WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

# Volume 88
# Formaldehyde, 2-Butoxyethanol and 1-*tert*-Butoxypropan-2-ol

## Summary of Data Reported and Evaluation

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Formaldehyde

2-Butoxyethanol

1-*tert*-Butoxypropan-2-ol

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**Posted December 2006**

# FORMALDEHYDE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

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## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Formaldehyde is produced worldwide on a large scale by catalytic, vapour-phase oxidation of methanol. Annual world production is about 21 million tonnes. Formaldehyde is used mainly in the production of phenolic, urea, melamine and polyacetal resins. Phenolic, urea and melamine resins have wide uses as adhesives and binders in wood product, pulp and paper, and synthetic vitreous fibre industries, in the production of plastics and coatings and in textile finishing. Polyacetal resins are widely used in the produc-tion of plastics. Formaldehyde is also used extensively as an intermediate in the manufacture of industrial chemicals, such as 1,4-butanediol, 4,4′-methylenediphenyl diisocyanate, pentaerythritol and hexamethylenetetramine. Formaldehyde is used directly in aqueous solution (formalin) as a disinfectant and preservative in many applications.

Occupational exposure to formaldehyde occurs in a wide variety of occupations and industries. The highest continuous exposures (2–5 ppm) were measured in the past during the varnishing of furniture and wooden floors, in the finishing of textiles, in the garment industry, in the treatment of fur and in certain jobs within manufactured board mills and foundries. Shorter-term exposures to high levels (3 ppm and higher) have been reported for embalmers, pathologists and paper workers. Lower levels have usually been encountered during the manufacture of man-made vitreous fibres, abrasives and rubber, and in formaldehyde production industries. A very wide range of exposure levels has been observed in the production of resins and plastic products. The development of resins that release less formaldehyde and improved ventilation have resulted in decreased levels of exposure in many industrial settings in recent decades.

Formaldehyde occurs as a natural product in most living systems and in the environment. In addition to these natural sources, common non-occupational sources of exposure include vehicle emissions, particle boards and similar building materials, carpets, paints and varnishes, food and cooking, tobacco smoke and the use of formaldehyde as a disinfectant. Levels of formaldehyde in outdoor air are generally below 0.001 mg/m$^3$ in remote areas and below 0.02 mg/m$^3$ in urban settings. The levels of formaldehyde in the indoor air of houses are typically 0.02–0.06 mg/m$^3$. Average levels of 0.5 mg/m$^3$ or more have been measured in ‘mobile homes’, but these have declined since the late 1980s as a result of standards that require that building materials emit lower concentrations of formaldehyde.

## 5.2 Human data

*Nasopharyngeal cancer*

Since the last monograph on formaldehyde (in 1995), the follow-up of three major cohort studies has been extended and three new case–control studies have been published.

In the largest and most informative cohort study of industrial workers exposed to formaldehyde, a statistically significant excess of deaths from nasopharyngeal cancer was observed in comparison with the US national population, with statistically significant exposure–response relationships for peak and cumulative exposure. An excess of deaths from nasopharyngeal cancer was also observed in a proportionate mortality analysis of the largest US cohort of embalmers and in a Danish study of proportionate cancer incidence among workers at companies that used or manufactured formaldehyde. In three other cohort studies of US garment manufacturers, British chemical workers and US embalmers, cases of nasopharyngeal cancer were fewer than expected, but the power of these studies to detect an effect on nasopharyngeal cancer was low and the deficits were small.

The relationship between nasopharyngeal cancer and exposure to formaldehyde has also been investigated in seven case–control studies, five of which found elevated risks for overall exposure to formaldehyde or in higher exposure categories, including one in which the increase in risk was statistically significant; three studies (two of which have been published since the last monograph) found higher risks among subjects who had the highest probability, level or duration of exposure.

The most recent meta-analysis, which was published in 1997, included some but not all of the above studies and found an increased overall meta-relative risk for nasopharyngeal cancer.

The Working Group considered it improbable that all of the positive findings for nasopharyngeal cancer that were reported from the epidemiological studies, and particularly from the large study of industrial workers in the USA, could be explained by bias or unrecognized confounding effects.

