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REVIEW ARTICLE

TOXIC ALCOHOLS: ALIPHATIC SATURATED ALCOHOLS

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Summary

Toxic alcohols that clinicians commonly encounter are ethylene glycol, methanol, and isopropanol. Adults ingest these either for suicidal intent or to achieve inebriation, since these substances are readily available and cheaper than alcohol. Nevertheless, assorted alcohols are used very often in many applications and any alcohol can be toxic if ingested in large enough quantities. Toxic alcohols discussed here include all saturated aliphatic alcohols containing from 1 to 6 carbons in their molecules.

Key words: toxic alcohols; methanol; ethanol; propanol; isopropanol; butanols; pentanols; hexanols; higher alcohols

INTRODUCTION

Although any alcohol can be toxic if ingested in large enough quantities, the term *toxic alcohol* has traditionally referred to methanol, isopropanol, and ethylene glycol (McMahon et al. 2009). Nevertheless, even other alcohols represent risk assessment substances with toxicologically important compounds. Intoxication by different compounds on the basis of alcohol is common in modern society, largely because of its widespread availability. These alcohols can be used as fuel and for many scientific, medical, and industrial utilities. Alcohols have applications in industry and science as reagents or solvents. This article discusses the most common aliphatic alcohols containing from one to six carbons in their molecules. Many of them represent a serious and potentially life-threatening problem (Harger and Forney 1963).

Some longer-chain alcohols such as n-propanol, isopropanol, n-butanol, t-butanol, and 2-methyl-2-butanol do have stronger sedative effects, but also have higher toxicity than ethanol (Bunc et al. 2006). These longer chain alcohols are found as contaminants in some alcoholic beverages and are known as fusel oil (Lachenmeier et al, 2008) and are reputed to cause severe hangovers although it is unclear if the fusel alcohols are actually responsible (Hori et al. 2005). Many longer chain alcohols are used in industry as solvents and are occasionally abused by alcoholics (Wiernikowski et al. 1997), leading to a range of adverse health effects (Bogomolova et al. 2004).

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Physico-chemical properties of saturated aliphatic alcohols

Saturated aliphatic alcohols contain a hydrocarbon fragment derived from a fatty, nonaromatic hydrocarbon. Chemical properties of any given aliphatic alcohol depend on the nature of the alkyl group in the molecule and on the properties of the hydroxyl group. Alcohols are very weak acids. They undergo substitution with strongly electropositive metals such as sodium. The hydroxyl group generally makes the alcohol molecule polar and can form hydrogen bonds to one another and to other compounds. This hydrogen bonding means that alcohols can be used as protic solvents. These alcohols exist as volatile liquids at ambient temperatures, and exposure can occur in both industrial and nonindustrial environments.

No gaseous alcohols are known. Lower members of homologous series of aliphatic alcohols are clear colourless liquids at room temperature. Alcohols from one to six carbons in molecules are volatile liquids with an odor that is often described as "biting". They have varying solubility in water, the higher alcohols being less soluble. Their most important physical constants are summarized in Table I.

Table I. Physico-Chemical Properties of Reported Saturated Aliphatic Alcohols

Alcohol	CAS Registry Number	Melting Point (°C)	Boiling Point (°C)	log P (octanol-water)	Water Solubility (g/litre)	Vapor Pressure (kPa)
Methanol	67-56-1	-97.6	64.8	-0.69	miscible	13.02
Ethanol	64-17-5	-114	78.2	-0.18	miscible	5.95
Propanol	71-23-8	-127	97.2	0.33	miscible	1.99
Isopropanol	67-63-0	-89.5	82.3	0.05	miscible	4.54
Butanol	71-36-3	-89.8	117.7	0.839	90	0.67
Isobutanol	78-83-1	-101.9	107.9	0.8	87	1.83
sec.Butanol	78-92-2	-108	108	3	35	0.9
tert.Butanol	75-65-0	25.4	82.4	0.35	miscible	4.07
1-Pentanol	71-41-0	-78	138	1.4	0.03	0.2
2-Pentanol	6032-29-7	-73	119.3	1.14	0.014	0.61
3-Pentanol	584-02-1	-69	116.2	1.27	5.15	0.88
3-Methyl-1-butanol	123-51-3	-117	131.2	1.16	26.7	0.24
3-Methyl-2-butanol	598-75-4	-12	112	1.28	120	1.06
2-Methyl-1-butanol	137-32-6	-117.2	127.5	1.3	31	0.476
2-Methyl-2-butanol	75-85-4	-9	102	0.89	120	0.3
2,2-Dimethyl-1-propanol	75-84-3	52.2	113.5	1.36	35	0.16
1-Hexanol	111-27-3	-47	157	2.03	0.58	0.124
2-Hexanol	626-93-7	-76	136	1.76	14	0.263
3-Hexanol	17015-11-1		135	1.61	16	0.339
2-Methyl-1-pentanol	105-30-6	4.8	149	1.78	8.1	0.15
3,3-Dimethyl-2-butanol	464-07-3	4.8	117.8	1.19	25	0.881
1-Octanol	111-87-5	-16	195		0.0003	0.007
2-Ethyl-1-hexanol	104-76-7	-76	184	2.84	1.379	0.006

Common mechanism of alcohol toxic action

Aliphatic alcohols themselves are only little toxic or nontoxic. Their major toxicities are a result of these being transformed to toxic metabolites (Jacobsen and McMartin 1986). Alcohols are metabolised via alcohol dehydrogenase to corresponding aldehydes which are subsequently

metabolised to carboxylic acids through interaction with aldehyde dehydrogenase. These metabolites are mainly responsible for the metabolic acidosis in alcohol poisoning. Alcohol toxicity is a complex and not fully understood action.

Acute intoxication with any of the alcohols can result in respiratory depression, aspiration, hypotension, and cardiovascular collapse.

Methanol

Methanol (methyl alcohol; $CH_3 – OH$) is widely used as a chemical reactant, an industrial solvent and a paint remover. It is also used in photocopying fluid, shellacs, and windshield-washing fluids. Although toxicity primarily occurs from ingestion (Hantson 2006), it can also occur from prolonged inhalation (Lanigan 2001) or skin absorption (Avella et al. 2005, Reese and Kimbrough 1993). Methanol is rapidly absorbed from gastric mucosa, and achieves a maximal concentration 30-90 minutes after ingestion.

Animal and human toxicity

Experimental toxicity data for methanol obtained in laboratory animals at different routes of apllication are summarized in Table II. Acute toxicity of methanol is highest at intravenous administration in all animals.

