3-Methylbutan-1-ol

(CAS No: 123-51-3)

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/085, The Hague, 22 October 2003

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. 3-Methylbutan-1-ol; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, jaartal; 2000/15OSH/2003.

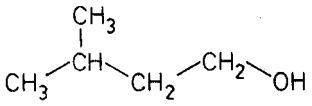
1 Introduction

The present document contains the assessment of the health hazard of 3-methylbutan-1-ol 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 AAE Wibowo, Ph.D. (Coronel Institute of the Academic Medical Centre, Amsterdam, the Netherlands).

In October 1997, literature was searched in the on-line databases Medline, Toxline, Embase, and Chemical Abstracts starting from 1966, 1967,1988, and 1970, respectively. CD-ROM versions of the databases HSELINE, CISDOC, MHIDAS, and NIOSHTIC (covering the period 1985/87 until 1997) were also consulted. The following key words were used: isoamyl alcohol and 123-51-3. The final literature search was carried out in Toxline and Medline in November 2002.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	3-methylbutan-1-ol
synonyms	:	Isoamyl alcohol; isopentanol; isopentyl alcohol; isobutyl carbinol; primary isoamyl alcohol
molecular formula	:	$C_5H_{12}O$
structural formula		
CAS number		123-51-3

3 Physical and chemical properties

molecular weight	:	88.2
boiling point	:	131°C
melting point	:	-117.2°C
flash point	:	43°C (closed cup)
vapour pressure	:	at 20°C : 0.37 kPa
solubility in water	:	slightly soluble (at 14°C: 2.0 g/100mL)
log $P_{octanol/water}$	:	1.16 (experimental); 1.26 (estimated)
conversion factors	:	at 20°C, 101.3 KPa: 1 mg/m^3 = 0.27 ppm 1 ppm = 3.67 mg/m^3

Data from ACG99, BGC90, NLM01, http://esc.syrres.com.

3-Methylbutan-1-ol is an oily colourless liquid, with a characteristic odour and a pungent, repulsive taste (ACG99). An air odour threshold of 0.15 mg/m^3 (0.042 ppm) has been reported (Amo83).

4 Uses

3-Methylbutan-1-ol is used in the manufacture of photographic chemicals and pharmaceutical products, as a solvent for oils, fats, resins, and waxes, as a component of paint stripper, and in the plastics industry in the spinning of polyacrylonitrile (ACG99, BGC90). 3-Methylbutan-1-ol is the primary constituent of fusel oil, a by-product of alcoholic carbohydrate fermentation (ACG99).

5 Biotransformation and kinetics

The respiratory uptake defined as ($C_{inhaled\ air} - C_{mixed\ exhaled\ air}/C_{inhaled\ air}$x100% for 3-methylbutan-1-ol was determined by exposing 4 healthy male volunteers to ca. 92 mg/m^3 (25 ppm) 3-methylbutan-1-ol at rest for 10 minutes. The percentage solvent in end-exhaled air and in mixed-exhaled air increased after the start of the exposure and reached a quasi-steady-state level within a few minutes. The mean respiratory uptake for the last 5 minutes of 3-methylbutan-1-ol respiration was 63% (Kum99). In rats, the nasal uptake for 3-methylbutan-1-ol was estimated to be 80%, using physiologically-based pharmacokinetic modelling

(PB-PK) in which nasal enzyme distribution as well as nasal airflow patterns were incorporated. Morris et al. concluded that gender differences in the upper respiratory tract deposition might not be widespread among vapours (Mor91, Mor93).

