Prop-2-yn-1-ol

(CAS No: 107-19-7)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

No. 2000/15OSH/137 The Hague, November 9, 2004

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. Prop-2-yn-1-ol; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2004; 2000/15OSH/137.

1 Introduction

The present document contains the assessment of the health hazard of prop-2-yn-1-ol, referred to as propynol in this document, by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by C de Heer, Ph.D., S Bosman-Hoefakker, Ph.D., and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of propynol has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 1997, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts covering the period 1966 to May 1997, 1965 to March 1997, and 1972 to April 1997, respectively, and using the following key words: propargyl alcohol, propynyl alcohol, ethynyl carbinol, propynol, and 107-19-7.

In February 1999, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: A Aalto (Ministery of Social Affairs and Health, Tampere, Finland) and M Beth-Hübner, Ph.D. (BG-Chemie, Heidelberg, FRG). These comments were taken into account in deciding on the final version of the document.

An additional literature search in Toxline and Medline in July 2004 did not result in information changing the committee's conclusions.

2 Identity

name	:	prop-2-yn-1-ol
synonyms	:	propargyl alcohol, 2-propyn-1-ol, acetylene carbinol, ethenyl methanol, ethynyl carbinol, propyn-(2)-ol, 1-propyn-3-ol, propiolic alcohol
molecular formula	:	C_3H_4O
structural formula	:	$HC{\equiv}C\text{-}CH_2OH$
CAS number	:	107-19-7

3 Physical and chemical properties

molecular weight	:	56.06
boiling point	:	114-115ºC
melting point	:	-48 to –52ºC
flash point	:	36ºC (open cup)
vapour pressure	:	at 20ºC: 1.5 kPa
solubility in water	:	soluble
log $P_{octanol/water}$	:	-0.38 (experimental); -0.47 (estimated)
conversion factors	:	(20ºC, 101.3 kPa): 1 ppm = 2.3 mg/m^3 1 mg/m^3 = 0.43 ppm

Data from BCG00, Lin94, NLM04, http://www.syrres.com/esc/est_kowdemo.htm.

Propynol is a moderately volatile, clear to slightly straw-coloured liquid with a mild geranium-like odour (ACG91).

4 Uses

Propynol has been used to prevent the hydrogen embrittlement of steel. It has also been employed as a corrosion inhibitor, a solvent for cellulose acetate, a stabiliser for chlorinated hydrocarbon formulations, a herbicide, a polishing agent in galvanotechnics, a soil fumigant, and as a chemical intermediate (ACG91, BGC00, Lin94).

5 Biotransformation and kinetics

The committee did not find data on biotransformation and kinetics in humans or on absorption following inhalation or oral exposure. From dermal lethality data on rabbits (see Table 1), it can be seen that propynol is readily absorbed through the skin (Ols57).

Banijamali et al. studied the metabolism of propynol in rats and mice by identifying urinary metabolites following oral administration of radiolabelled [1,2,3-^{13}C, 2,3-^{14}C]propynol. In male Sprague-Dawley rats, 56% of the radioactivity administered was excreted in the urine within 96 hours. The highest concentration was observed in the first 24-hour urine. The main metabolites were 2-propynoic acid, 3,3-bis[(2-(acetylamino)-2-carboxyethyl)thio]-1-propanol, 3-(carboxymethylthio)-2-propenoic acid, and 3-[[2-(acetylamino)-2-

carboxyethyl]sulphinyl]-3-[[2-(acetylamino)-2-carboxyethyl]thio]-1-propanol accounting for 27, 20, 20, and 15%, respectively, of the total radioactivity excreted in the urine during the first 24 hours post-administration (see Figure 1, Annex I). From the results, Banijamali et al. suggested that the metabolism of propynol in rats involves oxidation into 2-propynoic acid and multiple glutathione additions to the carbon-carbon triple bond yielding numerous metabolites (see Figure 2, Annex III for metabolism scheme) (Ban99). In mice, about 60% of the radiolabel administered was excreted in the urine by 96 hours. The highest concentration was observed in the first 24-hour urine. The main metabolites were (*E* + *Z*)-3-[(2-amino-2-carboxyethyl)thio]-2-propenoic acid, 3-[[2-(acetylamino)-2-carboxyethyl]thio]-3-[[2-(amino)-2-carboxyethyl]thio]-1-propanol, 3,3-bis[(2-(amino)-2-carboxyethyl)thio]-1-propanol, and 3-[(2-formylamino-2-carboxyethyl)thio]-2-propenoic acid accounting for 41, 17, 15, and 13%, respectively, of the total radioactivity excreted in the urine during the first 24 hours post-administration (see Annex II). The data suggested that metabolism of propynol in mice involves glucuronide conjugation to form 2-propyn-1-ol glucuronide as well as oxidation into 2-propynal which undergoes either multiple glutathione additions or oxidation into 2-propynoic acid (only ca. 2%) (see scheme in Annex III). Comparison of rat and mice data indicate quantitative and qualitative differences in formation of glucuronide conjugates and of 2-propynoic acid and metabolites derived from glutathione (see Annex III) (Ban00).