Table II. Toxic Parameters of Methanol Acute Toxicity

Organism	Test Type *	Route **	Reported Dose (mg/kg)	Reference
Mouse	LD_{50}	i.p.	10 765	Tichý et al. 1985
Mouse	LD_{50}	i.v.	4 710	Tichý et al. 1985
Mouse	LD_{50}	oral	7 300	Smith and Taylor 1982
Mouse	LD_{50}	s.c.	9 800	Goldenthal 1971
Rat	LD_{50}	i.p.	7 529	Tichý et al. 1985
Rat	LD_{50}	i.v.	2 131	Tichý et al. 1985
Guinea Pig	LD_{50}	i.p.	3 556	Tichý et al. 1985
Hamster	LD_{50}	i.p.	8 555	Tichý et al. 1985
Monkey	LD_{50}	oral	7 000	Cooper and Feliog 1961
Rabbit	LD_{50}	i.p.	1 826	Tichý et al. 1985
Rabbit	LD_{50}	i.v.	8 907	Tichý et al. 1985
Rabbit	LD_{50}	oral	14 200	FAO 1970
Man	TDLo	oral	9 540	Burns et al. 1998
Man	TDLo	oral	3 429	Jacobsen et al. 1982
Man	TDLo	oral	6 422	Handa 1983
Woman	TDLo	oral	4 000	Jacobsen et al. 1982

Note: * LD_{50} - Median Lethal Dose, TDLo - Lowest Published Toxic Dose
** i.p. – intraperitoneally, i.v. – intravenously, s.c. – subcutaneously, oral – perorally

Human poisoning

Ingestion of methanol provides unique therapeutic challenges for emergency personnel. If untreated, this agent can result in significant morbidity and mortality. Toxicity of methanol is dependent on endogenous metabolic processes rather than on ingestion of actual parent compound. Toxicity and clinical symptoms are due to the accumulation of his metabolites. These metabolites lead to the characteristic metabolic acidosis and cellular dysfunction typically seen with toxic alcohol ingestions (Cooper and Feliog 1961). Methanol is primarily metabolized in the liver into more toxic products (Castro et al. 2002). At first via alcohol dehydrogenase into formaldehyde and

formaldehyde is subsequently metabolized via aldehyde dehydrogenase into formic acid. Formic acid is subsequently metabolized to folic acid, folinic acid, carbon dioxide, and water. Formaldehyde is a neurotoxin with genotoxic and carcinogentic effects, which is due to production of DNA-protein cross-links. Low doses of formaldehyde, reducing an apoptotic activity, may also accumulate cells with such cross-links (Szende and Tyihák 2010). It looks like formic acid is responsible for the majority of toxicity associated with methanol. Without a competition for alcohol dehydrogenase, methanol undergoes zero-order metabolism, and is thus excreted at a rate of 8.5 mg/dL/h to 20 mg/dL/h. A small portion is excreted in an unchanged form by the lungs. Biotransformation of methanol may be slowing some potent inhibitors of alcohol dehydrogenase, for example by L-carnitine (Czech et al. 2004). Methanol poisoning has led to Parkinsonism and polyneuropathy (Reddy et al. 2010).

Methanol poisoning is seen in the form of isolated episodes, or intentional ingestion and epidemics. Despite its efficient treatment, methanol poisoning has high morbidity and mortality rates (Sanaei-Zadeh et al. 2011). Methanol-related intoxications of humans are relatively frequent (Kraut and Kurtz 2008) but the incidence differs enormously from country to country (Epker and Bakker 2010, Gülmen et al. 2006). In 2007, only in USA 2,252 cases of methanol intoxications were reported. Methanol intoxication is extremely rare in the Dutch population. On the other hand these intoxications are very frequent in East Europe, mainly in some parts of former Soviet Union (Paasma et al. 2007), very often with the consumption of surrogate alcohols (i.e., nonbeverage alcohols and illegally produced alcohols) (Lachenmeier et al. 2007). Even a low dose can already be potentially lethal. Patients are conventionally treated with hemodialysis (Burns et al. 1998). The death poisonings are not rare (Andersen et al. 2008, Davanzo et al. 2009, Liu et al. 2009, Paasma et al. 2009).

By examination of 12 fatalities attributed to methanol poisoning it was found that their postmortem methanol and formic acid concentrations ranged from 840 to 5430 mg/l and 640 to 1100 mg/l, respectively. Antemortem methanol and formic acid concentrations in other six individuals, with hospital treatment such as bicarbonate, ethanol infusion, and hemodialysis, ranged from 680 to 4270 mg/l and 370 to 910 mg/l, respectively, whereas corresponding postmortem methanol and formic acid levels ranged from undetectable to 490 mg/l and undetectable to 480 mg/l, respectively. Hospital treatment of formic acid toxicity resulted in significantly reduced postmortem methanol and formic acid concentrations (Wallage and Watterson 2008). Very similar results were published by Hantson and Mahieu (2000) who measured formic acid concentrations in three fatalities due to methanol poisoning. Admission blood methanol concentrations ranged from 280 to 4600 mg/l. Two patients had been admitted after a significant delay (>20 hours), and one patient was observed within 90 minutes following ingestion. Formic acid levels were determined in blood samples at admission and ranged from 302 to 680 mg/l. The patients died 44, 55, and 82 hours after poisoning. Formic acid determinations in postmortem tissues were performed by a gas chromatograph method. The authors found great variability in formic acid distribution among the patients and among organs.

Ethanol

Ethanol (ethyl alcohol; $CH_3 – CH_2 – OH$) is most widely known alcohol, which is derived from fermentation of sugars and cereals. It is widely available both as a beverage and as an ingredient in food extracts, cough and cold medications, and mouthwashes. In humans, ethanol is rapidly absorbed across both gastric mucosa and small intestines, reaching a peak concentration 20-60 minutes after ingestion (Wilkinson 1980). Ethanol is metabolized analogous to methanol and it is converted to acetaldehyde. This conversion involves 3 discrete enzymes: the microsomal cytochrome P450 isoenzyme CYP2E1, the cytosol-based enzyme alcohol dehydrogenase (ADH), and the peroxisome catalase system. Acetaldehyde is then converted to acetate, which is converted to acetyl CoA, and ultimately carbon dioxide and water (Jacobsen 1952). Genetic polymorphisms coding for alcohol dehydrogenase, the amount of alcohol consumed, and the frequency at which ethanol is consumed affect the speed of metabolism. Chronic alcoholics and those with severe liver disease have increased rates of metabolism. However, as a general rule, ethanol is metabolized at a rate of 20-25 mg/dL in nonalcoholics but at an increased rate in chronic alcoholics (Osby et al. 2010).

Although the majority of ethanol metabolism takes place in the liver (Lieber 1982), other tissues do contribute to alcohol metabolism. ADH is also located in gastric mucosa, but this gastric metabolism of alcohol is decreased in women. Decreased "first-

pass metabolism", combined with a smaller volume of distribution, may explain the enhanced vulnerability of women to acute complications of alcohol intoxication (Frezza et al. 1990).

Human poisoning and alcoholism

Alcohol intoxication is common in modern society, largely because of its widespread availability (Carr 2011). Acute intoxication with ethanol can result in behavioral effects, respiratory depression, hypothermia, cardiovascular collapse, and death. (David and Spyker 1979, Baker et al. 1986). Chronic use results in hepatic and gastrointestinal injuries. Chronic alcoholics, as well as children, are at risk of hypoglycemia (De Wolff and Bruyn 1995).

Alcoholism, also known as alcohol dependence, is a disabling addictive disorder that includes the following four symptoms:

1. Craving – a strong need, or urge, to drink.

2. Loss of control – not being able to stop drinking once drinking has begun.

3. Physical dependence – withdrawal symptoms, such as nausea, sweating, shakiness, and anxiety after stopping drinking.

4. Tolerance – the need to drink greater amounts of alcohol to get "high."

Alcoholism is a disease. It is characterized by compulsive and uncontrolled consumption of alcohol despite its negative effects on the drinker's health, relationships, and social standing. The craving that an alcoholic feels for alcohol can be as strong as the need for food or water. An alcoholic will continue to drink despite serious family, health, or legal problems. Alcoholism carries many serious dangers. Heavy drinking can increase the risk of certain cancers. It can cause damage to the liver, brain and other organs (Mackay et al. 2011). It can cause birth defects (Van Wieringen et al. 2010). It increases the risk of death from car crashes and other injuries as well as the risk of homicide and suicide (Wagenaar et al. 2010). Like other drug addictions, alcoholism is medically defined as a treatable disease, but therapy is little effective. Alcohol drinking is highly prevalent in many cultures and contributes to the global burden of disease. In fact, it was shown that alcohol constitutes 3.2% of all worldwide deaths in the year 2006 and is linked to more than 60 diseases, including cancers, cardiovascular diseases, liver cirrhosis, neuropsychiatric disorders, injuries and foetal alcohol syndrome (Spanagel et al. 2010).