Data on biotransformation and excretion of 3-methylbutan-1-ol were summarised by BG Chemie (BGC90) and Lington and Bevan (Lin94). Generally, both in humans and experimental animals, the compound is rapidly oxidised in the liver to its corresponding aldehyde and acid (3-methylbutanal or isovaleraldehyde and 3-methylbutanoic acid or isovaleric acid) following oral or parental administration. Shortly after administration, no or only very low levels of parent compound were found in the blood. As a minor pathway, the compound can be conjugated directly with glucuronic acid. In rabbits given a single oral dose of 2200 mg/animal, 9% of the dose was excreted in the urine within 24 hours, as the glucuronide conjugate (identified as triacetyl-ß-isoamylglucuronide methyl ester) (BGC90, Lin94). Following intraperitoneal injections of 1000 mg/kg bw to rats, small amounts of 3-methylbutan-1-ol were excreted in exhaled air and urine (0.97 and 0.27 of total dose, respectively). The maximum blood concentrations (measured at the first time point at t=1 h) were ca. 36 mg/100 mL, and the alcohol disappeared from the blood in less than 5 hours (Hag45). Similar findings were reported following oral doses of 3-methylbutan-1-ol of 2 g/kg bw. One hour after administration, a maximum blood level of parent compound of 17 mg/100 mL was found, with only trace amounts detectable after 4 hours (ca. 1 mg/mL); no parent compound was detected in the urine (BGC90, Lin94). From *in vitro* experiments studying the solubility of 3-methylbutan-1-ol in rabbit and human tissues, it was concluded that contrary to short-chain primary alcohols (methanol, ethanol), 3-methylbutan-1-ol was distributed in aqueous as well as anhydrous tissues and that there were no basic differences between human and rabbit tissues and between the various types of tissues (BGC90).

In vivo experiments showed that concomitant exposure to ethanol retarded the metabolism of 3-methylbutan-1-ol (BGC90). From *in vitro* experiments, it can be seen that 3-methylbutan-1-ol can interfere with cytochrome-P450-mediated metabolic processes. Louis et al. reported the induction of cytochrome P450 2H1/2 in cultured chick hepatocytes. 3-Methylbutan-1-ol combined with ethanol caused a synergistic induction of P450 2B1/2 in cultured rat hepatocytes and an additive to synergistic induction of P450 2H1/2 in cultured chick hepatocytes (Lou93). Kostrubsky et al. reported that 3-methylbutan-1-ol was more potent in the induction of cytochrome P450 in human hepatocytes than was previously shown in rat hepatocytes (Kos95). Genetic factors (ethnic

predisposition) may retard metabolism as well: in Orientals having a deficiency in low K_m aldehyde dehydrogenase isoenzyme oxidation of the aldehyde is delayed (Wil85a).

6 Effects

Human data

In a volunteer study, the majority of the male and female subjects (n=10) found exposure to calculated, nominal concentrations of 3-methylbutan-1-ol of 367 mg/m^3 (100 ppm) and 551 mg/m^3 (150 ppm), for 3 to 5 minutes, irritating to the throat and irritating to the eyes and nose, respectively. The extent of irritation was scored subjectively using 3 categories: no, slight, and very. Test vapours were generated by either continuously adding a known quantity of vapour-saturated air to a measured flow of air in case of volatile solvents or by dropping at a known rate on to a hot plate and introducing the resulting vapour into the air supply system in case of less volatile solvents (Nel43). Irritation of the throat was reported in a respiratory uptake study in which 4 healthy male volunteers were exposed through a mouthpiece to ca. 92 mg/m^3 (25 ppm) 3-methylbutan-1-ol for 10 minutes (Kum99). The committee considers the results of these studies not suitable for assessing an irritation-concentration relationship because of methodological flaws (subjective criteria, lack of detailed information on generating vapours and controlling and measuring of concentrations in the Nelson study, and direct introduction into the throat by using a mouth piece in the Kumagai study).

Applied at 8% in petrolatum in a 48-hour closed patch test, 3-methylbutan-1-ol did not cause skin irritation in human volunteers (unpublished report submitted to the Research Institute for Fragrance Materials - RIFM -, Inc, Englewood Cliffs NJ, USA, cited by Opd78). No skin sensitisation reactions were reported when a solution of 8% 3-methylbutan-1-ol in petrolatum was tested in 25 volunteers in a maximisation test (unpublished report submitted to RIFM, cited by Opd78). A positive reaction (i.e., the presence of erythema as well as filtration and/or papules-vesicles) to a 10% solution of 3-methylbutan-1-ol (as well as to some other alcohols) was found upon 48-hour epicutaneous testing of various concentrations of agents used for local treatment and routine test substances, among which 3-methylbutan-1-ol, in a 62-year-old housewife with a history of a post-thrombotic leg ulcer with periodic dermatitis for the previous 12 years (Fre63). In patch testing in low K_m aldehyde dehydrogenase

isoenzyme-deficient Oriental subjects, 3-methylbutan-1-ol gave positive results (erythema) caused by its aldehyde metabolite (Wil85a, Wil85b).