Overall, the Working Group concluded that the results of the study of industrial workers in the USA, supported by the largely positive findings from other studies, provided sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans.

*Leukaemia*

Excess mortality from leukaemia has been observed relatively consistently in six of seven studies of professional workers (i.e. embalmers, funeral parlour workers, pathologists and anatomists). A recently published meta-analysis of exposure to formaldehyde among professionals and the risk for leukaemia reported increased overall summary relative risk estimates for embalmers, and for pathologists and anatomists, which did not vary significantly between studies (i.e. the results were found to be homogeneous). The excess incidence of leukaemia seen in several studies appeared to be predominantly of a myeloid type. There has

been speculation in the past that these findings might be explained by exposures to viruses that are experienced by anatomists, pathologists and perhaps funeral workers. However, there is currently little direct evidence that these occupations have a higher incidence of viral infections than that of the general population or that viruses play a causal role in myeloid leukaemia. Professionals may also be exposed to other chemicals, but they have no material exposure to known leukaemogens. Furthermore, the exposure to other chemicals would differ between anatomists, pathologists and funeral workers, which reduces the likelihood that such exposures could explain the observed increases in risk.

Until recently, the findings for leukaemia in studies of professional workers appeared to be contradicted by the lack of such findings among industrial workers. However, some evidence for an excess of deaths from leukaemia has been reported in the recent updates of two of the three major cohort studies of industrial workers. A statistically significant exposure–response relationship was observed between peak exposures to formaldehyde and mortality from leukaemia in the study of industrial workers in the USA. This relationship was found to be particularly strong for myeloid leukaemia, a finding that was also observed in the study of anatomists and in several of the studies of embalmers. However, in the study of industrial workers in the USA, mortality from leukaemia was lower than expected when comparisons were made using the general population as the referent group. This raises concerns about whether these findings are robust with respect to the choice of a comparison group. Leukaemia has been found to be associated with socioeconomic status, and that of industrial workers tends to be low. Thus, the lack of an overall finding of an excess of deaths from leukaemia in the cohort of industrial workers in the USA might be explained by biases in the comparison between the study and referent populations. The study also failed to demonstrate an exposure–response relationship with cumulative exposure, although other metrics may sometimes be more relevant.

Mortality from leukaemia was also found to be in excess in the recent update of the study of garment workers exposed to formaldehyde in the USA. A small and statistically non-significant excess was observed for the entire cohort in comparison with rates among the general population. This excess was somewhat stronger for myeloid leukaemia, which is consistent with the findings from the study of industrial workers in the USA and several of the studies of medical professionals and embalmers. The excess was also stronger among workers who had a long duration of exposure and long follow-up, and who had been employed early in the study period when exposures to formaldehyde were believed to be highest. This pattern of findings is generally consistent with what might be expected if, in fact, exposure to formaldehyde were causally associated with a risk for leukaemia. The positive associations observed in many of the subgroup analyses presented in the study of garment workers in the USA were based on a relatively small number of deaths, and were thus not statistically stable.

The updated study of British industrial workers failed to demonstrate excess mortality among workers exposed to formaldehyde. The lack of positive findings in this study is difficult to reconcile with the findings from the studies of garment workers and industrial workers in the USA and studies of professionals. This was a high-quality study of adequate size and with sufficiently long follow-up to have had a reasonable chance to detect an excess of deaths from leukaemia. The British study did not include an evaluation of peak exposures, but neither

did the study of garments workers in the USA nor the studies of professionals. Also, the British study did not examine specifically the risk for myeloid leukaemia, which represented the strongest findings in the studies of garment workers and industrial workers in the USA and in several of the studies of medical professionals and funeral workers.

In summary, there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers.