For most adults, moderate alcohol use is not harmful. However, more than half a million people in Czech Republic are alcoholics – 25 % men and 10 % women – and these numbers grow year after year. Situation elsewhere is similar. For example in the United States, nearly 17.6 million adults are alcoholics or have alcohol problems. In some studies, more than half of all trauma patients are intoxicated with ethanol at the time of arrival to the trauma center. In addition, ethanol is a frequent accessory in suicide attempts (Lee et al. 2010).

Animal and human toxicity

Experimental toxicity data for ethanol obtained in laboratory animals at different routes of apllication are summarized in Table III. Data for humans are very different.

Propanol

Propanol (n-propanol, propan-1-ol, propyl alcohol; $CH_3 – CH_3 – CH_2 – OH$) is primary alcohol used as a chemical reactant, as a solvent for a wide variety of chemical industry applications, such as formulation of disinfectants, pharmaceuticals, cleaning products, paints, coating materials, printing inks, cosmetics, and for resins and cellulose esters. It is formed naturally in small amounts during many fermentation processes. Propanol has no clinically relevant dermal absorption (Lang et al. 1011). It is a defatting agent and may cause skin irritation. This compound is not corrosive. Prolonged or repeated skin contact may cause skin dryness or cracking but no systemic chronic effects have been reported in humans (Clemmensen et al. 2008). Inhalation of vapors have a mild narcotic effect and act as an upper respiratory tract irritant. Symptoms may include irritation of eyes, nose, and throat, drowsiness, headache, and incoordination. Excessive exposures may lead to narcosis and CNS depression. Aspiration into lungs may occur during swallowing or vomiting, resulting in lung damage. It may cause nausea, vomiting, drowsiness, gastrointestinal pain, cramps and diarrhea. Large doses may cause death.

The principal toxic effect of propanol following a single exposure is depression of the CNS. The available evidence for propanol suggests that its effects on the CNS are similar to those of ethanol, however, this alcohol appears to be more neurotoxic (Teramoto et al. 1993).

Table III. Toxic Parameters of Ethanol Acute Toxicity

Organism	Test Type *	Route **27	Reported Dose (mg/kg)	Reference
Mouse	LD_{50}	i.p.	528	Frik et al. 1965
Mouse	LD_{50}	i.v.	1 973	Saunders 1955
Rat	LD_{50}	i.p.	3.6	Winter et al. 1969
Rat	LD_{50}	i.v.	1 440	Kimura et al. 1971
Rat	LD_{50}	i.a.	11	Kimura et al. 1971
Rat	LD_{50}	oral	7 060	Wiberg et al. 1970
Guinea Pig	LD_{50}	i.p.	3 414	Tichý et al. 1985
Hamster	LD_{50}	i.p.	5 068	Tichý et al. 1985
Rabbit	LD_{50}	i.p.	963	Tichý et al. 1985
Rabbit	LD_{50}	i.v.	2374	Tichý et al. 1985
Bat	LD_{50}	i.p.	4 300	Greenwald et al. 1968
Dog	LD_{50}	i.v.	1 600	Kimura et al. 1971
Man	TDLo	oral	1.43	Griffiths et al. 1976
Man	TDLo	oral	3.37	David and Spyker. 1979
Man	TDLo	oral	700	Baker et al. 1986
Woman	TDLo	oral	1 200	Välimäki et al., 1983
Child	TDLo	oral	14 400	Gibson et al. 1985.

Note: * LD_{50} - Median Lethal Dose, TDLo - Lowest Published Toxic Dose
** i.p. – intraperitoneally, i.v. – intravenously, i.a. – intraarterially, s.c. – subcutaneously, oral – perorally

Animal and human toxicity

Acute toxicity of propanol after oral, inhalation and dermal exposure is low (Table IV). Availability of genotoxicity and repeated dose toxicity studies with propan-1-ol is very limited and there are no valid studies on bacterial or mammalian cell mutagenicity, or *in vivo* genotoxicity. Pregnant females exposed to 7 000 ppm propanol showed reduced weight gain, and female offsprings also had reduced weight gain through three weeks of age; there was also slight teratogenicity observed at this concentration (Nelson et al. 1985). Grant and Samson (1984) suggest that exposure to propanol in the growth of rat pups inhibits brain development.

Table IV. Toxic Parameters of Propanol Acute Toxicity

Organism	Test Type *	Route **	Reported Dose (mg/kg)	Reference
Mouse	LD_{50}	i.p.	3 125	Tichý et al. 1985
Mouse	LD_{50}	i.v.	697	Tichý et al. 1985
Mouse	LD_{50}	s.c.	4 700	Goldenthal 1971
Rat	LD_{50}	i.p.	2 164	Tichý et al. 1985
Rat	LD_{50}	i.v.	590	Tichý et al. 1985
Guinea Pig	LD_{50}	i.p.	1 208	Tichý et al. 1985
Hamster	LD_{50}	i.p.	2 338	Tichý et al. 1985

Note: * LD_{50} - Median Lethal Dose
** i.p. – intraperitoneally, i.v. – intravenously

Environmental toxicity

The main pathway of propanol entry into the environment is through its emission into the atmosphere during production, processing, storage, transport, use, and waste disposal. Due to the fact that propanol is mainly used as a volatile solvent, much of the production volume is released into the environment but this alcohol rapidly disappears from the atmosphere by reaction with hydroxyl radicals and through rain-out. Emissions into water and soil also occur. It is readily biodegradable. At concentrations normally encountered in the environment, propanol is not toxic for aquatic organisms, insects, or plants (Ananonymous, 2009).

Human poisoning

Cases of intoxication of humans by propanol are rare (Blanchet et al. 2007, Vujasinovic et al. 2007) but poisoning may be fatal (Durwald and Degen 1956).

Isopropanol

Isopropanol (isopropyl alcohol, propan-2-ol; CH_3 –CH(OH)-CH_3) is a low molecular weight secondary alcohol. It is commonly found as a solvent, a disinfectant, antifreeze, and an industrial solvent. It can be found in many mouthwashes, skin lotions, and rubbing alcohol. Because of its widespread availability, lack of purchasing restrictions, and profound intoxicating properties, it is commonly used as an ethanol substitute.

When ingested, isopropanol functions primarily as a CNS inebriant and depressant, and its toxicity and treatment resemble that of ethanol (Lobert 2000). Isopropanol is rapidly absorbed across gastric mucosa and reaches a peak concentration approximately 30-120 minutes after ingestion (Rich et al. 1990). Isopropanol is primarily metabolized via alcohol dehydrogenase to acetone. A small portion of unchanged isopropanol is excreted in urine. The peak concentration of acetone is not present until approximately 4 hours after ingestion (Adla et al. 2009).

