in one in vitro test each of gene mutation and of sister-chromatid exchanges in rodent cells. In bacteria, 1-butyl glycidyl ether showed consistent effects indicative of induction of base-pair substitution, but was without effects on frameshift mutations. Metabolic activation was not required for these effects; in fact, most studies showed that metabolic activation decreased the mutagenicity of 1-butyl glycidyl ether. 1-Butyl glycidyl ether was without effect in studies of the mutagenicity of urine after oral or dermal administration to mice. There is suggestive evidence that 1-butyl glycidyl ether is immunosuppressive; reduced thymus weight was seen in two studies in rodents. For other key characteristics of carcinogens, there is a paucity of available data. 1-Butyl glycidyl ether was found to be mostly without effects in the assay battery of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans regarding the carcinogenicity of 1-butyl glycidyl ether.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1-butyl glycidyl ether.

6.3 Mechanistic evidence

There is *strong evidence* in experimental systems that 1-butyl glycidyl ether exhibits key characteristics of carcinogens.

6.4 Overall evaluation

1-Butyl glycidyl ether is *possibly carcinogenic to humans (Group 2B)*.

6.5 Rationale

The evaluation of 1-butyl glycidyl ether as Group 2B is based on *sufficient evidence* of cancer in experimental animals, and on *strong* mechanistic evidence. The evidence for cancer in humans is *inadequate*, as no data were available. The *sufficient evidence* of carcinogenicity in experimental animals is based on the induction of malignant neoplasms in two species. There is also *strong evidence* in experimental systems that 1-butyl glycidyl ether exhibits key characteristics of carcinogens; 1-butyl glycidyl ether alters cell proliferation, cell death, or nutrient supply.

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