*Sinonasal cancer*

The association between exposure to formaldehyde and the risk for sinonasal cancer has been evaluated in six case–control studies that primarily focused on formaldehyde. Four of these studies also contributed to a pooled analysis that collated occupational data from 12 case–control investigations. After adjustment for known occupational confounders, this analysis showed an increased risk for adenocarcinoma in both men and women and also (although on the basis of only a small number of exposed cases) in the subset of subjects who were thought never to have been occupationally exposed to wood or leather dust. Moreover, a dose–response trend was observed in relation to an index of cumulative exposure. There was little evidence of an association with squamous-cell carcinoma, although in one of the two other case–control studies, a positive association was found particularly for squamous-cell carcinomas. An analysis of proportionate cancer incidence among industrial workers in Denmark also showed an increased risk for squamous-cell carcinomas.

Against these largely positive findings, no excess of mortality from sinonasal cancer was observed in other cohort studies of formaldehyde-exposed workers, including the three recently updated studies of industrial and garment workers in the USA and of chemical workers in the United Kingdom.

Most epidemiological studies of sinonasal cancer have not distinguished between tumours that arise in the nose and those that develop in the nasal sinuses. Thus, any effect on the risk for nasal cancer specifically would tend to be diluted if there were no corresponding effect on the risk for cancer in the sinuses, and would thus mask its detection, particularly in cohort studies that have relatively low statistical power. However, the apparent discrepancy between the results of the case–control as compared with the cohort studies might also reflect residual confounding by wood dust in the former. Almost all of the formaldehyde-exposed cases in the case–control studies were also exposed to wood dust, which resulted in a high relative risk, particularly for adenocarcinomas. Thus, there is only limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans.

*Cancer at other sites*

A number of studies have found associations between exposure to formaldehyde and cancer

at other sites, including the oral cavity, oro- and hypopharynx, pancreas, larynx, lung and brain. However, the Working Group considered that the overall balance of epidemiological evidence did not support a causal role for formaldehyde in relation to these other cancers.

### 5.3 Animal carcinogenicity data

Several studies in which formaldehyde was administered to rats by inhalation showed evidence of carcinogenicity, particularly the induction of squamous-cell carcinomas of the nasal cavities. A similar study in hamsters showed no evidence of carcinogenicity, and one study in mice showed no effect.

In four studies, formaldehyde was administered in the drinking-water to rats. One study in male rats showed an increased incidence of forestomach papillomas. In a second study in male and female rats, the incidence of gastrointestinal leiomyosarcomas was increased in females and in males and females combined. In a third study in male and female rats, the number of males that developed malignant tumours and the incidences of haemolymphoreticular tumours (lymphomas and leukaemias) and testicular interstitial-cell adenomas in males were increased. A fourth study gave negative results.

Skin application of formaldehyde concomitantly with 7,12-dimethylbenz[*a*]anthracene reduced the latency of skin tumours in mice. In rats, concomitant admi-nistration of formaldehyde and *N*-methyl-*N*´-nitro-*N*-nitrosoguanidine in the drinking-water increased the incidence of adenocarcinomas of the glandular stomach. Exposure of hamsters by inhalation to formaldehyde increased the multiplicity of tracheal tumours induced by sub-cutaneous injections of *N*--nitrosodiethylamine.

### 5.4 Other relevant data

*Toxicokinetics and metabolism*

The concentration of endogenous formaldehyde in human blood is about 2–3 mg/L; similar concentrations are found in the blood of monkeys and rats. Exposure of humans, monkeys or rats to formaldehyde by inhalation has not been found to alter these concentrations. The average level of formate in the urine of people who are not occupationally exposed to formaldehyde is 12.5 mg/L and varies considerably both within and between individuals. No significant changes in urinary formate were detected in humans after exposure to 0.5 ppm formaldehyde for up to 3 weeks. More than 90% of inhaled formaldehyde is absorbed in the upper respiratory tract. In rats, it is absorbed almost entirely in the nasal passages; in monkeys, it is also absorbed in the nasopharynx, trachea and proximal regions of the major bronchi. Absorbed formaldehyde can be oxidized to formate and carbon dioxide or may be incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways. Formaldehyde has a half-life of about 1 min in rat plasma. Rats exposed to [$^{14}$C]formaldehyde eliminated about 40% of the $^{14}$C as exhaled carbon dioxide, 17% in the urine and 5% in the faeces; 35–39% remained in the tissues and carcass. After dermal application of aqueous [$^{14}$C]formaldehyde, approximately 7% of the dose was excreted in the urine by rodents and 0.2% by monkeys. After oral administration, about 40% of [$^{14}$C]formaldehyde was excreted as exhaled carbon dioxide, 10% in the urine and 1% in

the faeces within 12 h.