DeMaster et al. stated that the oxidative metabolic conversion of propynol into its aldehyde is not likely to occur via alcohol dehydrogenase since propynol appeared to be a poor substrate for this enzyme. Based on *in vitro* experiments, they hypothesised that catalysis by liver catalase via a hydrogen peroxide-supported reaction could be an alternative oxidative pathway, but did not exclude other possible pathways such as oxidation by hydroxyl radicals and microsomal cytochrome P450 2E1 (DeM94). From *in vitro* experiments with rat hepatocytes, Moridani et al. concluded that propynol is preferentially oxidised by cytochrome P450 2E1 rather than by catalyse or alcohol dehydrogenase to form propynal that caused hepatocyte lysis as a result of glutathione depletion and lipid peroxidation (Mor01).

6 Effects and mechanism of action

Human data

The committee did not find data on adverse effects in humans following exposure to propynol.

Animal data

Irritation and sensitisation

When instilled into the conjunctival sac of the rabbit eye, undiluted material caused marked pain, irritation, and permanent corneal injury. A 10% solution caused slight pain and irritation that cleared up. A 1% solution was not irritating (BGC00, Tor64).

Undiluted propynol caused hyperaemia, oedema, and superficial necrosis after topical application to rabbits. A 10% aqueous solution produced mild irritation, and a 1% aqueous solution had no effect (BGC00, Tor64).

Propynol was not a skin sensitiser to guinea pigs (ACG91, BGC00, Lin94).

Acute and subacute exposure

Acute lethal toxicity data on propynol are summarised in Table 1.

Table 1 Acute lethal toxicity data for propynol.

species	route	LC_{50}/LD_{50}	reference
rat	inhalation (1 h)	2392-2760 mg/m^3	Ver77
rat	inhalation (2 h)	1955 mg/m^3	Ken91
rat	inhalation (2 h)	2000 mg/m^3	BGC00
mouse	inhalation (2 h)	2000 mg/m^3	BGC00
rabbit	dermal	16-88 mg/kg bw	BCG00, Ols57, Ver77
rat	oral	20-110 mg/kg bw	ACG91, BGC00, Ken91, Lin94, Ver77
mouse	oral	50 mg/kg bw	ACG91, BGC00, Lin94
guinea pig	oral	39-97 mg/kg bw	ACG91, BGC00, Lin94
rabbit	oral	19-39 mg/kg bw	BGC00
cat	oral	10-19 mg/kg bw	BGC00
mouse	intraperitoneal	44 mg/kg bw	BGC00

After oral and intraperitoneal administration, animals displayed excitation, accelerated breathing, lying on the side, apathy, atonia, diarrhoea, tonic spasms, paresis, and/or proteinuria. At autopsy, liver and kidney damage and haemorrhages in several organs were observed, irrespective of the species examined and the route of administration (BGC00).

Exposure to 790 to 4020 mg/m^3 (340 to 1730 ppm), for 6 hours, killed all animals (species not indicated) during exposure or within 48 hours post-exposure (depending on exposure level), while concentrations of 380 mg/m^3 (160 ppm) caused no deaths (Eas64).

In a preliminary study, 10 mice, 10 rats, 4 guinea-pigs, 2 rabbits, and 1 cat, all exposed for 1 hour to approximately 1300 ppm (ca. 2290 mg/m^3) propynol, showed slight irritation of the mucous membranes. Apathy, vomiting, and lying on the side were seen in the cat, which died 2 days after exposure. Clinical chemistry studies revealed functional disturbances in the liver and kidneys of the cat and the rabbits. In this study, 3/10 mice and 1/10 rats died after 1-3 days, whereas all guinea pigs and the rabbits survived (BGC00, review, original report unpublished). After exposure of 10 rats to 1490 ppm propynol vapour (ca. 3430 mg/m^3) for 1 hour, all animals died by day 2-3. The animals displayed languid behaviour, prostration, squinted eyes, and increased secretory responses during exposure. At necropsy, there were no lesions obviously related to the treatment (Ter89).

Exposure to an atmosphere saturated with propynol (at 20ºC) caused mortality in 6/12 and 6/6 rats after exposure for 3 and 10 minutes, respectively. Most of the animals died a few hours after the beginning of the study, although some survived for 1-2 days. Symptoms of acute toxicity included flight behaviour at the beginning of exposure, irritation of the mucous membranes, marked pallor of the ears and paws, and shortness of breath. Macroscopic examination revealed isolated bleeding in the gastro-intestinal region (BGC00, review, original report unpublished).