Animal and human toxicity

Isopropanol is a sedative-hypnotic agent whose toxicity closely resembles that of ethanol, with which it shares a strong structural similarity (Mańkowski et al. 2000). Acute effects of isopropanol ingestion include central nervous system depression, gastrointestinal irritation, impaired gluconeogenesis, delirium, hypotension, and coma (Hanawalt-Squires and Anfinson 2002). Like ethanol, isopropyl alcohol's precise mechanism of action in the CNS remains uncertain. Changes in membrane fluidity and/or function, and interactions with neurotransmitter receptors, are believed to account for the CNS effects of alcohols and other simple hydrocarbons. There is a linear relationship between molecular weight of alcohols and their sedative effects: as size

Table V. Toxic Parameters of Isopropanol Acute Toxicity

Organism	Test Type *	Route **	Reported Dose (mg/kg)	Reference
Mouse	LD_{50}	i.p.	4 477	Tichý et al. 1985
Mouse	LD_{50}	i.v.	1 509	Tichý et al. 1985
Rat	LD_{50}	i.p.	2 735	Tichý et al. 1985
Rat	LD_{50}	i.v.	1 088	Tichý et al. 1985
Guinea Pig	LD_{50}	i.p.	2 560	Tichý et al. 1985
Hamster	LD_{50}	i.p.	3 444	Tichý et al. 1985
Rabbit	LD_{50}	i.p.	667	Tichý et al. 1985
Rabbit	LD_{50}	i.v.	1 184	Tichý et al. 1985
Man	TDLo	oral	14 432	Freireich et al. 1967
Child	TDLo	oral	13 000	Parker and Lera 1992
Child	TDLo	oral	1 375	Mydler et al. 1993

Note: * LD_{50} - Median Lethal Dose, ** TDLo - Lowest Published Toxic Dose
** i.p. – intraperitoneally, i.v. – intravenously, s.c. – subcutaneously, oral – perorally

increases, so does sedation. Thus, isopropanol is marginally more potent than ethanol at comparable concentrations. Acute toxicity of isopropanol after oral, inhalation and dermal exposure is low, lower than that of propanol (Table V). In untreated animals, the median lethal dose lies between 4 and 8 g/kg. Many sources give an estimated lethal dose of 250 mL in humans.

Human poisoning

Isopropanol is a relatively common source of clinical intoxication (e.g. Gill et al. 1995, Steinmann et al. 2009, Jammalamadaka and Raissi 2010). For instance, in 2007, 7,447 cases of isopropanol ingestions were reported to the US Poison Control Centers. Out of these, 36 patients were classified as experiencing "major" morbidity with one patient dying. In the same year, 2,252 cases of methanol and 5,395 cases of ethylene glycol were reported. Following an isopropanol ingestion, the patient may not complain of anything specific. Rather, the patient may simply appear intoxicated, as with ethanol intoxication (Wrenn 1991, Mańkowski et al. 2000). Accidental and suicidal ingestion of isopropanol can sometimes be fatal if it goes unrecognized and untreated (Zaman et al. 2002). Nevertheless, fatality from isolated isopropyl alcohol toxicity is rare (Freireich et al. 1967), but can result from injury due to inebriant effects, such as untreated coma with airway compromise, or rarely, cardiovascular depression and shock following massive ingestion (Clark 2010). Supportive care can avert most morbidity and mortality. It is important to differentiate isopropyl alcohol from methanol and ethylene glycol, which are more dangerous (Jammalamadaka and Raissi 2010). Isopropanol does not cause elevated anion gap acidosis, retinal toxicity (as does methanol), or renal failure (as does ethylene glycol) (Patočka and Hon, 2010).

Butanol

Butanol (n-butanol, butan-1-ol, n-butyl alcohol; $CH_3 –CH_2 –CH_2 –CH_2OH$) is one of four isomeric alcohols of formula C_4H_9OH. Butanol is colorless, neutral liquid of medium volatility with a characteristic banana-like odor and is used for production of other chemicals, as an ingredient in formulated products such as cosmetics, and as a solvent. It has restricted miscibility (about 7-8%) in water, but is freely miscible with all common solvents such as glycols, ketones, alcohol, aldehydes, ethers, and aromatic and aliphatic hydrocarbons. Butanol is also developed as alternative automobile fuel (Butylfuel). Butanol may be produced from corn and other biomass and butylfuel aspire to become the industry leader in transforming the world's dominant automobile fuel from gasoline to biobutanol (Ezeji et al. 2007).

Animal and human toxicity

Butanol demonstrates an overall low order of toxicity in single-dose exposures to laboratory animals. Acute toxicity data for butanol are summarized in Table VI. These data suggest that butanol is only slightly acutely toxic to experimental animals via oral, dermal, and inhalation routes of exposure. Acute overexposures may cause irritation to eyes and skin or can be harmful if inhaled. Prolonged, excessive exposure to vapors may cause serious adverse effects, and even death. Repeated skin contact may aggravate preexisting dermatitis and result in absorption of harmful amounts through skin. In most cases, butanol is quickly metabolized to carbon dioxide.

A short-term exposure or a repeated overexposure to butanol can result in depression of the CNS, as is often observed with other short-chain aliphatic alcohols. This effect is usually transient (goes away after the exposure is removed and the body recovers/metabolizes the material). According to the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), there is no evidence that n-butanol exhibits genotoxicity (causes damage to DNA or cancer). There is a report of fetotoxicity (birth defects or malformations) in rats when the exposures are great enough to cause significant toxicity to the mother (Nelson et al. 1989b). Congenital malformations were noted for butanol only at concentrations in excess of 5000 ppm. These concentrations also produced toxicity in the maternal animals (Nelson et al. 1990). In a rat study without detailed information, butanol has caused birth defects at doses reported to be nontoxic to the mother (Sitarek et al. 1994). The dose levels producing theseeffects in both studies were many times higher than any dose levels expected from an exposure due to use of n-butanol. In fact, a newer study utilizing current protocols has shown no evidence of fetotoxicity at high levels that are toxic to the mother (Ema et al. 2005).

Table VI. Toxic Parameters of Butanol Acute Toxicity

Organism	Test Type *	Route **	Reported Dose (mg/kg)	Reference
Mouse	LD_{50}	i.p.	254	Maickel and McFadden 1979
Mouse	LD_{50}	i.v.	377	Chvapil et al. 1962
Mouse	LD_{50}	s.c.	3 200	Goldenthal 1971
Mouse	LD_{50}	oral	2 680	Rumyantsev et al. 1979
Mouse	ED_{50}	inhalation	3010 ppm (4 hr)	Korsak et al. 1993
Mouse	TCLo	inhalation	6 600 ppm (2 hr)	Patty 1978
Rat	LD_{50}	i.p.	1 122	Tichý et al. 1985
Rat	LD_{50}	i.v.	310	Tichý et al. 1985
Rat	LD_{50}	oral	2 510	Jenner 1964
Rat (male)	LD_{50}	oral	2 020	Purchase 1969
Rat (female)	LD_{50}	oral	790	Purchase 1969
Rat	EC_{50}	inhalation	6 530 ppm	Korsak et al. 1993
Hamster	LD_{50}	oral	1 200	Dubina and Maksimov 1976
Bird (wild)	LD_{50}	oral	2 500	Schafer et al. 1983
Rabbit	LD_{50}	dermal	5 300	Patty 1978
Rabbit	ND_{50}	oral	800	Munch and Schwarze 1925
Rabbit	LD_{50}	oral	3 500	Munch and Schwarze 1925
Dog	LD_{50}	oral	1 782	Von Oettingen 1943

Note: * LD_{50} - Median Lethal Dose, ED_{50} - Median Effective Dose, EC_{50} - Median Effective Concentration, TDLo - Lowest Published Toxic Dose
** i.p. – intraperitoneally, i.v. – intravenously, i.a. – intraarterially, s.c. – subcutaneously, oral – perorally

Environmental toxicity

Butanol enters the environment from either natural sources or, to a small extent, during its production, transport, storage and use as a chemical intermediate and a solvent. The primary route for entering the environment is the release to the atmosphere when used as a solvent. Butanol is readily degradable in water and readily decomposed in the air by photodegradation. Butaol degrades in air by reaction with hydroxyl radicals, having a half-life in air of 1.2 to 2.3 days (Gerhold and Malaney 1966). It does adsorb on soil, and favors partitioning to water versus air. Because degradation and decomposition is rapid, bioaccumulation or bioconcentration is unlikely (Chan and Lai 2008). Butanol exhibits low toxicity to fish, amphibians and aquatic invertebrates, plants, algae, bacteria and protozoans. However, some algal species are sensitive to butanol. Acute toxicity to aquatic life may occur at concentrations greater than 500 mg/l. Butanol has a low order of toxicity to environmental organisms at all levels of the food chain (Bengtsson et al. 1984).