Ingestion of 50 to 100 mL 3-methylbutan-1-ol was reported to have induced central nervous system depression, weakness pain, a burning sensation in the chest and stomach, nausea, headache, and sleep within 10 to 15 minutes, and terminal coma and death within 1 hour to 6 days. Asphyxiation was stated to be the cause of death; swollen tissues (brain and all other organs) and gastric mucosa and vascular effects were seen (Opd78).

The committee did not find human data on effects of long-term exposure to 3-methylbutan-1-ol.

Animal data

Irritation and sensitisation

When instilled into the eyes of rabbits, 3-methylbutan-1-ol scored an injury grade of 8 on a scale from 1 to 10, which was defined as producing a certain injury score, representative of 'severe injury', 18 to 24 hours after application of an 'excess' of a 5% solution (Smy69; see also Car46). Slowly diminishing reddening and swelling of the mucous membranes and a mist-like corneal opacity were seen when unknown amount of 3-methylbutan-1-ol was instilled into the eyes of rabbits (unpublished report cited in BGC90).

Following uncovered application of 0.01 mL of undiluted material to the clipped skin (abdomen) of albino rabbits (n=5), 3-methylbutan-1-ol scored an injury grade of 2 on a scale from 1 to 10, which was defined as giving rise to 'the least visible capillary injection from undiluted material' (Smy69; see also Smy62). In 2 separate studies, 3-methylbutan-1-ol was rated as moderately irritant following 24-hour occlusive application to the intact and abraded or scarified skin of rabbits (unpublished study cited in BGC90; unpublished report submitted to RIFM, cited by Opd78).

With respect to the respiratory tract, the sensory irritation in the upper part was studied by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}). Using different strains of mice and different protocols, RD_{50} values of 16,339 and 2624 mg/m^3 (4452, 708 ppm), respectively, were reported for 3-methylbutan-1-ol (Kan80, Mul84; see also Bos92, Sch93).

Acute toxicity

No mortality was found in rats (n=6; sex not indicated) following an 8-hour exposure to 'concentrated vapour' (concentration not reported; observation time: 14 days) (Smy69; see also Smy62) or in rats (n=12; sex not indicated) following a 7-hour exposure to an 'enriched atmosphere' (concentration not reported) (unpublished study cited in BGC90). In the latter study, panting and loss of pain reflex were reported (BCG90).

A dermal LD_{50} of 3.97 mL/kg bw (i.e., ca. 3200 mg/kg bw) has been reported for rabbits (24-hour covered application; observation time: 14 days) (Smy69; see also Smy62).

Oral LD_{50} values are presented in Table 1. In rabbits, the ND_{50} (narcotic dose; i.e., the dose producing stupor, loss of voluntary movements in half of the animals) was ca. 705 mg/kg bw (8 mMol/kg) (Mun72).

Table 1 Acute lethal oral toxicity data for 3-methylbutan-1-ol.

species	LD_{50} (mg/kg bw)	remarks	reference
rat (Carworth-Wistar; male; n=5)	5720	observation time: 14 days	Smy69; see also Smy62
rat (Sprague-Dawley; n=5/ sex)	>5000	doses administered: 2150, 5000 mg/kg; mortality in 1/5 females in each group; symptoms: dyspnoea, apathy, staggering, atonia, pareses of rear extremities, poor general condition; observation time: 14 days	BGC90 (unpublished study)
rat (male, female)	male: 1300 female: 4000	degenerative changes in liver and kidneys; observation time: 10 days	BCG90
rabbit (male, female)	3440		Mun72

Following intravenous injection, an LD_{50} of about 230 mg/kg bw was determined in 7-8-week-old female mice (BGC90) while in rabbits, 1570 mg/kg bw was reported to be the minimal lethal dose (Opd78).

Intraperitoneal injections of doses of 3-methylbutan-1-ol of 700 mg/kg bw caused mortality in 3/5 male and 3/5 female mice. Toxic symptoms were similar to those found after oral administration (see Table 1) (unpublished study cited in BGC90).