Dermal application of doses of 1894 mg/kg bw for >3 minutes was lethal to all 5 rats while no animals died when exposed for 1 minute. Symptoms of toxicity included apathy and irregular breathing. In animals exposed for 10 minutes, necrosis and bleeding were seen at the application site, as well as bleeding in the thymus and jejunum (BGC00, review, original report unpublished).

Subcutaneous injections of propynol doses of 237 or 474 mg/kg bw caused the death of rabbits within 2.5 hours. Another rabbit survived a subcutaneous dose of 47 mg/kg bw but died within 6.5 hours following a dose of 94 mg/kg bw given the next day (BGC00).

In a subacute inhalation toxicity study, exposure to ca. 1300 ppm propynol (ca. 2990 mg/m^3), 1 hour/day, for 5 days caused mortality in 4/10 rats, 7/10 mice, 0/4 guinea pigs, 1/2 rabbits, and 1/1 cats, mostly before the end of the experiment. Animals showed irritation of the mucous membranes. The deceased animals showed liver damage. In the surviving animals, body weight gain was normal, and examination of the blood, urine, liver, and kidneys revealed no adverse effects (BGC00, review, original report unpublished).

After exposure to 88 ppm (ca. 200 mg/m^3) propynol (purity: 99%) for periods of 4-14 days, mice displayed lesions of respiratory and olfactory epithelium. These lesions were of maximum severity after 4 days of exposure; severity after 14 days of exposure was similar. Trachea and lungs were not affected. Exposure to 25 ppm (58 mg/m^3) did not induce such respiratory tract effects. Systemic toxicity was not addressed in the study report (Zis95).

In a 14-day dose range-finding study for a subsequent 90-day inhalation study, exposure of rats (n=5/sex/group) to propynol (purity: 99.4%) concentrations of 0, 10, 50, and 200 ppm (0, 23, 114, and 460 mg/m^3), 6 hours/day, 5 days/week, for 2 weeks, caused clinical signs including apathy, red-coloured nasal secretions, and irregular breathing at 200 ppm while no clinical signs were seen in the animals of the two lower concentrations groups. One female animal of the 200-ppm group died. Decreased body weight gain was found at 50 in males and at 200 ppm in males and females. Changes in blood chemistry parameters associated with liver lesions (increased alanine aminotransferase (ALAT) and alkaline phosphatase (ALP) serum activities, increased thromboplastin times, increased bilirubin serum levels, decreased total protein, triglyceride and cholesterol serum levels) were seen at 50 and 200 ppm. Relative liver and kidney organ weights were significantly increased at 200 ppm and at 50 and 200 ppm, respectively. In the liver, hepatocyte hypertrophy and single cell necrosis were seen at 200 ppm and, due to an irritating effect, changes of the respiratory epithelial cells of the nasal mucosa were observed in the form of inflammatory processes (at 200 ppm) as well as metaplastic changes (at 50 and 200 ppm) (confidential study report cited in BGC00; the original study report was available to the committee). From these results, it can be concluded that the NOAEL in rats for 14-day inhalation exposure to propynol is 10 ppm (23 mg/m^3).

Rats orally exposed to doses of propynol (purity: 97%) of 0.1-10 mg/kg bw/day for 14 days did not show effects on body weight gain, organ weights, and hepatic microsomal enzyme activities, as well as several histological and haematological parameters examined (Kom89).

Groups of 10 Bor:WISW (SPF:Cpb) rats/sex received daily oral (gavage) doses of propynol (purity: 99%) (vehicle: water) of 0, 5, 15, or 45 mg/kg bw for 4 weeks. The study was performed in accordance with OECD guideline 407 ('Repeated dose 28-day oral toxicity study in rodents'). Significant and dose-dependent increases in relative liver and kidney weights were seen in all treated groups. At 15 and 45 mg/kg bw, significantly decreased red blood cell counts and haemoglobin and haematocrit levels were observed in both sexes. Reticulocyte counts were increased in males. At 45 mg/kg bw, mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were decreased in males. The authors concluded these changes to be indicative of hypochromic anaemia. No changes were observed in leukocyte numbers, thrombocyte numbers, and differential counts. In addition to the haematological and organ weight effects, a dose of 45 mg/kg retarded body weight gain and increased ALAT, ALP, and glutamate dehydrogenase (GLDH) activities in male rats. Furthermore, plasma cholinesterase activity was significantly decreased (by 60%) in females and plasma creatinine levels were significantly decreased in both sexes. Histological changes in the liver were noted in a dose-dependent manner in animals treated with 15 and 45 mg/kg propynol. No changes were noted at microscopic examination of the kidneys and in urinalysis (Mih84). In a second study described in the same report, the suggested direct action of propynol on microsomal liver enzymes was addressed in a 4-week gavage study in Bor:WISW (SPF:Cpb) rats. Fifteen animals/sex were daily administered 60 mg/kg bw propynol. Because of the occurrence of marked symptoms of toxicity (apathy, atonia, bloody salivation) and the death of one of the 15 treated male rats, the daily dose was lowered to 50 mg/kg bw from day 4 to 21. From day 22 to 28, animals were given 60 mg/kg bw propynol again. After 28 days, the treated animals displayed decreased body weight, increased relative liver and kidney weights, and haematological changes comparable to the first experiment. No effects were noted in urinalysis. Clinical chemistry analysis indicated increased plasma activities of ALAT, GLDH, ALP, and γ-glutamyl transferase in both sexes and of aspartate aminotransferase in males. Plasma cholinesterase activity was decreased in females. Creatinine levels were decreased in both sexes, whereas urea nitrogen levels were increased in females. In liver tissue, the activities of *N*-demethylase (both sexes), *O*-demethylase (males), and cytochrome P450 (both sexes) were significantly decreased. Triglyceride levels were not affected in liver tissue. In addition, macroscopic changes were noted in the liver of males, whereas microscopic changes (e.g., focal necrosis, increased mitotic rates in liver parenchyma, and unusual mitotic figures) were noted in all treated animals (Mih84). Based on these results, Mihail et al. concluded that