Human poisoning

Human exposure to butanol may occur in the workplace during manufacture and industrial/commercial use, during consumer use of products containing butanol and from presence of butanol in the environment. Inhalation and dermal absorption are the expected routes of exposure in the workplace and from the use of consumer products containin butanol. Butanol ingestion may result in vomiting, abdominal pain, headache, drowsiness and unconsciousness (Bunc et al. 2006). No relevant informations were found for death intoxication.

Isobutanol

Isobutanol (2-methyl-1-propanol, isobutyl alcohol; $(CH_3)_2CH\text{-}CH_2OH$), primary aliphatic alcohol, is an inflammable colourless liquid with

a sweet odour similar to that of amyl alcohol. Isobutanol is useful in organic synthesis as a chemical intermediate and as a solvent in coating applications. In property, isobutanol is similar to n-butyl alcohol. It may be used as a suppleent or a replacement for butylalcohol in many applications and as a relatively slow evaporating latent solvent in lacquers and ambient-cured enamels.

Animal and human toxicity

Isobutanol is rapidly absorbed following inhalation and oral exposures. It is rapidly metabolised to isobutyraldehyde and isobutyric acid in rodents and humans (Bilzer et al. 1990). Isobutanol is a slight to moderate skin irritant and a severe eye irritant. Repeated exposures to moderate to high concentrations of isobutanol are well tolerated in rats.

Isobutanol has low acute toxicity by all routes, its toxicity is comparable with butanol (Table VII). Subchronic inhalation of isobutanol has slight neurotoxicity in rats (Li et al. 1999). In animals, isobutanol is absorbed through skin, lungs, and gastrointestinal tract. It is metabolized by alcohol dehydrogenase to isobutyric acid via aldehyde and may enter the tricarboxylic acid cycle (Klimisch and Hellwig 1995). In rabbits, metabolites found in urine include acetaldehyde, acetic acid, isobutylaldehyde, and isovaleric acid.

Table VII. Toxic Parameters of Isobutanol Acute Toxicity

Organism	Test Type *	Route **	Reported Dose (mg/kg)	Reference
Mouse	LD_{50}	i.p.	544	Maickel and McFadden 1979
Mouse	LD_{50}	i.p.	417	Tichý et al. 1985
Rat	LD_{50}	i.p.	720	Tichý et al. 1985
Rat	LD_{50}	i.v.	340	Tichý et al. 1985
Hamster	LD_{50}	i.p.	1 401	Tichý et al. 1985
Rabbit	LD_{50}	i.p.	322	Tichý et al. 1985
Guinea Pig	LD_{50}	i.p.	1 201	Tichý et al. 1985

Note: * LD_{50} - Median Lethal Dose,
** i.p. – intraperitoneally, i.v. – intravenously,

Environmental toxicity

Isobutanol is readily biodegradable and does not bioaccumulate (Schaefer et al. 2010). It is not directly toxic for fish, crustacea, amphibia, or algae. When released into soil or water, this material is expected to readily biodegrade. It is not expected to significantly bioaccumulate. When released into the air, isobutanol is expected to be readily degraded by reaction with photochemically produced hydroxyl radicals (Staples 2001). Isobutanol is not expected to be toxic to aquatic life. The LC_{50}/96-hour values for fish are over 100 mg/l (Anonymous 1987).

Human poisoning

For human subjects, reported effects of a long-term exposure to isobutanol are primarily irritation of eyes and mucous membranes, and also some dizziness. Reported cases include no information on exposure levels (Anonymous, 1984). Experimental animals have shown effects on the central nervous system after an exposure to relatively high doses of isobutanol (Li et al. 1999). It is not known, however, whether similar effects can appear in a man.

Sec-Butanol

Sec-butanol (butan-2-ol, 2-butanol, sec-butyl alcohol; $CH_3 – CH_2 – CH(OH) – CH_3$) is flammable, colorless liquid with a characteristic sweet odour. Sec-butanol is a chiral molecule and thus can be obtained as any of the two stereoisomers designated as (*R*)-(−)-2-butanol and (*S*)-(+)-2-butanol. It is normally found as an equal mixture of the two stereoisomers — a racemic mixture (Weast 1981). Sec-butanol is produced on a large scale, primarily as a precursor to the industrial solvent methyl ethyl ketone. It is used for the extraction of fish meal to produce fish protein concentrate. It is also used for

the production of fruit essences, as a flavouring in food, and as a solvent.

Animal and human toxicity

Acute oral LD_{50} for 2-butanol in rats is 6.5 g/kg body weight and similar low toxicity was obtained for other laboratory animals; therefore, it is practically non-toxic, according to the scale of Hodge and Sterner (1949). Toxic effects from an acute exposure are ataxia and narcosis. Potency of 2-butanol for intoxication is approximately 4times that of ethanol. Sec-butanol is irritating to eyes and non-irritating to skin. It is not possible to determine a no-observed-adverse-effect level on the basis of available animal studies. No published data are available concerning other animal toxicity. No adequate data are available on mutagenicity, carcinogenicity, teratogenicity, or effects on reproduction (Nelson et al. 1989a).

Human poisoning

In humans, the most likely acute effect of sec-butanol is alcoholic intoxication. No published data are available concerning other effects on humans.

Environmental toxicity

When sec-butanol is released into soil, it is expected to readily biodegrade. When released into soil, this material is expected to quickly evaporate and in a small amount it is expected to leach into groundwater. The half-life of sec-butanol in water and atmosphere is expected between 1 and 10 days. The LC_{50}/96-hour values for fish are over 100 mg/l. This material is not expected to be toxic to aquatic life.

Tertiary-butanol

Tert-butanol (2-methylpropan-2-ol, tert-butyl alcohol; $(CH_3)_3C - OH$) is the smallest tertiary aliphatic alcohol that is used as a solvent or an alcohol denaturant and as a perfume carrier in cosmetics. Tert-butanol is an important intermediate in an industrial chemical synthesis, particularly that of fuel oxygenates. Ethyl tertiary-butyl ether (ETBE) is one such compound (Mc Gregor 2007).

Animal and human toxicity

There is little acute oral toxicity in animals; e.g., acute oral LD_{50} in rats was 3.0 to 3.7 g/kg. Acute LD_{50} in mice at i.p. administration was 399 mg/kg (Maickel and McFadden 1979) and 1538 mg/kg at i.v. administration (Chvapil et al. 1962). In short-term oral studies in rats, terc-butanol at 2% (w/v) or less in drinking water did not cause a gross organ or tissue damage in mice, although weight loss was reported and a microscopic damage to livers and kidney and alterations such as centrilobular necrosis, vacuolation in hepatocytes, and a loss of hepatic architecture were noted. Subchronic oral dosing with tert-butanol increased mineralization of kidney, nephropathy, and urinary bladder transitional cell epithelial hyperplasia in rats (Lindamood et al. 1992). Also a liver damage, chronic inflammation, hyperplasia of transitional cell epithelium urinary, and proliferative changes including hyperplasia and neoplasia in the thyroid in mice were observed (Chen 2005).