Repeated-dose toxicity including carcinogenicity

In a range-finding study, rats (SPF-Wistar; n=3/sex/group) were given 3-methylbutan-1-ol (purity: >98%) in the drinking water at concentrations of about 1360 mg/kg bw for 2 weeks and of 1160 mg/kg bw for the next 2 weeks (20,000 and 16,000 ppm, respectively). Treatment did not affect body weight gain or food consumption. In the females, there was a reduction in water consumption during the first 2 weeks, but no difference among treated and control animals was found during the next 2 weeks when the dose was lowered. No treatment-related effects were seen upon gross post-mortem examination. Based on the palatability problems observed in females at 20,000 ppm, the authors concluded that the maximum drinking water concentration that could be tested would be 16,000 ppm. In the subsequent 90-day study, performed according to OECD Guideline 408 and OECD GLP principles, animals (n=10/sex/group) were given daily drinking water concentrations of 0, 1000, 4000, and 16,000 ppm (males: 0, 73, 295, 1068 mg/kg bw/d; females: 91, 385, 1657 mg/kg bw/d). Treatment did not induce any effect on mortality, body weight, various clinical chemistry parameters, or organ weights or any abnormality at gross and microscopic examination. The only effects found were marginal increases in red blood cell counts in the male animals of the mid- and high-dose groups (8.18±0.37 and 8.41±0.38x10^{12}/L, respectively, vs. 7.76±0.20x10^{12}/L in controls; $p<0.05$ and <0.01, respectively) and slight decreases in mean corpuscular volume (by 4.3%; $p<0.05$) and in mean corpuscular haemoglobin content (by 5.7%; $p<0.01$) in the male animals of the high-dose group (Sch97). The committee concludes that in this 13-week drinking water study in rats, 1068 and 1657 mg/kg bw/day, the highest levels tested, are the NOAELs for males and females, respectively.

In a separate study, Ash/CSE rats were 3-methylbutan-1-ol by oral intubation at daily (7 days/week) doses of 0, 500, or 1000 mg/kg bw, for 3 or 6 weeks (n=5/sex/group), or to 0, 150, 500, or 1000 mg/kg bw, for 17 weeks (n=15/sex/group). Parameters/end points included clinical observations, body weights, food and water consumption, haematology, clinical chemistry, urinalysis, organ weights (brain, heart, liver, spleen, stomach, small intestine, caecum, adrenals, gonads, pituitary, and thyroid), and macroscopic and microscopic evaluation. Apart from 2 high-dose rats dying from lung congestion, claimed to be caused by accidental introduction of the test substance into the lungs, no deaths or abnormalities in behaviour occurred during the experiment in any of the groups. In male rats dosed with 1000 mg/kg bw for 3 weeks, the absolute weights of most organs and the terminal body weights were significantly lower than those of controls. The

males dosed with 500 mg/kg bw for 3 weeks had significantly lower absolute brain, kidneys, stomach, small intestine, and testes weights. When expressed relative to body weight, only the relative testes weights were decreased. No effects were seen in females exposed for 3 weeks. After 6 weeks of treatment, the only effect observed was a decrease in absolute pituitary weight in male rats receiving 1000 mg/kg bw. Treatment for 17 weeks induced slight decreases in body weight (gain) in the high-dose male animals, being statistically significant from week 9 onwards, which were ascribed to a consistently 5-10% lower food intake (when compared to controls) during the first 6 weeks. No other consistent, compound-related effects were seen in any of the groups exposed for 17 weeks. To investigate the changes in organ weights, the authors performed a 3-week pair-feeding study. Eight male rats received daily doses of 1000 mg/kg bw in corn oil and were fed *ad libitum* while 2 other groups of 8 male rats were both given corn oil and pair-fed to the exposed group and fed *ad libitum*, respectively. There were no differences in absolute or relative weights of any organ among these groups. Body weight gains of the treated group and pair-fed controls were similar but slightly less than those of controls given free access to food indicating that the body weight decreases in the 17-week experiment are most likely to be due to a reduced food intake rather than a toxic effect of 3-methylbutan-1-ol (Car73). In agreement with Carpanini et al., the committee concludes that oral exposure of rats to doses up to 1000 mg/kg bw/day, the highest level tested, for 17 weeks, was not accompanied by adverse effects.