propynol has a specific effect on liver mixed function oxidases and induces liver cell damage. Other effects were on red blood cells and the kidneys. Because the changes in relative liver and kidney weights at 5 mg/kg bw were not accompanied by clinical chemistry or histological changes, the authors considered this dose level to be a 'limit dose'. However, the committee concludes that the effects noted at 5 mg/kg bw are toxicologically significant, since the organ weight effects were dose-dependent and statistically significantly increased. Moreover, at higher dose levels, they were accompanied by changes in clinical chemistry and histology. Therefore, the effects noted at the lowest dose level were judged to be a precursor stage of the effects noted at the higher dose levels. In conclusion, the committee considers 5 mg/kg bw dose level to be a LOAEL for 4-week oral exposure to propynol.

In rabbits, no mortality occurred following administration of propynol of 9.7 mg/kg bw/day, 5 days/week, for 4 weeks, while all animals died within 9-23 days at doses of 18.9 mg/kg bw. Examination of the dead animals showed dilation of the peripheral vessels, signs of lung congestion and oedema, haemorrhages in the gastrointestinal tract and heart, and slight histological changes in the liver and the kidneys (BCG00; unpublished study not available to the committee).

Two cats given oral doses of 9.7 mg/kg bw, 5 days/week, died on treatment 16 and 17, animals showing liver and kidney damage upon post-mortem examinations. Toxic signs and effects included vomiting, loss of appetite, weight loss, and considerably disturbed liver function (in one cat) (BGC00).

Subchronic exposure

Propynol vapour was tested for its inhalation toxicity in Wistar rats in a 90-day study performed in accordance with OECD guideline 413 ('Subchronic inhalation toxicity; 90-day study'). Ten animals/sex/group were exposed to concentrations of propynol (purity: 99.4%) of 0, 1, 5, or 25 ppm (0, 2.3, 11.5, or 57.5 mg/m^3, respectively; 6 hours/day, 5 days/week, total 65 'whole body' exposures). Parameters examined included clinical signs, body weight, ophthalmology, blood chemistry, haematology, and macroscopic and microscopic evaluation. At 25 ppm, body weight gain was retarded in males (during the first 2 weeks of the exposure period), relative kidney and liver weights were increased in males and females, and serum cholinesterase activity was decreased in females. No other abnormalities were observed upon macroscopic and microscopic evaluations. At 1 and 5 ppm, no treatment-related effects were noted. The NOAEL for 90-day inhalation toxicity of propynol in rats was concluded to be 5 ppm (11.5 mg/m^3) (BGC92, BGC00).

Rats (n=12/sex/group) that inhaled 80 ppm (184 mg/m^3) propynol, 7 hours/day, 5 days/week, for 3 months, initially appeared to have eye irritation and to be lethargic. Relative liver weights in males and relative liver and kidney weights in females were increased by 18%, 43%, and 17%, respectively. Other organ weights appeared normal. Histological examination showed hepatic and renal degeneration. There was a statistically significant elevation of white blood cell counts with no change in red blood cells (counts, haemoglobin, haematocrit). In females, lymphocyte counts were significantly increased, whereas differential counts in males were normal. Terminal serum alkaline phosphatase and urea nitrogen values were normal, but ALAT values were increased. Bone marrow smears were considered normal (Tor64, only limited data description).

In a dermal study, propynol was applied to the abraded or intact skin of young adult rabbits at daily doses of 1 or 3 mg/kg bw/day over a 90-day period, or 10 mg/kg bw/day for day 1-62 and subsequently 20 mg/kg bw/day for day 63-90. No systemic effects (including body weight gain, haematology, and histology) were noted (Git65).