Tert-Butanol was a moderate to severe ocular irritant to rabbits and caused mild to moderate dermal irritation to rabbits. In animal studies, fetotoxicity generally increased with concentration, and fetal weights were slightly depressed at concentrations of 0.5% to 1% tert-butanol. Tert-Butanol was not mutagenic in several bacterial and mammalian test systems. The principal effects from 2 years of exposure to tert-butanol in drinking water (up to 10 mg/ml for rats and 20 mg/ml for mice) were proliferative lesions (hyperplasia, adenoma, and carcinoma) in the kidneys of exposed male rats, and nephropathy in all exposed groups of female rats (Cirvello et al. 1995). Tert-Butanol has no genotoxic and reproduction toxicity. Clearly identified target organs for toxicity are kidney in male rats and urinary bladder, particularly in males, of both rats and mice. Observed increased tumour incidences were renal tubule cell adenomas in male rats and thyroid follicular cell adenomas in female mice and, non significantly, at an intermediate dose in male mice (McGregor 2010). Based on the available animal and clinical data in this report, it was concluded that tert-butanol is safe as used in cosmetic products.

Human poisoning

A human exposure to tert-butanol may occur following fuel oxygenate metabolism or biodegradation. It is poorly absorbed through skin, but is rapidly absorbed upon inhalation or ingestion and distributed to tissues throughout the body. Elimination from blood is slower and the half-life increases with dose. It is largely metabolised by oxidation via 2-methyl-1,2-propanediol to 2-hydroxyisobutyrate, the dominant urinary metabolites. Conjugations also occur and acetone

may be found in urine at high doses. The single-dose systemic toxicity of tert-butanol is low, but it is irritant to skin and eyes; high oral doses produce ataxia and hypoactivity and a repeated exposure can induce dependence (McGregor 2010).

Pentanols

There are 8 alcohols with five carbon atoms ($C_5H_{11}OH$) in a molecule. Four primary alcohols (1-pentanol, 2-methyl-1-butanol, 3-methyl-1-butanol and 2,2-dimethyl-1-propanol), three secondary alcohols (2-pentanol, 3-pentanol and 3-ethyl-2-butanol) and one tertiary alcohol (2-methyl-2-butanol). In addition, 2-pentanol, 2-methyl-1-butanol, and 3-methyl-2-butanol have chiral centers and hence two enantiomeric forms. The term amyl alcohol is commonly applied to mixtures of these isomers, which are used as solvents for resins and oily materials and in the manufacture of other chemicals, especially amyl acetate, a solvent for nitrocellulose lacquers. The odd-carbon structure and the extent of branching provide amyl alcohols with unique physical and solubility properties and often offer ideal properties for solvent, surfactant, extraction, gasoline additive, and fragrance applications. Mixtures of isomeric amyl alcohols (1-pentanol and 2-methyl-1-butanol) are often prefered because they are less expensive to produce commercially and have a more desirable combination of properties. With the exception of neopentyl alcohol (m.p. 53°C), amyl alcohols are clear, colorless liquids under atmospheric conditions, with characteristic, slightly pungent and penetrating odors.

Pentanols show low acute and repeat dose toxicity with high-dose effects related to minimal liver toxicity. The main effects of a prolonged exposure to amyl alcohols are irritation to mucous membranes and upper respiratory tract, significant depression of the central nervous system, and narcotic effects from vapor inhalation or oral absorption. All the alcohols are harmful if inhaled or swallowed. A prolonged exposure causes nausea, coughing, diarrhea, vertigo, drowsiness, headache, and vomiting (Papa 2000). These chemicals do not show evidence of activity in genetic toxicity tests or to the reproductive system or the developing organism (Veenstra et al. 2009), with the exception of 3-methyl-butan-2-ol which has demonstrated carcinogenic activity in animal studies (Nakajima et al. 2006).

1-Pentanol

1-Pentanol (n-pentyl alcohol, amyl alcohol; CH_3-CH_2-CH_2-CH_2-CH_2OH) is colourless liquid, slightly soluble in water, and having a characteristic penetrating odour. 1-Pentanol was a moderate to severe ocular irritant to rabbits and caused mild to moderate dermal irritation to rabbits. Irritation of respiratory and digestive mucous membranes were obseved (Gurzo 1954).

Animal and human toxicity

Acute toxicity is comparable to n-butanol (Butterworth et al. 1976). Acute oral LD_{50} for 1-pentanol in some laboratory animals are summarized in Table VIII. The treatment of rats had no

Table VIII. Toxic Parameters of 1-Pentanol Acute Toxicity

Organism	Test Type *	Route **	Reported Dose (mg/kg)	Reference
Mouse	LD_{50}	i.p.	140	Tichý et al. 1985
Mouse	TDLo	inhalation	14 000/m^3 (6 hr)	Scala and Burtis 1973
Rat	LD_{50}	i.p.	579	Tichý et al. 1985
Rat	LD_{50}	i.v.	196	Tichý et al. 1985
Guinea Pig	LD_{50}	i.p.	615	Tichý et al. 1985
Guinea Pig	TDLo	inhalation	14 000/m^3 (6 hr)	Scala and Burtis, 1973
Hamster	LD_{50}	i.p.	626	Tichý et al. 1985
Rabbit	LD_{50}	i.p.	140	Tichý et al. 1985

Note: * LD_{50} - Median Lethal Dose, TDLo - Lowest Published Toxic Dose
** i.p. – intraperitoneally, i.v. – intravenously, i.a. – intraarterially, s.c. – subcutaneously

demonstrable effect on body-weight gain, food and water consumption, haematological values, serum and urine analyses, renal function, organ weights or histopathology, when 1-pentanol was oraly administered to animals at dose levels of 0 (control), 50, 150 or 1000 mg/kg body weight/day for 13 wk (Butterworth et al. 1976). The no-untoward-effect level was 1000 mg/kg/day, which is about 2000 times the estimated maximum likely intake by a human. Inhalation of pentanol at the concentrations of 14,000, 3500, and 850 mg/m^3 can produce limited maternal toxicity, but it was not teratogenic to rats (Nelson et al. 1989c).

Human poisoning

In humans, the most likely acute effect of 1-pentanol may be visual function disorders, neuropsychic disorders and irritation dermatitis (Lachenmeier et al. 2007). No published data are available concerning other effects on humans.

2-Pentanol and **3-pentanol**

2-Pentanol, also called sec-amyl alcohol (CH_3-CH_2-CH_2-CH(OH)-CH_3), and 3-pentanol (CH_3-CH_2-CH(OH)-CH_2-CH_3) are secondary five-carbon alcohols. They are used as a solvent and an intermediate in manufacture of other chemicals. 2-Pentanol is a component of many mixtures of amyl alcohols sold industrially (Lappe 2000). They are less toxic than 1-pentanol. Oral rat LD_{50} for 2-pentanol is 1470 mg/kg (MSDS No SLP5197, 2005a) and for 3-pentanol 1870 mg/kg (MSDS No SLP5197, 2005a). Oral rabbit LD_{50} for 2-pentanol is 2800 mg/kg (MSDS No SLP2368, 2005b). No published data are available concerning toxic effects on humans.

3-Methyl-1-butanol

3-Methyl-1-butanol (isopentanol, isopentyl alcohol, isoamyl alcohol, CH_3-CH(CH_3)-CH_2-CH_2OH), branched primary five-carbon alcohol is used as a fragrance ingredient (McGinty et al. 2010). When 3-methyl-1-butanol was given in daily doses of 0 (control), 150, 500 or 1000 mg/kg /kg body weight for 17 wk to rats, no negative effects on hematological examinations, serum analyses, urinary cell counts, renal concentration tests or organ weights were observed. A slightly reduced rate of body-weight gain at the highest dose level was shown to be due to a reduced food intake. Two rats given 1000 mg/kg/day died, but histopathological examination showed that these deaths were due to dosing into the lungs and not to any toxic effects of 3-methyl-1-butanol. A female rat given 500 mg/kg/day developed a lipoma, which was not considered to be due to treatment. The no-untoward-effect level in this study was 1000 mg/kg/day, a level estimated to be 350-400 times the maximum likely intake of a human (Carpannini et al., 1973). On the model of isolated perfused rat liver, Strubelt and co-workers (1999) found that 3-methyl-1-butanol is not hepatotoxic.