*Toxic effects in humans*

Many studies have evaluated the health effects of inhalation of formaldehyde in humans. Most were carried out in unsensitized subjects and revealed consistent evidence of irritation of the eyes, nose and throat. Symptoms are rare below 0.5 ppm, and become increasingly prevalent in studies in exposure chambers as concentrations increase. Exposures to up to 3 ppm formaldehyde are unlikely to provoke asthma in an unsensitized individual.

Nasal lavage studies show increased numbers of eosinophils and protein exudation following exposures to 0.5 $mg/m^3$ formaldehyde. Bronchial provocation tests have confirmed the occurrence of occupational asthma due to formaldehyde in small numbers of workers from several centres. The mechanism is probably hypersensitivity, because the reactions are often delayed, there is a latent period of symptomless exposure and unexposed asthmatics do not react to the same concentrations. One case of pneumonitis was reported in a worker who was exposed for 2 h to a level that was sufficient for his breath to smell of formaldehyde. High levels of formaldehyde probably cause asthmatic reactions by an irritant mechanism. Formaldehyde is one of the commoner causes of contact dermatitis and is thought to act as a sensitizer on the skin.

*Toxic effects in animals*

Formaldehyde is a well documented irritant that causes mild inflammation to severe ulceration. It caused direct toxicity in the upper respiratory system in a concentration- and location-specific manner. There is evidence that formaldehyde can induce irritation to the forestomach after high-dose oral exposure. Formaldehyde is also a sensory irritant that induces a decrease in respiratory rate in rodents; mice are more sensitive than rats, as measured by respiratory depression. This respiratory depression is thought to be secondary to stimulation of the trigeminal nerve by the irritant effect of formaldehyde. Formaldehyde can also result in pulmonary hyperactivity through transient bronchoconstriction. It can also act as a skin contact sensitizer via a type IV T-cell mediated hypersensitivity reaction. Formaldehyde does not induce haematological effects.

*In-vitro toxicity*

Formaldehyde exerts dose-dependent toxicity in cell cultures. Cytotoxicity involves loss of glutathione, altered $Ca^{2+}$-homeostatis and impairment of mitochondrial function. Thiols, including glutathione, and metabolism through alcohol dehydrogenase 3, act in a protective manner.

*Reproductive and developmental effects*

Eleven epidemiological studies have evaluated directly or indirectly the reproductive effects of occupational exposures to formaldehyde. The outcomes examined in these studies included spontaneous abortions, congenital malformations, birth weights, infertility and endometriosis. Inconsistent reports of higher rates of spontaneous abortion and lowered birth weights were

reported among women occupationally exposed to formaldehyde. Studies of inhalation exposure to formaldehyde in animal models have evaluated the effects of formaldehyde on pregnancy and fetal development, which have not been clearly shown to occur at exposures below maternally toxic doses.

*Genetic and related effects*

There is evidence that formaldehyde is genotoxic in multiple in-vitro models and in exposed humans and laboratory animals. Studies in humans revealed increased DNA–protein cross-links in workers exposed to formaldehyde. This is consistent with laboratory studies, in which inhaled formaldehyde reproducibly caused DNA–protein cross-links in rat and monkey nasal mucosa. A single study reported cytogenetic abnormalities in the bone marrow of rats that inhaled formaldehyde, while other studies did not report effects in bone marrow.