Male and female Crl:CD(SD)BR rats (n=30/sex/group) were dosed orally (gavage) with 0, 5, 15 or 50 mg/kg bw of propynol (purity: >99%) (at 10 mL/kg in deionised water) daily for 13 weeks. The first 10 rats of each group were sacrificed on days 28-29 after dosing and the remaining rats were sacrificed on days 91 or 92 after dosing. Parameters examined included clinical signs, body and organ weight changes, food consumption, ophthalmology, haematology, blood chemistry and histological evaluations. Treatment-related mortality was reported for 4/30 males in the high-dose group. The most prevalent clinical sign was salivation, occurring mainly at 50 mg/kg bw. Body weights were significantly lower in the high-dose animals. Haematological changes observed in the high-dose animals comprised decreased haemoglobin, MCV (also at 15 mg/kg bw), MCH, and mean corpuscular haemoglobin concentration (MCHC) values. Enzyme changes characteristic of liver damage were seen in the mid- and high-dose animals. These changes included significantly increased ALAT, ASAT, LDH, and ALP serum activities. Moreover, decreased glucose, sodium, total cholesterol, total protein, albumin, globulin, and creatinine serum levels were seen, whereas inorganic phosphate and total bilirubin serum levels were significantly higher. The haematological and blood chemistry changes were considered to be treatment-related. Absolute and relative liver and kidney weights were significantly increased in males and/or females at 15 and 50 mg/kg bw/day. At 5 mg/kg bw, mean absolute and relative liver weights were higher compared to controls, but statistical significance was not reached. Macroscopic findings were confined to the liver (15 and 50 mg/kg bw) and the stomach (50

mg/kg bw). Hepatocytic megalocytosis with a less prominent proliferation of the bile ducts and cytoplasmic vacuolation of hepatocytes was observed in the majority of rats in the mid- and high-dose groups. In the low-dose group, megalocytosis was seen only in one rat treated for 3 months. Karyomegaly of renal tubular epithelial cells was reported to occur in a dose-response fashion in the mid- and high-dose groups, but not in the low-dose group. Treatment-related effects at 15 mg/kg bw included increased liver weights in both genders, increased kidney weights in females, and megalocytosis of the liver after 4 and 13 weeks of dosing. The daily oral administration of 5 mg/kg bw/day of propynol produced no apparent treatment-related effects and hence this dose level was considered a NOAEL for subchronic oral exposure to propynol (Mar88).

Chronic toxicity and carcinogenicity

The committee did not find data from chronic toxicity, including carcinogenicity, studies on propynol.

Mutagenicity and genotoxicity

Propynol (tested at 4-2500 µg/plate) was negative in mutagenicity tests in *S. typhimurium* strains TA97, TA98, TA100, TA102, TA1535, TA1537, and TA1538 with and without metabolic activation. At high concentrations (>500 µg/plate), the product was cytotoxic. Propynol was weakly mutagenic to one unusual strain of *S. typhimurium,* D3052 (BGC00, Bla94, Lin94).

Propynol induced chromosomal aberrations in CHO cells *in vitro* when tested with and without metabolic activation (Bla94).

In vivo, propynol (purity: 97%) did not induce an increase in micronuclei in bone-marrow cells of male and female C57BL mice given oral (gavage) doses of 24, 48, and 72 mg/kg bw for 2 days. The high dose caused mortality preventing evaluation of the bone marrow for micronuclei (Bla94). Similarly, negative results were obtained in male and female NMRI mice given single oral (gavage) doses of 70 mg/kg bw (purity: 99.4%). In preceding experiments, this dose was found to be the maximum dose tolerated (BCG00).

Reproduction toxicity

The committee did not find data from reproduction or developmental toxicity studies on propynol.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for propynol in the Netherlands is 2 mg/m^3 (1 ppm), 8-hour TWA, with a skin notation.

Existing occupational exposure limits for propynol in some European countries and in the USA are summarised in Annex IV.

8 Assessment of health hazard

The committee did not find data on the biotransformation and kinetics of propynol following inhalation or dermal exposure. Following oral administration of radiolabelled compound to rats and mice, 56-60% of the radiolabel administered was excreted in the urine within 96 hours. Analysis of the urinary metabolites indicated quantitative and qualitative differences in their formation between rats and mice. In rats, metabolism might involve oxidation into 2-propynoic acid and multiple glutathione additions to the carbon-carbon triple bond yielding numerous metabolites. In mice, glucuronide conjugation to form 2-propyn-1-ol glucuronide as well as oxidation into 2-propynal which undergoes either multiple glutathione additions or oxidation into 2-propynoic acid (only ca. 2%) might occur. *In vitro* experiments suggested metabolic activation by cytochrome P450 2E1 rather than catalase or alcohol dehydrogenase.