When 3-methyl-1-butanol was tested for prenatal inhalation toxicity in pregnant Wistar rats or Himalayan rabbits, the concentration of 10 mg/l caused a slight retardation of body weight gain in the dams of either species exposed to 3-methyl-1-butanol during the first days of the exposure period. The fetuses of either species exhibited no signs of embryo-/fetotoxicity or teratogenic effects caused by 3-Methyl-1-butanol (Klimisch and Hellwig 1995).

3-Methyl-2-butanol

3-Methyl-2-butanol (CH_3-CH(CH_3)-CH(OH)-CH_3), branched secondary five-carbon alcohol, is used as a fragrance ingredient (McGinty et al. 2010). 3-Methyl-2-butanol occurs naturally in alcoholic beverages as a by-product of alcoholic fermentation (Baraud and Genevois 1958). Recently, concerns have been raised about the levels of higher alcohols in surrogate alcohol (i.e., illicit or home-produced alcoholic beverages) that might lead to an increased incidence of liver diseases in regions where there is a high consumption of such beverages (Lachenheimer et al. 2008).

2-Methyl-1-butanol

2-Methyl-1-butanol (active amyl alcohol, CH_3-CH_2-CH(CH_3)-CH_2OH) is branched primary alcohol with five carbons in a molecule. It is used as a solvent and an intermediate in the manufacture of other chemicals. 2-Methyl-1-butanol is a component of many mixtures of amyl alcohols sold industrially.

2-Methyl-1-butanol showed a low acute toxic potential in rats treated orally and in rabbits treated dermally. It produced severe eye damage in rabbits, but did not cause significant skin irritation . Vapors and mists are irritating to the upper respiratory tract. Vapors and mist cause eye irritation, liquid alcohol is absorbed through skin. Percutaneous rabbit LD_{50} is 3540 µl/kg (Smyth et al. 1962).

2-Methyl-2-butanol

2-Methyl-2-butanol (*tert*-amyl alcohol or amylene hydrate, CH_3-CH_2-$C(CH_3)_2$-OH) is one of the isomers of amyl alcohol. It is a clear, colorless liquid with a strong odour of peppermint or camphor. In humans it possesses sedative, hypnotic, and anticonvulsant effects similar to ethanol through ingestion or inhalation.

2-Methyl-2-butanol was previously used in medicine as hypnotic (Brandenberger and Maes 1997). It is active in doses of 2,000-5,000 mg, making it some 20 times more potent than regular ethanol. Its hypnotic potency is between that of chloral hydrate and paraldehyde. In humans, 2-methyl-2-butanol is metabolized primarily via gluconoridation and oxidation to 2,3-dihydroxy-2-methylbutane. Overdose produces symptoms similar to alcohol poisoning and is a medical emergency.

2-Methyl-2-butanol is misused in some countries by young drug users and in drug scene is known as 2M2B. According to addicts, 2M2B is more potent than ethanol, has longer duration and less negative side effects. (Anonymous 2005).

Vapors and mists are irritating to the upper respiratory tract. High concentrations may have a narcotic effect, causing headaches, nausea, and vomiting. Ingestion may produce narcotic effects, with headache, nausea, vomiting and diarrhea (Patnaik 2006). Vapors and mist cause eye irritation, liquid alcohol is absorbed through skin and causes irritation. Oral rat LD_{50} is 1000 mg/kg (Schaffarzick and Brown 1952) and oral rabbit LD_{50} is 2026 mg/kg (MSDS No A6408, 2008). Acute i.v. LD_{50} in mice is 610 mg/kg (Smyth et al. 1962) and subcutaneous LD_{50} in mice is 2100 mg/kg (Soehring et al. 1955).

2,2-Dimethyl-1-propanol

2,2-Dimethyl-1-propanol is branched primary five-carbon alcohol (neopentyl alcohol, CH_3-$C(CH_3)_2$-CH_2OH) and is unique solid alcohol (m.p. 55-57 °C). It is soluble in both polar and non-polar solvents. It is used to improve oxidative stability in some lubricants, in the synthesis of stericaly hindered esters, and in ink-jet printer cartridges to prevent plugging.

Occupational exposure to 2,2-Dimethyl-1-propanol can occur through dermal contact, inhalation, and ingestion (Parmeggiani 1983). The exposure of 2,2-dimethyl-1-propanol for 5 min induced erythema in only 17% of the 12 human subjects over the subsequent 60 min (Snyder 1992). 2,2-Dimethyl-1-propanol (at concn of 50 mM) stimulates the peptidase activity (by 160%) *in vitro* but inhibits the esterase activity (by 76%) of carboxypeptidase A and inhibits the cytochrome p450 dependent mixed function oxidases, specifically aniline hydroxylase, in suspensions of rat liver microsomes (Snyder 1992).

Hexanols

Hexanols (hexyl alcohols) are aliphatic six-carbon alcohols. There are 17 isomeric alcohols derived from the molecular formula $C_6H_{13}OH$. They are colorless and highly flammable liquids, slightly soluble in water and less dense than water. They may cause toxic effects if inhaled or absorbed through skin. Inhalation or contact with this material may irritate or burn skin and eyes. Fire will produce irritating, corrosive and/or toxic gases. Vapors may cause dizziness or suffocation (Flick 1998).

Toxicology and environmental health information concerning hexanols are restricted to several hexanol isomers. Only some of them are manufactued in bigger amounts as pure substances and represent risk for human health. Therefore only for a limited number of isomers there exist some toxicological data.

1-Hexanol

1-Hexanol (n-hexanol, hexan-1-ol, hexyl alcohol, capryl alcohol, capric alcohol; CH_3-CH_2- CH_2-CH_2-CH_2-CH_2OH, CAS Registry Number 111-27-3) is colorless liquid, slightly soluble in water (5.9 g/litre), but miscible with ether and ethanol. Melting point – 52 °C, boiling point 156-157 °C, log P = 2.03).

Acute toxicity (LD_{50}) is 1950 mg/kg at oral and 103 mg/kg at intravenous administration in mice (Chvapil et al. 1962). Inhalation of vapor or mist is irritating to mucous membrane and upper respiratory tract. Aspiration into the lungs may occur during swallowing or vomiting, resulting in lung damage. It is harmful when swallowed and may have central nervous system effects. It may cause headache, nausea, drowsiness and dizziness.

2-Hexanol

2-Hexanol (hexan-2-ol, 2-hexyl alcohol; CH_3-$CH(OH)$-CH_2-CH_2-CH_2-CH_3, CAS Registry number 626-93-7) is colorless liquid, slightly soluble in water (14 g/litre) with b.p. 136 °C (Lide 1998). No relevant toxicological data are available.

3-Hexanol

3-Hexanol (hexan-3-ol, 3-hexyl alcohol, ethyl propyl carbinol; CH_3-CH_2-CH(OH)-CH_2-CH_2-CH_3, CAS Registry number 623-37-0) is colorless liquid with b.p. 134.8 °C and log P = 1.65, slightly soluble in water (16 g/litre). It occurs naturally in flavor and aroma of plants such as pineapple and is used as a food additive to add flavor (Lide 1998). No relevant toxicological data are available.