*Mechanistic considerations*

The current data indicate that both genotoxicty and cytoxicity play important roles in the carcinogenesis of formaldehyde in nasal tissues. DNA–protein cross-links provide a potentially useful marker of genotoxicity. The concentration–response curve for the formation of DNA–protein cross-links is bi-phasic, and the slope increases at formaldehyde concentrations of about 2–3 ppm in Fischer 344 rats. Similar results are found in rhesus monkeys, although the dose–response curve is less well defined in this species. Cell proliferation, which appears to amplify greatly the genotoxic effects of formaldehyde, is increased considerably at concentrations of formaldehyde of about 6 ppm, and results in a marked increase in the occurrence of malignant lesions in the nasal passages of rats at concentrations above this level.

Several possible mechanisms were considered for the induction of human leukaemia, such as clastogenic damage to circulatory stem cells. The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukaemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans.

## 5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of formaldehyde.

There is *sufficient evidence* in experimental animals for the carcinogenicity of formaldehyde.

**Overall evaluation**

Formaldehyde is *carcinogenic to humans (Group 1)*.

For definitions of the italicized terms, see Preamble evaluation.

**Previous evaluations**: Vol. 29 (1982); Suppl. 7 (1987); Vol. 62 (1995)

## Synonyms

- Formaldehyde, gas
- Formic aldehyde
- Methaldehyde
- Methyl aldehyde
- Methylene oxide
- Oxomethane
- Oxymethylene

# 2-BUTOXYETHANOL
# (Group 3)

For definition of Groups, see Preamble Evaluation.

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**CAS No.**: 111-76-2

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

2-Butoxyethanol is a glycol ether that is widely used as a solvent in surface coatings (paints and varnishes), paint thinners, printing inks and glass- and surface-cleaning products (including those used in the printing and silk-screening industries), and as a chemical intermediate. It is also used in a variety of personal care and other consumer products. Occupational exposure occurs through dermal absorption or via inhalation during its manufacture and use as a chemical intermediate, and during the formulation and use of its products. Highest mean exposures have been measured for silk screeners. Exposure of the general population can occur through dermal contact or inhalation during the use of consumer products, particularly cleaning agents.

### 5.2 Human carcinogenicity data

A case–control study of acute myeloid leukaemia and myelodysplasia found no elevation of risk with exposure to a group of glycol ethers, including 2-butoxyethanol. However, the information provided by this study on 2-butoxyethanol specifically was limited.

### 5.3 Animal carcinogenicity data

2-Butoxyethanol was tested for carcinogenicity by inhalation exposure in male and female mice and rats. Clear increases in tumour incidence were observed in a single species. Exposure to 2-butoxyethanol induced a dose-related increase in the incidence of haemangiosarcomas of the liver in male mice and a dose-related increase in the incidences of combined forestomach squamous-cell papillomas or carcinomas (mainly papillomas) in female mice. In female rats, a positive trend was observed in the occurrence of combined benign or malignant pheochromocytomas (mainly benign) of the adrenal medulla, but this equivocal result could not be attributed with confidence to exposure to 2-butoxyethanol. There was no increase in the incidence of tumours in male rats.

### 5.4 Other relevant data

*Toxicokinetics and metabolism*

2-Butoxyethanol is rapidly absorbed following ingestion, inhalation and dermal exposure in humans and experimental animals. Uptake and metabolism in rats are linear up to 400 ppm. The elimination half-life of 2-butoxyethanol from the blood is much longer in humans than in rats or mice. The principal pathway of metabolism in humans and experimental animals involves oxidation to butoxyacetaldehyde and butoxyacetic acid (the putatively active metabolite for 2-butoxyethanol-induced haematological effects) via alcohol and aldehyde dehydrogenases, respectively. Based on limited data and the results of a physiologically based parmacokinetic model, humans appear to metabolize 2-butoxyethanol to butoxyacetic acid to a lesser extent than rats, which results in greater concentrations of butoxyacetic acid in the blood of rats than in that of humans. The elimination half-life of butoxyacetic acid in the urine is about 6 h in humans, and at least 15–55% of the inhaled dose of 2-butoxyethanol is excreted as free butoxyacetic acid. Although mice metabolize 2-butoxyethanol to butoxyacetic acid at a greater rate than rats, the metabolite is cleared much more slowly in rats, which is consistent with the greater sensitivity of rats to its effects in the blood. Similarly, slower clearance in female rats probably accounts for their greater sensitivity compared with male rats. Detoxification via conjugation of butoxyacetic acid with glutamine and excretion in the urine has been demonstrated in humans, but not to date in rats. The extent of glutamine conjugation varies within and between individuals, with a mean of around 70%. 2-Butoxyethanol may also be *O*-dealkylated to ethylene glycol, based on limited information in humans and more extensive evidence in rodents (conjugation of 2-butoxyethanol with glucuronide or sulfate has been observed in rats, but only tentatively in human hepatocytes *in vitro*).