Propynol has a dose-dependent irritant to corrosive effect on the skin, eyes, and respiratory tract of animals. It has no skin-sensitising properties. Based on lethal toxicity data, the committee considers propynol as toxic following inhalation, dermal, and oral exposure.

Subchronic (13-week) exposure of animals to propynol by inhalation to 25 ppm (57.5 mg/m^3) and 80 ppm (184 mg/m^3) or by gavage to 15-50 mg/kg bw/day caused haemotological changes and liver and kidney damage. Irritation was observed after inhalation exposure but was not addressed in oral studies. Haemorrhages occurred in several organs, irrespective of the route of administration. Considerable mortality was observed in several species after intermittent exposure to 100 ppm (230 mg/m^3) for 75 days. Dermal application of propynol to the abraded or intact skin of young adult rabbits at daily doses of 1

or 3 mg/kg bw/day over a 90-day period, or 10 mg/kg bw/day on day 1 to 62 and subsequently 20 mg/kg bw/day on day 63 to 90, did not induce systemic toxicity.

An NOAEL of 5 ppm (11.5 mg/m^3) was derived from a 90-day inhalation study in rats, based on the occurrence of liver and kidney effects at the next higher dose level (25 ppm). No respiratory irritation was observed in rats and mice after 14-day exposures to 10 (23 mg/m^3) and 25 ppm (57.5 mg/m^3), respectively, while an oral NOAEL for systemic effects was set at 5 mg/kg bw in rats after a 13-week exposure.

In mutagenicity tests with *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, propynol was negative. In the unusual strain D3052, a weakly positive effect was noted. Propynol induced chromosomal aberrations in CHO cells *in vitro* when tested with and without metabolic activation. *In vivo,* it did not induce an increase in micronuclei in bone-marrow cells in two strains of mice at oral (gavage) doses up to 72 mg/kg bw.

The committee did not find data on the long-term, including carcinogenicity, or reproduction toxicity of propynol.

The committee takes the NOAEL of 11.5 mg/m^3 from the 90-day inhalation study in rats (BGC92, BGC00) as a starting point for deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, the committee establishes an overall assessment factor of 18. This factor covers the following aspects: inter- and intraspecies variation and the duration of exposure. Comparison of the results of the 14-day and 90-day inhalation studies and the 4-week and 13-week oral studies in rats indicate that the nature and severity of effects are not significantly affected by prolonged exposure which justifies a small factor for the duration of exposure. Thus, applying this factor and the preferred-value approach, a health-based occupational exposure limit of results in a HBROEL of 0.5 mg/m^3 (0.2 ppm) is recommended for propynol.

The committee recommends a health-based occupational exposure limit (HBROEL) for prop-2-yn-1-ol of 0.5 mg/m^3 (0.2 ppm), as an 8-hour time-weighted average (TWA).

Because dermal lethality data in rabbits indicate that prop-2-yn-1-ol is readily absorbed through the skin, a skin notation is recommended.

References

ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Propargyl alcohol. In: Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati OH, USA: ACGIH®, 1991; 1290-1.

ACG04a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2004. Cincinnati OH, USA: ACGIH®, 2004: 121.

ACG04b American Conference of Governmental Industrial Hygienists (ACGIH). 2004 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, 2004: 47.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 49 (At-vejledning C.0.1).

Ban99 Banijamali AR, Xu Y, Strunk RJ, et al. Identification of metabolites of [1,2,3-^{13}C]propargyl alcohol in rat urine by ^{13}C NMR and mass spectrometry. J Agric Food Chem 1999; 47: 1717-29.

Ban00 Banijamali AR, Xu Y, DeMatteo V, et al. Identification of metabolites of [1,2,3-^{13}C]propargyl alcohol in mouse urine by ^{13}C NMR and mass spectrometry and comparison to rat. J Agric Food Chem 2000; 48: 4693-710.

BGC92 Berufsgenossenschaft der Chemischen Industrie (BG Chemie). Study on the inhalation toxicity of propargylalkohol as a vapour in rats, 90-day test. Heidelberg, FRG: BG Chemie, 1992 (study performed by BASF AG, Department of Toxicology, Ludwigshafen, FRG by order of BG Chemie ; project no: 501969/88100; confidential report submitted to the committee by BG Chemie).

BGC00 Berufsgenossenschaft der Chemischen Industrie (BG Chemie). Propargylalkohol. CAS-Nr 107-19-7. Heidelberg, FRG: BG Chemie, 2000; Toxikologische Bewertung Nr. 116.

Bla94 Blakey DH, Maus KL, Bell R, et al. Mutagenic activity of 3 industrial chemicals in a battery of in vitro and in vivo tests. Mutat Res 1994; 320: 273-83.