2-Methyl-1-pentanol

2-Methyl-1-pentanol (2-methylpentan-1-ol; CH_3-CH_2- CH_2-CH(OH)-CH_2-CH_3, CAS Registry Number 105-30-6) is colorless liquid with b.p. 149 °C, slightly soluble in water (8.1 g/litre). Oral acute toxicity data reported for rats is LD_{50} 1410 mg/kg and for mice > 3200 mg/kg (Papa 2011).

3,3-Dimethyl-2-butanol

3,3-dimethyl-2-butanol (pinacolyl alcohol; CH_3-$C(CH_3)_2$-CH(OH)-CH_3, CAS Registry Number 20281-91-8) is secondary alcohol, m.p. 5.6 °C, b.p. 120.4 °C, solubility in water 25 g/litre (Lide 1998). Pinacolyl alcohol appears on the List of Schedule 2 substances (CWC) as a precursor for the nerve agent soman.

CNS depression and nephrotoxicity has been observed in animal studies with pinacolyl alcohol. Inhalation studies with rats have shown ataxia, mild hypoxemia, hypercapnia, and lacrimation (James et al. 1987b). LCLo in rat was 4930 mg/kg for a 6 hours exposure period per day for 13 week inhalation study (James et al. 1987a). The rats also showed depressed respiration and reduced motor activity upon an exposure. Biochemical investigations showed increased serum cholesterol and bilirubin. An exposure affected kidney, ureter, and bladder showing changes in tubules including acute tubular necrosis and renal failure. These findings suggest that the primary target organ of pinacolyl alcohol, when given by inhalation, is kidney in male rats and possibly ovaries in female rats. Renal changes in high-dose males were not fully reversible during a recovery period (James et al.1987a).

Higher aliphatic saturated alcohols

Higher aliphatic saturated alcohols with seven or more atoms of carbons in a molecule are compounds toxicologically nonsignificant. They are very often in different biological sources and have near relation to fatty acids (Stetten and Schoenheimer 1940) and to waxes (Motiuk 1989). Higher aliphatic alcohols (C_7–C_{18}) are produced in a number of important industrial processes using petroleum-based raw materials. By far the largest volume synthetic alcohol is 2-ethylhexanol, $C_8H_{17}OH$, used mainly in production of poly(vinyl chloride) plasticizer bis(2-ethylhexyl) phthalate (Wagner and al. 2000). In chemical laboratories n-octanol is used for measurement of partition coefficients (De Bruijn et al. 1989).

1-Octanol

1-Octanol (n-octanol, caprylic alcohol; CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2OH, CAS Registry Number 11-87-5) is colorless liquid with b.p. 195 °C, slightly soluble in water (0.54 g/litre), with log P = 3.0. Oral acute toxicity data reported for rats is LD_{50} > 3200 mg mg/kg (Opdyke 1973), intravenous for mice 69 mg/kg (Chvapil et al., 1962) and percutaneous for guinea pigs > 1000 mg mg/kg (Opdyke 1973). No relevant toxicological data are available for humans.

2-Ethylhexanol

2-Ethylhexanol (2-ethyl-1-hexanol, CH_3-CH_2-CH_2-CH_2-CH(CH_2-CH_3)-CH_2OH ;CAS Registry Number 104-76-7) is colorless liquid with b.p. 184.6 °C, slightly soluble in water (0.88 g/litre), with log P = 3.73. 2-Ethylhexanol is rapidly absorbed by rats following oral administration. On dermal administration to rats, 5.2 % is absorbed. The main metabolites detected in urine are 2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid, 2-ethyl-1,6-hexanediacid and 6-hydroxy-2-ethylhexanoic acid, which exist almost exclusively as glucuronides. Acute toxicity of 2-ethylhexanol in animals is low. Oral acute toxicity data reported for rats is LD_{50} > 3730 mg mg/kg (Scala and Burtis 1973). LD_{50} in mice is 2500 mg/kg (Chvapil et al. 1962), in rabbits 1180 mg/kg (Schmidt et al. 1974) and in guinea pigs 1860 mg/kg (Schmidt et al. 1974). LD_{50} in mice at intraperitoneal application is 759 mg/kg (Schmidt et al. 1974) and percutaneous for guinea pigs > 1000 mg mg/kg (Opdyke 1973). Liver is a target organ on repeated oral administration of 2-ethylhexanol to rats (Keller et al. 1990).

2-Ethylhexanol demonstrated no carcinogenic activity at the maximum tolerated doses in chronic oral studies carried out over 2 years in rats and 18 months in mice. No effect levels for systemic toxicity were 50 mg/kg body weigh/day in rats and 200

mg/kg body weight/day in mice. At higher doses tested, reduced body weight gain, increased mortality, clinical signs of toxicity and changes in organ weights were observed, but there were no macroscopic or microscopic effects. 2-Ethoxyethanol was not embryotoxic or teratogenic in rats or mice on oral administration or in rats on dermal application at doses that were not maternally toxic (Anonymous 1995).

Environmental toxicity

2-Ethylhexanol is a possibly causative chemical in sick building symptoms, although this alcohol has received little attention as a hazardous substance in studies on indoor air pollution.

Airborne 2-ethylhexanol concentrations were measured from 2002 to 2004 in 99 rooms of 42 non-domestic buildings in Nagoya, Japan. Concentrations were 16.5 μg/m^3 in indoor air and 1.9 μg/m^3 in outdoor air. The maximum concentration of 2-ethylhexanol in indoor air and outdoor air was 2709 μg/m^3 and 12.4 μg/m^3, respectively. These results suggest that the predominant source of 2-ethylhexanol was in indoor areas (Sakai et al. 2006).

Human toxicity

2-Ethylhexanol is a volatile organic compound that is often found in indoor air generated by degradation of plastic building materials or in new buildings (Andersson et al. 1984). The objective was to assess acute effects from a controlled exposure of volunteers to 2-ethylhexanol (Ernstgard et al. 2010). Sixteen males and fourteen females were in random order exposed to 1 mg/m^3 of vapors of 2-ethylhexanol or to clean air (control exposure) in an exposure chamber during 2 h at rest. The subjects performed symptom ratings on Visual Analog Scales. During the exposure to 2-ethylhexanol, subjective ratings of smell and eye discomfort were minimal but significantly increased. Ratings of nasal irritation, throat irritation, headache, dyspnoea, fatigue, dizziness, nausea, and intoxication were not significantly affected. No exposure-related effects on measurement of blinking frequency by electromyography, measurement of the eye break-up time, vital staining of the eye, nasal lavage biomarkers, transfer tests, spirometric and rhinometric measures were seen. No differences in response were seen between sexes or between atopics and non-atopics. This study showed weak subjective symptoms of irritation in the eyes (Ernstgard et al. 2010).

CONCLUSIONS

Toxic alcohols are poisonous alcohols that can damage the heart, kidneys, and nervous system. Several toxic alcohols are of medical and toxicological importance; the principal ones include ethanol, ethylene glycol, methanol, and isopropanol. Even if interest of physicians is focused namely on ethylene glycol and methanol (McMahon et al. 2009), other alcohol may be also dangerous. Alcohols are used very often in many applications and any alcohol can be toxic if ingested in large enough quantities. Aliphatic alcohols themselves are only little toxic or nontoxic. Their major toxicities are a result of these being transformed to toxic metabolites. Alcohols are metabolised via alcohol dehydrogenase to corresponding aldehydes which are subsequently metabolised to carboxylic acids through interaction with aldehyde dehydrogenase. Alcohol toxicity is a complex and not fully understood action.

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