*Toxic effects*

Several case reports that involved the consumption of up to several hundred millilitres of glass-cleaning liquid that contained various amounts of 2-butoxyethanol described a variety of effects (hypotension, coma, metabolic acidosis, renal impairment, haematuria, haemoglobinuria, hypochromic anaemia) in adults. In a survey of childhood poisonings, no symptoms were reported in children who had ingested comparable amounts of glass-cleaning liquids.

Incidental cutaneous exposures were not reported to produce adverse skin reactions or skin sensitization. Repeated dermal exposure produced increasing erythema. Exposure to 2-butoxyethanol vapour is irritating to the eyes, nose and throat.

In studies of occupational exposure to airborne 2-butoxyethanol (mean concentrations of 2–4 mg/m$^3$), effects on blood parameters (lower haematocrit values), but no changes in renal or hepatic function and no correlation with concentrations of 2-butoxyacetic acid in the urine of exposed workers were observed. In one study, airborne levels of 100–300 ppm [483–1450 mg/m$^3$] 2-butoxyethanol caused acute and severe irritation of the eyes and respiratory tract and the appearance of cherry angiomas (benign cutaneous vascular lesions) after 3 months, which persisted and continued to develop.

Effects on the blood appear to be the most sensitive parameter in experimental animals following acute, short-term, subchronic or chronic exposure via oral, inhalation and dermal routes, based on an extensive database. Alterations in haematological parameters that are

consistent with haemolytic anaemia have repeatedly been observed in multiple species, including mice and rats. There is substantial evidence from in-vivo and in-vitro investigations that rats are more sensitive to 2-butoxyethanol-induced haemolysis than other experimental species, and alterations in relevant parameters were observed following long-term exposure to concentrations as low as 31.2 ppm [151 mg/m$^3$]. Female rats are more sensitive to the haematological effects associated with exposure to 2-butoxyethanol than male rats, which is consistent with sex-related differences in the clearance of the putatively active metabolite, butoxyacetic acid, and greater activity of the enzymes involved in its formation. On the basis of several in-vitro investigations in erythrocytes of humans and rats, humans appear to be much less sensitive. Although the physical–chemical pathway for haemolysis by 2-butoxyethanol has not been fully elucidated, it has been reported that haemolysis involves cell swelling, morphological changes and decreased deformability.

Haemolysis has been proposed to be linked mechanistically to the induction of liver neoplasia in male mice by 2-butoxyethanol. Damage to red blood cells results in the deposition of haemosiderin in Kupffer cells of both mice and rats which in turn apparently mediates the induction of hepatic oxidative stress that has been observed in both species *in vivo*. In mice, but not in rats, oxidative stress results in the formation of the oxidative, mutagenic DNA lesion, 8-hydroxydeoxyguanosine, as well as an increase in the proliferation of endothelial cells; both of these effects are assumed to contribute to the development of liver tumours. The apparent protection of rats against these consequences of oxidative stress, which is not observed in mice, has been attributed to a higher level of protective antioxidants in rat liver than in mouse liver. In view of the much lower sensitivity to haemolysis of human erythrocytes than those of mice and rats, and the fact that the concentration of the antioxidant, vitamin E, is approximately 100-fold higher in human liver than in mouse liver, the induction of liver tumours in humans is unlikely to occur through this pathway. Other potential mechanisms have not been investigated.