DeM94 DeMaster EG, Dahlseid T, Redfern B. Comparative oxidation of 2-propyn-1-ol with other low molecular weight unsaturated and saturated primary alcohols by bovine liver catalase in vitro. Chem Res Toxicol 1994; 7: 414-9.

DFG04 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2004. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag GmbH & Co. KGaA, 2004: 99 (rep no 40).

Eas64 Eastman Kodak Co: Lab Ind Med. Toxicity and health hazard summary for 2-propyn-1-ol with cover letter dated 042886. Rochester NY, USA: Eastman Kodak Co, 1964, (report submitted to US EPA; availabe from NTIS, Springfield VA, USA: order no OTS0510348).

EC04 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs). http://europe.eu.int/comm/employment_social/health_safety/areas/oels_en.htm.

Git65 Gittes HR, Shelanski MV. 90-Day chronic skin absorption study with propargyl alcohol with cover letter dated 041086. Midland MI, USA: Dow Chem Co, Ind Bio Labs Inc, 1965 (report submitted to US EPA; availabe from NTIS, Springfield VA, USA; order no OTS0510181).

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), UK: HSE Books, 2002: 24.

Ken91 Kennedy GL, Graepel GJ. Acute toxicity in the rat following either oral or inhalation exposure. Toxicol Lett 1991; 56: 317-26.

Kom89 Komsta E, Secours VE, Chu I, et al. Short-term toxicity of nine industrial chemicals. Bull Environ Contam Toxicol 1989; 43: 87-94.

Lin94 Lington AW, Bevan C. Propargyl alcohol. In: Clayton GD, Clayton FE, eds. Toxicology 4th ed. New York, USA: J. Wiley & Sons, 1994: 2727-9 (Patty's industrial hygiene and toxicology; Vol II, Pt D).

Mar88 Markiewicz VR, Payne BJ. Rat oral subchronic toxicity study with propargyl alcohol. Muskegon MI, USA: Toxicity Research Laboratories Ltd, 1988.

Mih84 Mihail F, Luckhaus G, Nash G. Propargylalkohol. Subakute orale Toxizitätsversuche an Ratten. Wuppertal-Elberfeld, Germany: Bayer AG, Institut für Toxikologie, 1994; report no 12653.

Mor01 Moridani MY, Khan S, Chan T, et al. Cytochrome P450 2E1 metabolically activates propargyl alcohol: propiolaldehyde-induced hepatocyte toxicity. Chem Biol Interact 130-132: 931-42.

NLM04 US National Library of Medicine (NLM), ed. Propargyl alcohol. In: The Hazardous Substances Data Bank (HSDB) (last revision date propynol file: March 2003; last review date: June 1992); http://toxnet.nlm.nih.gov.

Ols57 Olson KJ. Range finding skin absorption tests on propargyl alcohol with cover letter dated 060986. Midland MI, USA: Dow Chem Co, Dow Biochem Res Lab, 1957 (report submitted to US EPA; availabe from NTIS, Springfield VA, USA; order no OTS0510183).

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW04 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2004. The Hague, the Netherlands: Sdu Uitgevers, 2004: 39.

Ter89 Terrill JB. Acute inhalation study with propargyl alcohol in the rat with cover letter dated 040489. Rockville MD, USA: Hazleton Lab, 1989 (report submitted to US EPA by GAF Chemicals Corp, Wayne NJ, USA; availabe from NTIS, Springfield VA, USA; order no OTS0516716).

Tor64 Torkelson TR. Results of repeated exposure of male and female rats to 80 ppm of propargyl alcohol in air with cover letter dated 041086. Midland MI, USA: Dow Chem Co, Dow Biochem Res Lab, 1964 (report submitted to US EPA; availabe from NTIS, Springfield VA, USA; order no OTS0510182).

TRG04 TRGS 900. Technische Regeln für Gefahrstoffe. Grenzwerte in der Luft am Arbeitsplatz. BArbBl 2004; (7/8).

Ver77 Vernot EH, MacEwen JD, Haun CC, et al. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol Appl Pharmacol 1977; 42: 417-23.

Zis95 Zissu D. Histopathological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. J Appl Toxicol 1995; 15: 207-13.