Gibel et al. (Gib75) studied the potential carcinogenicity of 3-methybutan-1-ol (an analytical grade, double-distilled batch was tested; purity: unknown) in male and female Wistar rats. Doses of 0.1 and 0.04 mL/kg bw (i.e., ca. 81 and 32 mg/kg bw) were given orally twice a week to a total of 15 or subcutaneously once a week to a total of 24 animals, respectively (mean total doses 27 and 38 mL or 21,843 and 30,742 mg/kg, respectively, suggesting experimental dosing periods of 135 and 95 weeks, respectively). All animals were observed until they died naturally. The average survival times were 527 and 592 days for the oral and subcutaneous route, respectively, vs. 643 in oral and subcutaneous control male and female animals (n=25/dosing route). Oral administration induced 4 malignant tumours: 2 liver cell carcinomas, 1 forestomach carcinoma, and one myeloid leukaemia. Following subcutaneous administration, a total of 10 malignant tumours were reported: one liver carcinoma, one liver sarcoma, one spleen sarcoma, one glandular stomach carcinoma, and 2 myeloid leukaemias. No malignant tumours were found in the respective control groups. Benign tumours, mostly forestomach papillomas and papillomatosis and mammary

fibroadenomas, were found in 3/15 orally and in 5/24 subcutaneously treated animals vs. 3/25 and 2/25 in their respective controls. Furthermore, 'nearly all rats' showed liver damage including congestion, steatosis, necrosis, fibrosis, cirrhosis, and metaplasia, hyperplasia of the haematopoietic bone marrow parenchyma, and spleen metaplasia (Gib75).The committee noted the small numbers of animals used in the experiments, the unknown sex ratios in the experimental groups, the irregular pattern of administration, the lack of statistical analysis, the exceeding of the maximum tolerated dose as evidenced by the effects on the liver and the haematopoietic system, and the poorly detailed description of neoplastic and non-neoplastic effects. Despite the flaws in design, the committee recommends confirmation of this study

Mutagenicity and genotoxicity

Reporting on 29 chemicals including food additives in an abstract without presenting experimental details suggested that 3-methylbutan-1-ol was negative when tested in the presence and absence of a metabolic activation system in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (spot test and plate incorporation assay) (Slo82). It did not induce mutations in the HPRT assay in the Chinese hamster lung fibroblast cell line V79 when tested with and without the addition of a metabolic activation system at an adequate dose range (Sei99). 3-Methylbutan-1-ol did not induce DNA damage (strand breaks; alkali-labile sites) in blood cells obtained from healthy volunteers in the Comet assay (Sei99).

In vivo, a positive effect was found in bone marrow cells from rats (n=8) sacrificed 48 hours after a single intragastric dose of 1/5 LD_{50}. Results of cytogenetic analyses (a total of 500 cells examined) showed increases in the number of cells with chromosomal aberrations (2.6±0.7% vs. 0% in controls) while no changes were found in the number of polyploid cells (0.6±0.3% vs. 0.5±0.3%) and cells with chromosome gaps (0.4±0.2% vs. 0.3±0.2%) (Bar88).

1-Methylbutan-1-ol inhibited metabolic cooperation between 6-thioguanine-sensitive and resistant Chinese hamster V79 cells (Che84), a phenomenon thought to reflect carcinogenic promotion ability and not to be indicative of genotoxic potential (WHO90).

Reproduction toxicity

Klimisch and Hellwig studied the prenatal toxicity of 3-methylbutan-1-ol by exposing female rats (Wistar; n=25/group) and rabbits (Himalayan; n=15/group) to concentrations of 0, 500, 2500, and 10,000 mg/m^3 (0, 135, 675, 2700 ppm), 6 hours/day, on gestational days 6-15 and 7-19, respectively. All rats and rabbits were killed on study days 20 and 29, respectively. In both species, maternal toxicity manifested by slight retardation of body weight gain during the first days of the exposure period was observed in the animals of the high-concentration groups. The rabbits of this group had eye irritation (reddish, lid closure, or slight discharge) during exposure. There were no compound-related signs of embryo/ fetotoxicity or teratogenicity in any of the treated rat groups. In rabbits, there was a statistically significantly increased incidence of total fetal soft tissue variations that was mainly caused by a significant increase in the incidence of 'separated origin of carotids'. Because figures were within the range of biological variation and unexpectedly low in control animals, Klimisch and Hellwig considered these findings to be incidental (Kli95). From this study, the committee concludes the NOAEL for maternal toxicity in both rats and rabbits to be 2500 mg/m^3 (675 ppm), and the NOAEL for developmental toxicity to be 10,000 mg/m^3 (2700 ppm).