Toxic effects have been observed in the forestomach of mice and rats following both oral and inhalation exposure to 2-butoxyethanol; mice were more sensitive than rats. In a chronic inhalation study in mice, toxicity was observed at all concentrations investigated, i.e. at 62.5 ppm [302.5 mg/m$^3$] and higher. The effects on the forestomach were increased in incidence and severity with increasing exposure concentration, and included irritation, inflammation, hyperplasia and ulceration. Increases in tumour incidences were observed in mice at the higher concentrations. The formation of forestomach tumours in mice is associated with high local exposure of the forestomach to 2-butoxyethanol, even during inhalation exposure, and to high metabolic activity in certain areas of the forestomach, which results in high local concentrations of the toxic metabolite, 2-butoxyacetic acid.

*Reproductive and developmental effects*

In developmental toxicity studies in rats and mice that involved oral and inhalation exposure to 2-butoxyethanol, embryotoxic or fetotoxic effects were observed at doses or concentrations similar to or greater than those which induced toxicity (including haematological effects) in the dams. Alterations in haematological parameters were also observed in fetuses of exposed dams. Effects on reproductive ability and reproductive organs were also only observed at doses or concentrations of 2-butoxyethanol much greater than those associated with

haematological effects.

*Genetic and related effects*

The available data on 2-butoxyethanol support the concept that the compound itself exhibits no appreciable genotoxicity. The oxidative metabolite, 2-butoxyacetaldehyde, appears to have a weak capacity to cause genotoxic effects *in vitro*, largely at the chromosomal level. The product of further oxidation, 2-butoxyacetic acid, does not appear to be genotoxic.

### 5.5 Evaluation

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

There is *limited evidence* in experimental animals for the carcinogenicity of 2-butoxyethanol.

**Overall evaluation**

2-Butoxyethanol is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definitions of the italicized terms, see Preamble evaluation.

**Synonyms**

- Butoxyethanol
- β-Butoxyethanol
- *n*-Butoxyethanol
- 2-*n*-Butoxyethanol
- 2-Butoxy-1-ethanol
- 2-*n*-Butoxy-1-ethanol
- O-Butyl ethylene glycol
- Butylglycol
- Butyl monoether glycol
- EGBE
- Ethylene glycol butyl ether
- Ethylene glycol *n*-butyl ether
- Ethylene glycol monobutyl ether
- Ethylene glycol mono-*n*-butyl ether
- Glycol butyl ether
- Glycol monobutyl ether
- Monobutyl ether of ethylene glycol
- Monobutyl glycol ether
- 3-Oxa-1-heptanol

# 1-*tert*-BUTOXYPROPAN-2-OL
# (Group 3)

For definition of Groups, see Preamble Evaluation.

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**CAS No.**: 57018-52-7

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

1-*tert*-Butoxypropan-2-ol is a glycol ether that has been increasingly used since the 1980s as a solvent in coatings, glass-cleaning and surface-cleaning products, inks, adhesives and cosmetic products. No data are available on levels of occupational or consumer exposure to 1-*tert*-butoxypropan-2-ol.

### 5.2 Human carcinogenicity data

No data were available to the Working Group.

### 5.3 Animal carcinogenicity data

1-*tert*-Butoxypropan-2-ol was tested for carcinogenicity by inhalation in mice and rats. In a single study, a dose-related increase in the combined incidences of liver tumours (hepatocellular adenomas and carcinomas), including hepatoblastomas, was observed in both male and female mice. A significant trend in the increase in malignant tumours was observed in females when hepatocellular carcinomas and hepatoblastomas were combined. In male rats, marginal, non-significant increases in the incidences of renal tubule adenomas (with one carcinoma at the highest dose) and hepatocellular adenomas were observed, but these findings were considered to be equivocal. In female rats, no dose-related increases in tumour incidence were found.

### 5.4 Other relevant data

No data were available to the Working Group on the kinetics, metabolism, toxic effects, reproductive effects or genetic and related effects of 1-*tert*-butoxypropan-2-ol in humans.