Annex I

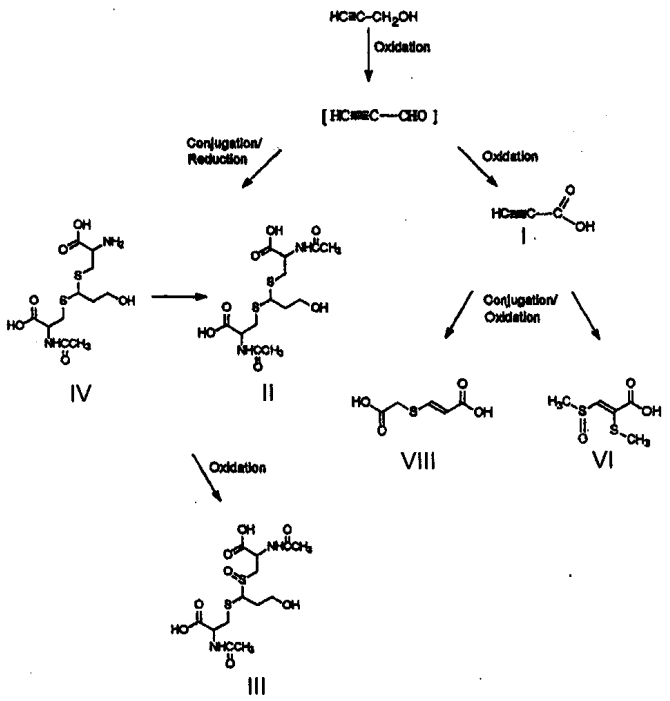

Figure 1 Metabolism scheme of propynol in rats (Ban00) (Roman numericals refer to names in Annex III).

Annex II

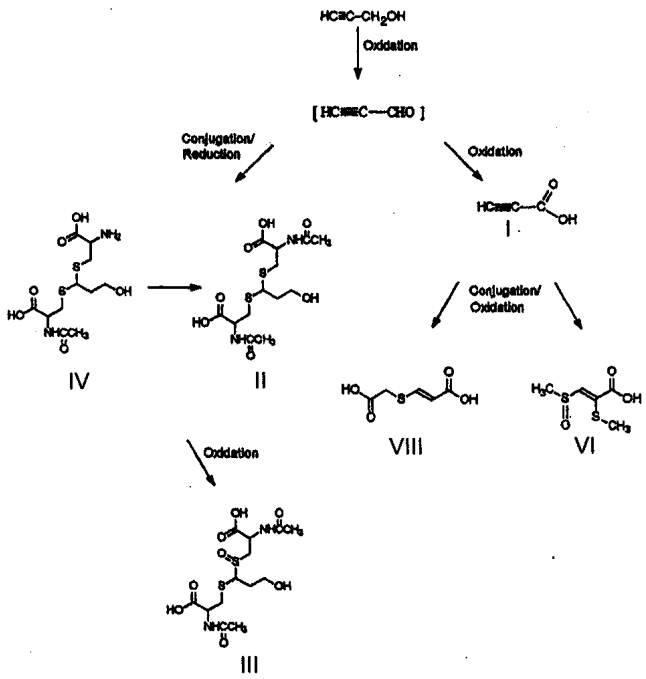

Figure 2 Metabolism scheme of propynol in mice (Ban99).
(Roman numericals refer to names in Annex III)

Annex III

Metabolites of propynol in rats and mice as % of total urinary radioactivity in first 24-h urine (Ban99, Ban00).

metabolite		rat	mouse
2-propynoic acid	I	27	ca. 2
3,3-bis[(2-(acetylamino)-2-carboxyethyl)thio]-1-propanol	II	20	6
3-[[2-(acetylamino)-2-carboxyethyl]sulphinyl]-3-[[2-(acetylamino)-2-carboxyethyl]thio]-1-propanol	III	15	0
3-[[2-(acetylamino)-2-carboxyethyl]thio]-3-[[2-(amino)-2-carboxyethyl]thio]-1-propanol	IV	8	17
3,3-bis[(2-(amino)-2-carboxyethyl)thio]-1-propanol	V	0	15
2-(methylsulfinyl)-3-(methylthio)-2-propenoic acid	VI	7	0
propynol glucuronide	VII	0	6
3-(carboxymethylthio)-2-propenoic acid	VIII	20	0
(*E* + *Z*)-3-[(2-amino-2-carboxyethyl)thio]-2-propenoic acid	IX	0	41
3-[(2-formylamino-2-carboxyethyl)thio]-2-propenoic acid	X	0	13

Annex IV

Occupational exposure limits for propynol in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	1	2	8 h	administrative	S	SZW04
Germany						
- AGS	2	4.7	8 h			TRG04
	4	9.4	15 min			
- DFG MAK-Kommission	2	4.7	8 h		S,[d]	DFG04
	4	9.4	15 min[c]			
Great-Britain						
- HSE	1	2.3	8 h	OES	S	HSE02
	3	7.0	15 min			
Sweden	-	-				Swe00
Denmark	1	-	8 h		S	Arb02
USA						
- ACGIH	1	-	8 h	TLV	S	ACG04b
- OSHA	-	-	8 h	PEL	S	ACG04a
- NIOSH	1	2	10 h	REL	S	ACG04a
European Union						
- SCOEL	-	-				EC04

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Maximum number per shift:: 4, with a minimum interval between peaks of 1 hour.

[d] Listed among substances with MAK values but no pregnancy risk group classification.