7 Assessment of health hazard

Following exposure by inhalation, respiratory uptake was found to be ca. 60% in human volunteers (at exposure to 92 mg/m^3 for 10 minutes) and 80% in rats. Oral and parental human and animal data showed a rapid conversion into its corresponding alcohol and acid. This metabolism may be retarded by concomitant exposure to ethanol or by genetic factors, e.g., the low K_m aldehyde dehydrogenase isoenzyme-deficiency in Orientals resulting in increased aldehyde blood levels.

Unpublished information did not indicate an irritating or sensitising potential, but increased aldehyde levels as occurred in the aforementioned deficient Orientals caused skin irritation.

Although irritation may be an important effect, the committee did not find adequate human data on local as well as systemic effects.

Experimental animal data showed 3-methylbutan-1-ol to be severely irritating to the eyes and hardly or moderately irritating to the skin of rabbits. Eye irritation was observed in (pregnant) rabbits exposed to vapour concentrations of

10,000 mg/m^3 (2700 ppm), 6 hours/day, but not at 2500 mg/m^3 (675 ppm), while these levels were not irritating to rats.

Inhalation exposure of rats to 'concentrated vapours' or 'enriched atmospheres' for 7-8 hours did not result in mortality. A dermal LD_{50} of ca. 3200 mg/kg bw has been reported in rabbits. Oral LD_{50} values were 3440 and 5720 mg/kg bw in rabbits and rats, respectively.

No compound-related, toxicologically relevant effects were found in adequately performed studies in which male and female rats were exposed by oral intubation to doses up to 1000 mg/kg bw/day, 7 days/week, for 17 weeks (Car73), or in the drinking water to doses up to 1068 (males) or 1657 (females) mg/kg bw/day, 7 days week, for 13 weeks (Sch97). Oral administration of ca. 81 mg/kg bw, twice a week, for (probably) 135 weeks or subcutaneous injection of ca. 32 mg/kg bw, once a week, for 95 weeks, induced an increase in the incidence of malignant tumours in rats (4 and 10, respectively). However, due to methodological shortcomings, the committee cannot assess the relevance of these results but verification is recommended. The committee did not find data from subchronic or chronic inhalation studies.

3-Methylbutan-1-ol did not induce mutations in *S. typhimurium* or in Chinese hamster V79 cells or DNA damage (strand breaks; alkali-labile sites) in human blood cells. Single intragastric dosing of rats caused an increase in the number of bone marrow cells with chromosomal aberrations, but not in the number of polyploid cells or cells with chromosomal gaps. 3-Methylbutan-1-ol inhibited metabolic cooperation in Chinese hamster V79 cells, a phenomenon thought to reflect carcinogenic promotion ability and not to be indicative of genotoxic potential.

3-Methylbutan-1-ol did not induce developmental toxicity in rats and rabbits exposed to concentrations up to 10,000 mg/m^3 (2700 ppm) during organogenesis.

From the repeated oral studies by Carpanini et al. (Car73) and Schilling et al. (Sch97), the committee takes 1000 mg/kg bw/day - the highest dose tested - as NOAEL as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week, this NOAEL from continuous (i.e., 7 days/week) exposure studies is adjusted by multiplying with a factor of 7/5, resulting in a NAEL of 1400 mg/kg bw/day. For the extrapolation to a HBROEL, a factor of 4 for the allometric scaling from rat to man, based on basal metabolic rate, and an overall factor of 18, covering inter- and intraspecies variation and differences between the experimental conditions and the exposure pattern of the worker, are applied resulting in an NAEL for humans of 19.4 mg/kg bw/d. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%, and

applying the preferred-value approach, a health-based occupational limit of 100 mg/m^3 (27 ppm) is recommended for 3-methylbutan-1-ol. In view of the - inadequate - human data on irritation (see first paragraph of Chapter 6), the committee expects (nevertheless) that this limit will protect workers from eye and respiratory tract irritation.