*Kinetics and metabolism*

1-*tert*-Butoxypropan-2-ol is rapidly absorbed and eliminated in rats and mice. It is eliminated from blood following concentration-dependent non-linear kinetics, with a half-life of approximately 16 and 10 min in rats and mice, respectively. Elimination kinetics were saturable following a single inhalation exposure to 1200 ppm, but saturation was less obvious following repeated exposures. Urinary excretion accounted for 48–67% of an orally

administered dose of 1-*tert*-butoxypropan-2-ol; the principal urinary metabolites identified were glucuronide (23–52%) and sulfate (7–13%) conjugates, while expired carbon dioxide accounted for up to 26%. Metabolites resulting from other potential pathways of metabolism have not been investigated experimentally. Biliary excretion of conjugated 1-*tert*-butoxypropan-2-ol may be significant (up to 40% following intravenous administration), although reabsorption may also occur, based on a recovery of only 4–11% of the administered dose in the faeces, which suggests enterohepatic circulation.

*Toxic effects*

1-*tert*-Butoxypropan-2-ol has low acute toxicity in experimental animals, although it may be irritating to the skin and eyes. Target organs following short-term, subchronic and chronic exposure include the kidneys and liver. Renal effects consistent with $\alpha_{2u}$-globulin-associated nephropathy, including hyaline droplet accumulation, cell proliferation in the renal cortex and alterations in urinary parameters, were observed in male Fischer 344/N rats following exposure to 1-*tert*-butoxypropan-2-ol, but not in female Fischer 344/N or in male NBR rats, a strain that does not produce $\alpha_{2u}$-globulin. However, effects on the kidneys were also observed in female Fischer 344/N rats in subchronic and chronic inhalation studies, including increased relative weights, altered urinary parameters and a concentration-related increase in age-related nephropathy, although generally to a lesser degree than that noted in similarly exposed male rats of this strain.

Toxic effects in the liver have also been observed in short-term, subchronic and chronic investigations in both male and female rats and mice, including increased weight and histopathological changes. However, these observations do not elucidate a potential mode of induction of the reported hepatic tumours in mice.

*Reproductive and developmental effects*

Although there is some evidence for a reproductive effect in female mice exposed to 1-*tert*-butoxypropan-2-ol (altered estrus cycle), this was only observed at concentrations greater than those associated with effects on the liver.

Based on the limited available data, 1-*tert*-butoxypropan-2-ol does not appear to induce developmental toxicity in experimental animals.

*Genotoxicity*

1-*tert*-Butoxypropan-2-ol, the structure of which does not carry any structural alert to genotoxicity, has been reported to be weakly mutagenic in *Salmonella* strain TA97 and to cause a statistically significant but very weak increase in the frequency of micronuclei in the peripheral blood of female but not male mice. No genotoxicity was observed in assays for the induction of sister chromatid exchange and chromosomal aberrations in the presence or absence of exogenous metabolic activation *in vitro*. In view of the scarcity of the data available, it is not possible to draw any meaningful conclusion regarding the potential

genotoxic effects of 1-*tert*-butoxypropan-2-ol in mammalian cells or in mammals *in vivo*.

### 5.5 Evaluation

NOTE: After thorough discussion, several members of the Working Group favoured an evaluation of the evidence of carcinogenicity in experimental animals as *sufficient*. This view emphasizes the dose-related induction of hepatoblastomas in male and female mice, because that hepatoblastoma is a rare neoplasm with a low spontaneous incidence in mice, especially in females. However, the majority of the Working Group considered the evidence to be *limited* for the reasons discussed in Section 5.3.

There is *inadequate evidence* in humans for the carcinogenicity of 1-*tert*-butoxypropan-2-ol.

There is *limited evidence* in experimental animals for the carcinogenicity of 1-*tert*-butoxypropan-2-ol.

**Overall evaluation**

1-*tert*-Butoxypropan-2-ol is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definitions of the italicized terms, see Preamble evaluation.

**Synonyms**

- 1-*tert*-Butoxy-2-propanol
- 1-Methyl-2-*tert*-butoxyethanol
- Propylene glycol 1-(*tert*-butyl ether)
- Propylene glycol mono-*tert*-butyl ether, α-isomer