The committee recommends a health-based occupational exposure limit for 3-methylbutan-1-ol of 100 mg/m^3 (27 ppm), as an 8-hour time-weighted average (TWA).

References

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Isoamyl alcohol. In: TLVs® and other occupational exposure values -1999. [CD-ROM]. Cincinnati OH, USA: ACGIH®, Inc, 1999.

ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 74.

ACG03b American Conference of Governmental Industrial Hygienists (ACGIH). 2003 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®, Inc, 2003: 36.

Am083 Amoore JF, Hautala E. Odor as aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983; 3: 272-90.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 34 (At-vejledning C.0.1).

Bar88 Baryliak IR, Kozachuk SY. Investigation of the cytogenetic effect of a number of monohydric alcohols on rat bone marrow cells. Cytol Genet 1988; 22 (2): 51-4.

BGC90 Berufsgenossenschaft der chemischen Industrie (BG Chemie). 3-methylbutan-1-ol. In: Toxicological evaluations, potential health hazards of existing chemicals. Berlin, FRG: Springer-Verlag, 1990: 283-96 (vol 1).

Bos92 Bos PMJ, Zwart A, Reuzel PGJ, et al. Elevation of the sensory irritation test for the assessment of occupational health risk. CRC Crit Rev Toxicol 1992; 21: 423-50.

Car46 Carpenter CP, Smyth HF Jr. Chemical burns of the rabbit cornea. Am J Ophthalmol 1946; 29: 1363-72.

Car73 Carpanini FMB, Gaunt IF, Kiss IS, et al. Short-term toxicity of isoamyl alcohol in rats. Food Cosmet Toxicol 1973; 11: 713-24.

Che84 Chen Th, Kavanagh TJ, Chang CC, et al. Inhibition of metabolic cooperation in Chinese hamster V79 cells by various organic solvents and simple compounds. Cell Biol Toxicol 1984; 1: 155-71.

DFG02 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2002. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH, 2002: 69 (rep no 38).

EC03 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs). http://europe.eu.int/comm/employment_social/h&s/areas/oels_en.htm.

Fre63 Fregert S, Hakanson R, Rorsman H, *et al*. Dermatitis from alcohols. J Allergy 1963; 34: 404-8.

Gib75 Gibel W, Lohs K, Widner GP. Experimentelle Untersuchungen zur kanzerogenen Wirkung von Lösungsmitteln am Beispiel von Propanol-1, 2-Methylpropanol-1 und 3-methylbutan-1-ol. Arch Geschwulstforsch 1975; 45: 19-24.

Hag45 Haggard HW, Miller DP, Greenberg LA. The amyl alcohols and their ketones: their metabolic fates and comparative toxicities. J Ind Hyg Toxicol 1945; 27: 1-14.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 21.

Kan80 Kane LE, Dombroske R, Alarie Y. Evaluation of sensory irritation from some common industrial solvents. Am Ind Hyg Assoc J 1980; 41: 451-5.

Kli95 Klimisch HJ, Hellwig. J Studies on the prenatal toxicity of 3-methyl-1-butanol and 2-methyl-1-propanol in rats and rabbits following inhalation exposure. Fundam Appl Toxicol 1995; 27: 77-89.

Kos95 Kostrubsky VE, Strom SC, Wood SG, et al. Ethanol and isopentanol increase CYP3A and CYP2E in primary cultures of human hepatocytes. Arch Biochem Biophys 1995; 322: 516-20.

Kum99 Kumagai S, Oda H, Matsunaga I, et al. Uptake of 10 polar solvents during short-term respiration. Toxicol Sci 1999; 48: 255-63.

Lin94 Lington AW, Bevan C. Alcohols. In: Clayton GD, Clayton FE, eds. Toxicology. 4th ed. New York, USA: John Wiley & Sons, Inc, 1994: 2585-2760 (Patty's Industrial hygiene and toxicology; Vol II, Pt D).

Lou93 Louis CA, Sinclair JF, Wood SG, et al. Synergistic induction of cytochrome P450 by ethanol and isopentanol in cultures of chick embryo and rat hepatocytes. Toxicol Appl Pharmacol 1993; 118: 169-76.

Mor91 Morris JB, Clay RJ, Trela BA, et al. Deposition of dibasic esters in the upper respiratory tract of the male and female Sprague-Dawley rat. Toxicol Appl Pharmacol 1991; 108: 538-46.

Mor93 Morris JB, Hassett DN, Blanchart KT. A physiologically based pharmacokinetic model for nasal uptake and metabolism of nonreactive vapors. Toxicol Appl Pharmacol 1993; 123: 120-9.

Mul84 Muller J, Greff G. Recherche de relations entre toxicité de molécules d'interêt industriel et propriétés physico-chimiques: test d'irritation des voies aériennes supérieures appliqué à quatre familles chimiques. Food Chem Toxicol 1984; 22: 661-4.

Mun72 Munch JC. Aliphatic alcohols and alkyl esters: narcotic and lethal potenties to tadpoles and rabbits. Ind Med 1972; 41: 31-3.

Nel43 Nelson KW, Edge JF, Ross M, et al. Sensory respons to certain industrial solvent vapors. J Ind Hyg Toxicol 1943; 25: 282-5.

NLM01 US National Library of Medicine (NLM), ed. Isoamyl alcohol. In: Hazardous Substances Data Bank (HSDB) (last revision date benzenethiol file: 8 February 2000; last review date: 29 September 1994); http://toxnet.nlm.nih.gov.

Opd78 Opdyke DLJ. Fragrance raw materials monographs. Isoamylalcohol. Food Cosmet Toxicol 1978; 16: 785-8.

Sch93 Schaper M. Development of a database for sensory irritants and its use in establishing occupational exposure limits. Am Ind Hyg Assoc J 1993; 54: 488-544.

Sch97 Schilling K, Kayser M, Deckardt K, et al. Subchronic toxicity studies of 3-methyl-1-butanol and 2-methyl-1-propanol in rats. Hum Exp Toxicol 1997; 16: 722-6.

Sei99 Seidel HJ, Plappert U. Zur Toxikologie zweier häufig nachgewiesener MVOCs: 1-Octen-3-ol und 3-Methyl-1-Butanol. Umweltmed Forsch Prax 1999; 4: 285-8.

Slo82 Sloop FV, Baker FT. Screening selected chemical food additives for mutagenicity. Abstr Annu Meet Am Soc Microbiol 1982; 82: 124.

Smy62 Smyth HF Jr, Carpenter CP, Weil CS, et al. Range finding toxicity data: List VI. Am Ind Hyg Ass J 1962; 23: 95-107.

Smy69 Smyth HF Jr, Carpenter CP, Weil CS, et al. Range finding toxicity data: List VII. Am Ind Hyg Ass J 1969; 30: 470-6.

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.

SZW03 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2003. The Hague, The Netherlands: Sdu, Servicecentrum Uitgevers, 2003: 34.

TRG00 TRGS 900: Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

WHO90 World Health Organization: International Programme on Chemical Safety (WHO/IPCS). 2-Propanol. Geneva, Switzerland: WHO, 1990; Environmental Health Criteria 103.

Wil85a Wilkin JK, Fortner G. Cutaneous vascular sensitivity to lower aliphatic alcohols and aldehydes in Orientals. Alcohol Clin Exp Res 1985; 9: 522-5.

Wil85b Wilkin JK, Fortner G. Ethnic contact urticaria to alcohol. Contact Dermatitis 1985; 12: 118-20.

Annex

Occupational exposure limits for 3-methylbutan-1-ol 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	100	360	8 h	administrative		SZW03
Germany						
- AGS	100	360	8 h		[c]	TRG00
	400	1440	15 min			
- DFG MAK-Kommission	100	370	8 h		[c]	DFG02
	200	740	15 min[d]			
Great-Britain						
- HSE	100	366	8 h	OES		HSE02
	125	458	15 min			
Sweden	-	-				Swe00
Denmark	100	360	8 h		[e]	Arb02
USA						
- ACGIH	100	-	8 h	TLV		ACG03b
	125	-	15 min	STEL		
- OSHA	100	360	8 h	PEL		ACG03a
- NIOSH	100	360	10 h	REL		ACG03a
	125	450	15 min	STEL		
European Union -SCOEL						
	-	-				EC03

[a] S = skin notation; which mean 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] Classified in pregnancy risk group C, i.e., among substances for which there is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT (Biological Tolerance Value for Working Materials) values are observed.

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

[e] For all pentanol isomers.